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C Black, E Cummins, P Royle, S Philip and N Waugh

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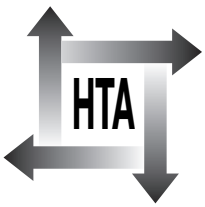

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Abstract

The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation

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Objectives: To review the clinical effectiveness and cost-effectiveness of a new technology, the inhaled insulin, Exubera® (Pfizer and Sanofi-Aventis, in collaboration with Nektar Therapeutics), a short-acting insulin.

Data sources: Electronic databases were searched up to November 2005.

Review methods: A systematic literature review was conducted and economic modelling carried out. An industry model was used for modelling.

Results: Nine trials of inhaled insulins were found, but only seven used the Exubera form of inhaled insulin. The other two used inhaled insulins that have not yet been licensed. There were five trials in type 1 and two in type 2 diabetes. Inhaled insulin is clinically effective, and is as good as short-acting soluble insulin in controlling blood glucose, plus it works slightly more quickly. None of the published trials compared it with short-acting analogues. Most patients in the trials were on combinations of short-acting, and either long- or intermediate-acting insulin, and both were changed, making it more difficult to assess the effects of only the change from soluble to inhaled insulin. Patient preference was the only significant difference between inhaled and soluble insulin in the trials. Most patients preferred inhaled to injected short-acting insulin, and this has some effect on quality of life measures. However, the control groups mostly used syringes and needles, rather than pens. As pens are more convenient, their use might have narrowed the patient satisfaction difference. There were no trials of inhaled insulin against continuous subcutaneous insulin infusion (CSII). No serious adverse experiences of inhaled insulin in the lung have been seen to date, but it is too soon yet to judge long-term effects. The manufacturer's model appears to be a high-quality one, although the results depend more on the assumptions fed into the model than on the model itself. The key assumptions are the size of the gain in quality of life utility from inhaling rather than injecting insulin, the effect of having an inhaled option on the willingness to start insulin among people with poor diabetic control on oral drugs, and the effect on glycaemic control. We consider that these assumptions make the cost-effectiveness appear better than it really would be. The manufacturer's submission assumed utility gains of 0.036–0.075 in patients with type 1 diabetes, and 0.027–0.067 in those with type 2, based on an unpublished utility elicitation study sponsored by the manufacturer. We thought that these gains were optimistic and that gains of 0.02 or less were more likely, on average. However, patients with particular problems with injection sites might have more to gain, although they might also be a group with much to gain from CSII. A key factor is the cost of inhaled insulin. Much more insulin has to be given by inhaler than by injection, and so the cost of inhaled insulin is much higher than injected. The extra cost depends on dosage but ranges from around £600 to over £1000 per patient per year.

Conclusions: The inhaled insulin, Exubera, appears to be as effective, but no better than injected short-acting insulin. The additional cost is so much more that it is unlikely to be cost-effective. The long-term safety is uncertain. Additional research is recommended into the safety, efficacy and cost-effectiveness of inhaled insulin.

Contents

List of abbreviations

ADA	American Diabetes Association
ANOVA	analysis of variance
BMI	body mass index
BNF	British National Formulary
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CSII	continuous subcutaneous insulin infusion
CxR	chest X-ray
DAFNE	Dose Adjustment For Normal Eating
DAWN	Diabetes Attitudes, Wishes, and Needs
DCCT	Diabetes Control and Complications Trial
DESMOND	Diabetes Education and Self-Management for Ongoing and Newly Diagnosed
DINLINK	Doctors' Independent Network Patient Database
DLCO	carbon monoxide diffusing capacity
DPP IV	dipeptidyl peptidase IV
EAGLE	Economic Assessment of Glycaemic Control and Long-term Effects
EASD	European Association for the Study of Diabetes
EQ-5D	EuroQol 5 Dimensions
FEV_1	forced expiratory volume in one second
FPG	fasting plasma glucose
FVC	forced vital capacity
HbA_{1c}	major fraction of glycosylated haemoglobin
HIIP	human insulin inhalation powder
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
iDMS	insulin diabetes management system
INH	inhaled insulin
ITT	intention-to-treat analysis
NICE	National Institute for Health and Clinical Excellence
NPH	isophane insulin
NR	not reported
ns	not significant
OHA	oral hypoglycaemic agent
OQLS	overall quality of life score
OR	odds ratio
OSSS	overall satisfaction summary score
PEF	peak expiratory flow
PPAR-γ	peroxisome proliferator-activated receptor-gamma
PSIT	Patient Satisfaction with Insulin Therapy

continued

List of abbreviations *continued*

PVD	peripheral vascular disease
QALY	quality-adjusted life-year
QoL	quality of life
QWB-SA	Quality of Well Being index – Self Administered
RCN	Royal College of Nursing
RCT	randomised controlled trial
RR	relative risk
SC	subcutaneous
SD	standard deviation
TLC	total lung capacity
TTO	time trade-off
UKPDS	United Kingdom Prospective Diabetes Study
URTI	upper respiratory tract infection
VAS	visual analogue scale
WMD	weighted mean difference
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

The two main types of diabetes are type 1 (formerly called insulin-dependent diabetes) and type 2 (formerly called non-insulin-dependent diabetes). In type 1, insulin is always required because the insulin-producing islet cells in the pancreas have been destroyed. In type 2, the pancreas can still produce insulin, and treatment is initially with diet and exercise, but the disease often progresses, with deteriorating control and rising blood glucose levels, and a need next for oral hypoglycaemic agents (OHAs), and later for insulin in about 30%. The aim of insulin therapy is to reduce blood glucose to normal levels, without going too low and causing hypoglycaemia.

Insulin currently has to be given by injection. There are various types according to duration of action – short, intermediate and long. Short- and long-acting insulin both come in two forms: traditional and the newer analogues. The traditional form of short-acting insulin is known as soluble. It is given by injection using an insulin pen, or a syringe and needle. Insulin can also be given by continuous subcutaneous infusion by an insulin pump, usually only in selected patients with type 1 diabetes.

Objective

The aim was to review the clinical effectiveness and cost-effectiveness of a new technology, the inhaled insulin, Exubera® (Pfizer and Sanofi-Aventis in collaboration with Nektar Technologies), a short-acting insulin.

Methods

A systematic literature review was conducted and economic modelling carried out. Literature searches were done up to November 2005. The industry model, EAGLE, was used for modelling.

Results

Clinical effectiveness

Nine trials of inhaled insulins were found, but only seven used the Exubera form of inhaled insulin. The other two used inhaled insulins that have not yet been licensed. There were five trials in type 1 and two in type 2 diabetes.

Inhaled insulin is clinically effective, and is as good as short-acting soluble insulin in controlling blood glucose. The frequency of hypoglycaemia is similar. It works slightly more quickly than soluble insulin. None of the published trials compared it with short-acting analogues, which would have provided a better comparison since they also work slightly more rapidly than soluble. There is also a problem in most of the trials in that patients were on combinations of short-acting, and either long- or intermediate-acting insulin, and both were changed, making it more difficult to assess the effects of only the change from soluble to inhaled insulin.

The only significant difference between inhaled and soluble insulin in the trials was in patient preference. Most patients preferred inhaled to injected short-acting insulin, and this has some effect on quality of life measures. However, there could be some bias operating in the trials. The control groups mostly used syringes and needles, rather than pens. As pens are more convenient, their use might have narrowed the patient satisfaction difference.

The manufacturer, Pfizer, argues that this patient preference could lead to improved control in some type 1 patients, through improved compliance with treatment, and in some type 2 patients poorly controlled on oral agents, because a switch to insulin therapy would be more acceptable if people could use inhaled rather than injected insulin. These assertions are unproven.

There were no trials of inhaled insulin against continuous subcutaneous insulin infusion (CSII).

Safety

Concern has been raised about the long-term effects of inhaled insulin in the lung. So far, no serious adverse effects have been seen, but until many thousands of people have used inhaled insulin for many years, one cannot rule out some uncommon or rare, but serious, adverse effects.

Cost-effectiveness

The manufacturer's model (EAGLE) appears to be a high-quality one. However, the results depend more on the assumptions fed into the model than on the model itself. The key assumptions are the size of the gain in quality of life utility from inhaling rather than injecting insulin, the effect of having an inhaled option on the willingness to start insulin among people with poor diabetic control on oral drugs, and the effect on glycaemic control. We consider that the assumptions used in the industry submission make the cost-effectiveness appear better than it really would be. The manufacturer's submission assumed utility gains of 0.036–0.075 in patients with type 1 diabetes, and 0.027–0.067 in those with type 2, based on an unpublished utility elicitation study sponsored by the manufacturer. We thought that these gains were optimistic and that gains of 0.02 or less were more likely, on average. However, patients with particular problems with injection sites might have more to gain, although they might also be a group with much to gain from CSII.

A key factor is the cost of inhaled insulin. Much more insulin has to be given by inhaler than by injection, and so the cost of inhaled insulin is much higher than injected. The extra cost depends on dosage, but ranges from around £600 to over £1000 per patient per year.

Conclusion

The inhaled insulin, Exubera, appears to be effective and safe, but the cost is so much more that it is unlikely to be cost-effective.

Recommendations for the further research

Additional research is recommended into the safety, efficacy and cost-effectiveness of inhaled insulin.

Chapter 1
Background

Introduction

Diabetes mellitus is a chronic metabolic disorder resulting from a defect in insulin production, insulin action, or both. The two main types are type 1 diabetes mellitus (formerly known as insulin-dependent diabetes mellitus) and type 2 diabetes mellitus (formerly known as non-insulin dependent diabetes). In type 1 diabetes, there is an absolute loss of the insulin-producing cells (β cells) in the pancreas, and insulin is required for survival. In type 2 diabetes, there is a combination of resistance to the effect of insulin in the tissues, and initially overproduction of insulin (though insufficient relative to the increased needs); over time, insulin production may fall as the pancreas fails to maintain higher than normal production.[1] People with type 2 diabetes usually start on diet and exercise alone, but most need oral hypoglycaemic agents (OHAs) (also known as oral glucose-lowering drugs) in addition, and over time many require insulin treatment.

Good glycaemic control is critical in the management of diabetes mellitus in terms of symptom control and minimising long-term complications, as well as improving long-term survival.

In the non-diabetic person, there is continuous production of insulin throughout the day and night with sharp peaks of increased production to cover the metabolic needs after meals. For people with diabetes who require insulin, various insulin regimens exist and seek to mimic the natural secretion of insulin.

The degree to which the natural secretion pattern is replicated is determined not only by the bioavailability of the existing insulin treatments, but also by the complexity of the regimens, tolerance of adverse events (particularly hypoglycaemia), clinical appropriateness and patient preferences.[2]

Insulin treatment has a number of limitations:

- None of the existing insulins (either mealtime or basal insulins) mimics the natural state. Short-acting insulins are absorbed more slowly than ideal (see review[3]), with a slower rise than insulin released by the normal pancreas in response to a meal. Long-acting insulins do not last quite long enough.
- There is a lack of tightly regulated feedback control of insulin delivery into the circulation in response to the body's constantly changing requirements and limited flexibility to adjust insulin delivery to meet these changing needs.
- Patients on intensive regimens have to take multiple daily injections, usually consisting of one long-acting basal insulin plus injections of short-acting insulin to cover mealtime needs.
- Insulin absorption can be erratic, and vary from day to day.
- Insulin treatment can cause hypoglycaemia.
- Self-monitoring of blood glucose is required.
- Restrictions to occupation can occur as a result of insulin treatment (largely in response to the increased risk of hypoglycaemic episodes).
- Insulin delivery has been dependent on injections.

At present, insulin cannot be given by mouth because it is digested and denatured. Research is underway into new forms of insulin that do not need to be injected.[4] One such option is inhaled insulin, delivering insulin over a wide area of lung with a large potential surface for rapid absorption. The aim of this review is to assess the clinical effectiveness and cost-effectiveness of inhaled insulin in the management of type 1 and type 2 diabetes mellitus.

The following background section provides a brief overview of diabetes mellitus and highlights some key issues when considering the role of inhaled insulin therapy:

- the progression of diabetes mellitus in terms of insulin production failure
- treatment of people with insulin
- lung disease in diabetes mellitus
- lipohypertrophy, the lung and insulin.

Diabetes mellitus

Clinical and epidemiological overview

Diabetes is one of the most common chronic disorders in the UK. Estimates of the prevalence

vary. Diabetes UK estimates that more than 2 million people in the UK have diagnosed diabetes, with as many as 1 million as yet undiagnosed.[5] Approximately 80% have type 2 diabetes. The prevalence of diabetes (particularly type 2) is increasing rapidly. Around 90,000 people are newly diagnosed each year.[6]

Diabetes causes a range of symptoms and chronic complications. Symptoms include:

- weight loss
- polyphagia (frequently hungry)
- polyuria (frequently urinating)
- polydipsia (frequently thirsty)
- blurred vision
- severe fatigue
- poor wound healing (cuts, scrapes, etc.)
- dry or itchy skin
- recurrent infections such as vaginal yeast infections, groin rash or external ear infections.

Complications include:

- atherosclerosis (leading to cardiovascular diseases: coronary heart disease, stroke, peripheral vascular disease)
- diabetic nephropathy (and kidney failure)
- diabetic retinopathy (and blindness)
- diabetic neuropathy
- diabetic foot ulceration (leading to infection and potentially amputation).

Glycaemic control

Evidence from studies such as the Stockholm Diabetes Intervention Study,[7] the Diabetes Control and Complications Trial (DCCT),[8] the Kumamoto study[9] and the UK Prospective Diabetes Study (UKPDS)[10] demonstrated that the onset and severity of diabetic complications are associated with glycaemic control. The UKPDS demonstrated that intensive glucose control reduced microvascular end-points, such as eye disease, and macrovascular end-points, such as heart attacks.

Lower glycosylated haemoglobin (HbA_{1c}) levels lowered the rate of cardiac events.[11] In the European Prospective Investigation of Cancer and Nutrition Study[12] the lower the HbA_{1c} achieved within the accepted normal range, the lower the rate of cardiac events, cardiac mortality and total mortality. The current recommendations from the American Diabetes Association (ADA)[13] are that the target should be 7% or less. The American College of Endocrinology and the International Diabetes Federation suggest a lower target of 6.5%.

The National Institute for Health and Clinical Excellence (NICE) recommended, based on the UKPDS trial, that the target HbA_{1c} should be as close to the normal range as possible and suggested a target of between 6 and 7.5% unless this is not possible owing to side-effects such as hypoglycaemia or to patient factors such as non-compliance or significant co-morbidity.

These targets are very much aspirational. Tight control has a higher incidence of hypoglycaemia and greater weight gain (in people with type 2 diabetes). Complex treatment regimens and intensive monitoring also mean that in some individuals control has to be a trade-off against other factors.

In addition to suggesting HbA_{1c} targets, there are also published targets for fasting/preprandial and postprandial blood glucose levels.

Preprandial versus postprandial glucose levels

As type 2 diabetes progresses it is important to consider the relative significance of fasting and preprandial, versus postprandial, glucose levels in affecting HbA_{1c} when choosing insulin regimens. Monnier and colleagues[14] (*Figure 1*) reported that the higher the HbA_{1c} in type 2 diabetes mellitus, the greater the contribution of fasting (preprandial) glucose levels; this is logical, since most people spend most of the day in a non-postprandial state. At low levels of HbA_{1c}, under 7.3%, postprandial has twice as much effect on HbA_{1c} as fasting and preprandial glucose.

In the lowest quintile (mean HbA_{1c} of 6.45%), postprandial glucose contributed 70% of the elevation in HbA_{1c}. If the aim is to reduce fasting plasma glucose, then it is logical to use a basal insulin, perhaps with oral agents at mealtimes. However, if oral agents fail adequately to control postprandial excursions in blood sugar, addition of mealtime insulin will be necessary, especially if aiming for the more aggressive HbA_{1c} target of 6.5%. The progression in type 1 diabetes is more rapid and therefore the relative contributions of preprandial and postprandial glucose to HbA_{1c} are of little clinical relevance.

Insulin production failure

Type 1 diabetes occurs as a consequence of the immune-mediated destruction of pancreatic islet β cells,[15] presenting clinically after a progressive decline in the function of β cells when the majority of β cells have been damaged or

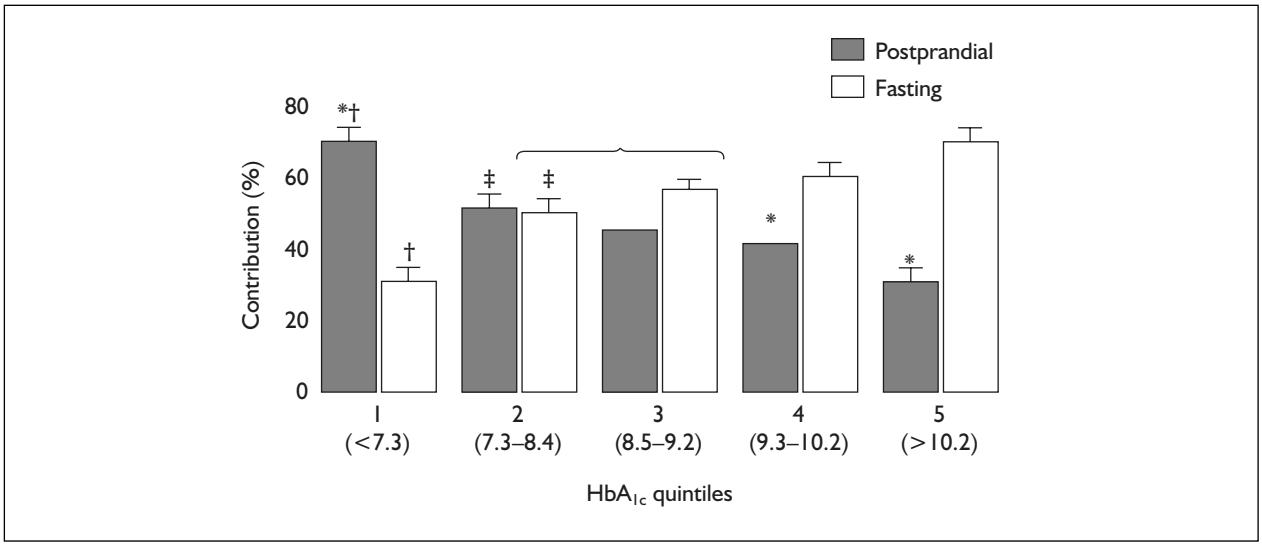

FIGURE 1 *Relative contributions of preprandial and postprandial glucose to HbA_{1c}.* Significant difference between fasting and postprandial (paired t-test); † significantly different from all other quintiles (ANOVA); ‡ significantly different from quintile 5 (ANOVA). © American Diabetes Association from* Diabetes Care *2004;**27**(Supp 1): S15–35.*[14] *Reprinted with permission from the American Diabetes Association.*

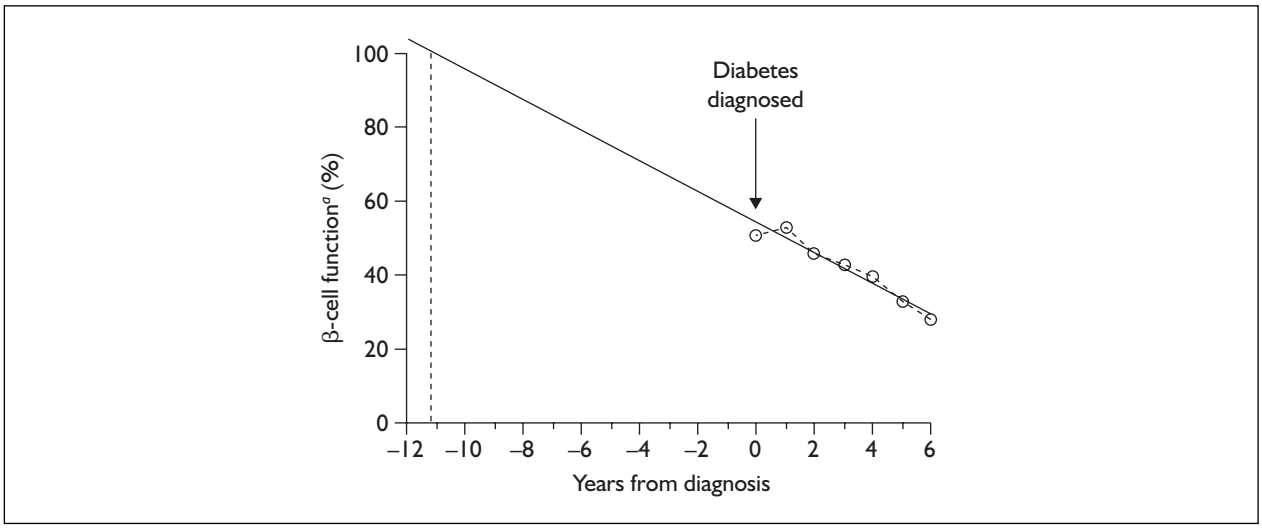

FIGURE 2 *β-Cell function over time in type 2 diabetes mellitus. [a] β-Cell function measured by HOMA (Homeostasis Model Assessment). Adapted with permission from Holman RR. Assessing the potential for alpha-glucosidase inhibitors in prediabetes states.* Diabetes Res Clin Pract *1998;**40**(Suppl): S21–5. © Elsevier.*

destroyed. At the onset of clinical symptoms most islets are deficient in β cells.[16,17]

In contrast, type 2 diabetes mellitus is a progressive disease preceded by an asymptomatic prediabetic condition (insulin resistance, impaired glucose tolerance or impaired fasting glucose). The condition progresses eventually to symptomatic diabetes. While insulin resistance may have a pivotal role in the pathogenesis, diabetes only develops when β cells fail to compensate for increased demand.[18,19] *Figure 2* illustrates the decline in β-cell function over time with data from UKPDS.[1]

β-Cell exhaustion, whatever its cause, is the key cause of disease progression.[1,20] Type 2 diabetes mellitus can be managed by dietary and lifestyle changes in some, but eventually requires pharmacological intervention in most. The Belfast Diet Study followed newly diagnosed people with type 2 diabetes mellitus for 10 years. The authors demonstrated that β-cell deterioration determined the rate of progression towards a failure of dietary measures to control blood glucose.[21]

Initially the pancreatic cells still respond to drugs that stimulate insulin production and release,

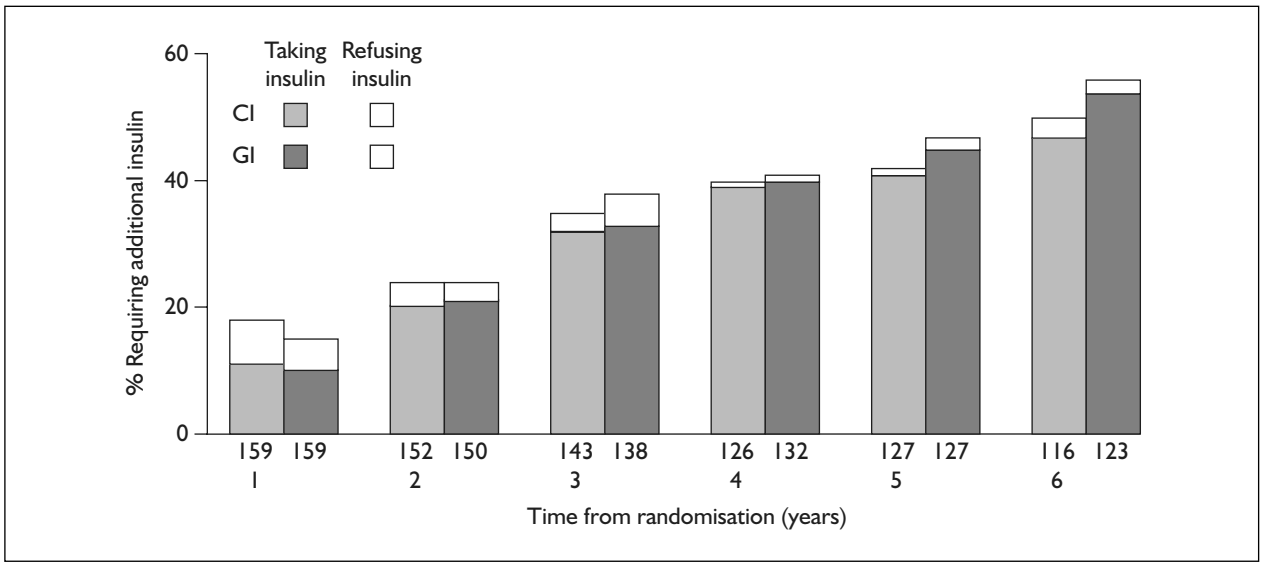

FIGURE 3 *Proportion of patients allocated chlorpropamide (CI) or glipizide (GI) who required addition of insulin each year because of high fasting plasma glucose levels. The number below each column is the number of patients per year. Note for later consideration that the proportion refusing insulin despite clinical need is low. © American Diabetes Association. From* Diabetes Care *2002;**25**:330–6, 2002.*[23] *Reprinted with permission from the American Diabetes Association.*

known as insulin secretagogues (such as the sulphonylureas). Over time, the β cell's secretory capacity further declines and an absolute insulin deficiency develops. At this point, patients will require treatment with insulin, alone or in combination with multiple oral agents, to achieve adequate glycaemic control.

In the UKPDS there was a linear overall failure rate of 7% per year in all treatment groups. Over 50% of subjects required additional therapy by the end of the 11-year study. Rather than a linear progression, some have proposed a slow initial decline in function until a 'functional crisis', after which a more rapid decline occurs, based on the Belfast Diet Study.[22] With either model, the net result is a progression to failure of insulin production in people with type 2 diabetes.

Similarly, UKPDS 57[23] described the steady rise in numbers of patients allocated to chlorpropamide or glipizide who, over time, progressed to insulin because of failure to control fasting plasma glucose below 6.0 mmol/l on maximal sulphonylurea dose (*Figure 3*). Those requiring, but refusing, additional insulin are indicated separately.

Therefore, whereas people with type 1 diabetes start on insulin therapy immediately, people with type 2 diabetes progress at variable rates and will require increasing intensity of therapy over time.

Insulin in the management of diabetes

Type 1 diabetes

People with type 1 diabetes need basal insulin throughout the 24 hours, and more at mealtimes.

Various regimens exist combining short- and longer acting insulins (*Box 1*). The choice is determined by individual patient needs and preferences, in particular in relation to number and timing of injections. Different regimens are summarised in the NICE clinical guidelines (No. 15: Diagnosis and management of type 1 diabetes mellitus in adults).[2] The chosen insulin regimen should be offered as part of an integrated package of diabetes education, blood glucose monitoring and dietary review.

Mealtime insulin is provided by injection of unmodified ('soluble') insulin or rapid-acting insulin analogues (e.g. lispro, aspart) before main meals. Basal insulin supply (including nocturnal insulin supply) is provided by the use of intermediate-acting insulin [usually isophane insulin (NPH)] or long-acting insulin analogues (glargine or detemir). If rapid-acting insulin analogues are given at mealtimes, or the midday insulin dose is small or can be omitted, then one option is to provide basal by giving isophane insulin twice daily. Long-acting insulin analogues should be used when nocturnal hypoglycaemia is a problem on isophane insulin, or morning

BOX 1 *Examples of insulin regimens in type 1 diabetes*

- Twice-daily premixed insulin (i.e. using a fixed mixture of short- and intermediate-acting insulin which comes in one vial; more convenient, but with no scope for varying the proportions)
- Twice-daily combinations of mixed intermediate- and short-acting insulin, mixed just before injection
- Premixed insulin in the morning, quick-acting at teatime and intermediate-acting isophane at bedtime
- Basal–bolus regimen (multiple daily injections)
- Continuous subcutaneous insulin infusion using an insulin pump

hyperglycaemia on isophane insulin results in difficult daytime blood glucose control. Absorption of isophane may vary from day to day; the long-acting analogues provide more predictable levels and cause less hypoglycaemia.

Insulin therapy in type 2 diabetes mellitus

Current practice in the UK varies, but there is usually a stepped approach to clinical management, progressing through:[24,25]

1. diet and exercise
2. usually metformin (where tolerated and not contraindicated)
3. combination therapy such as metformin plus a sulphonylurea
4. triple therapy, usually with a glitazone, perhaps with a meglitinide
5. insulin, alone or in combination with an 'insulin sensitiser' such as metformin, or other OHAs.

Intensive glucose control with metformin appears to decrease the risk of diabetes-related complications in overweight diabetic patients, and is associated with less weight gain and fewer hypoglycaemic attacks than insulin or sulphonylureas. Metformin is the first line pharmacological therapy of choice in these patients.[26] Sulphonylureas are still frequently used in lean people with type 2 diabetes.

In the UK, insulin is usually considered the treatment of last resort. Peyrot and colleagues[27] report that many patients, and health professionals, have concerns about:

- perceived complexity
- hypoglycaemia
- occupational issues (e.g. driving, offshore work)
- fear of weight gain.

Peyrot and colleagues did not report having to give injections as a reason for delaying insulin therapy. One of the main reasons for delaying insulin therapy was that it was not expected to be effective in this group.[27]

As for type 1 diabetes, a variety of insulin regimens exists and the choice of which regimen to use in an individual patient is determined by factors including clinical need and patient preference:

- Basal insulin, such as ultralente, glargine or detemir, usually once daily. (NB. Glargine is currently not recommended by NICE for routine use in type 2 diabetes; the same would presumably apply to detemir, although NICE has not issued guidance on detemir.) However, with the withdrawal of ultralente, the place of glargine and detemir may be revised.
- Prandial insulin with short-acting soluble insulin or analogues (lispro, aspart). Inhaled insulin could replace these.
- A biphasic insulin given twice daily;[28–30] less flexible, but more convenient.
- Basal–bolus regimens, consisting of a long-acting insulin plus short-acting to cover mealtimes.[23]

The Treating To Target in Type 2 diabetes (4T) study is currently comparing the first three of these. The Oxford Centre for Diabetes, Endocrinology and Metabolism in collaboration with Novo Nordisk is conducting a study to find out the answer to the question 'How to start and intensify insulin treatment in type 2 diabetes?'[31]

NICE issued guidelines in 2002 (http://www.nice.org.uk/pdf/NICE_INHERITEG_guidelines.pdf) on the management of type 2 diabetes, supporting the stepwise approach to the management of type 2 diabetes mellitus and emphasising the need for education and involvement on the part of the person with diabetes. The flow diagram guiding management of blood glucose is summarised in *Figure 4*.[32]

The different insulin regimens outlined reflect the clinical balance between achieving levels as close as possible to the natural insulin pattern, the clinical needs of the individual, and their preferences. As noted previously, injected insulin cannot provide a perfect match for the normal insulin response. Intensive regimens such as basal–bolus or continuous subcutaneous insulin infusion are the closest current match, but require multiple daily injections (or continuous infusion using a pump) and intensive glucose monitoring.

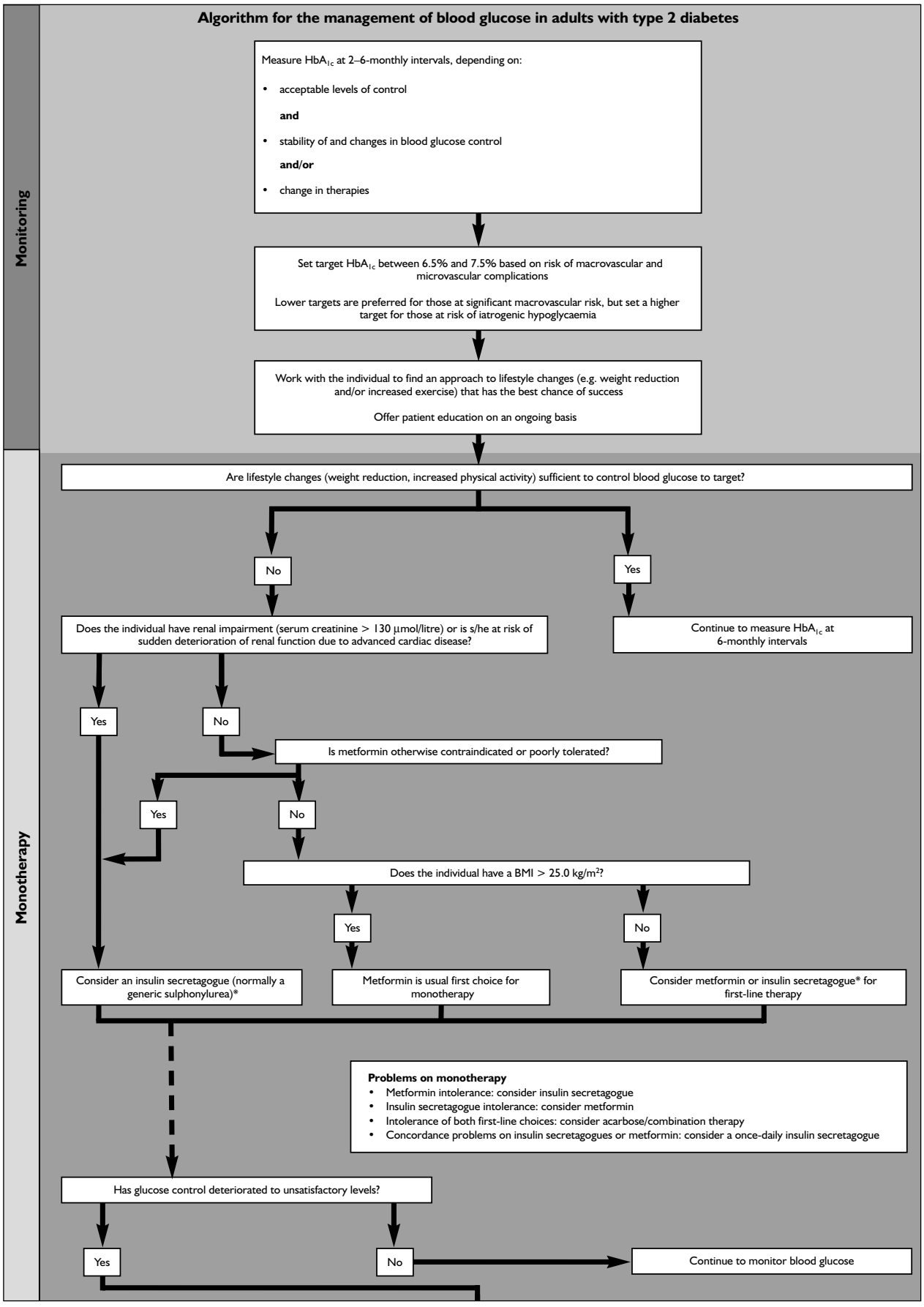

FIGURE 4 *Summary of NICE guidelines for the management of type 2 diabetes mellitus. (cont'd opposite)*

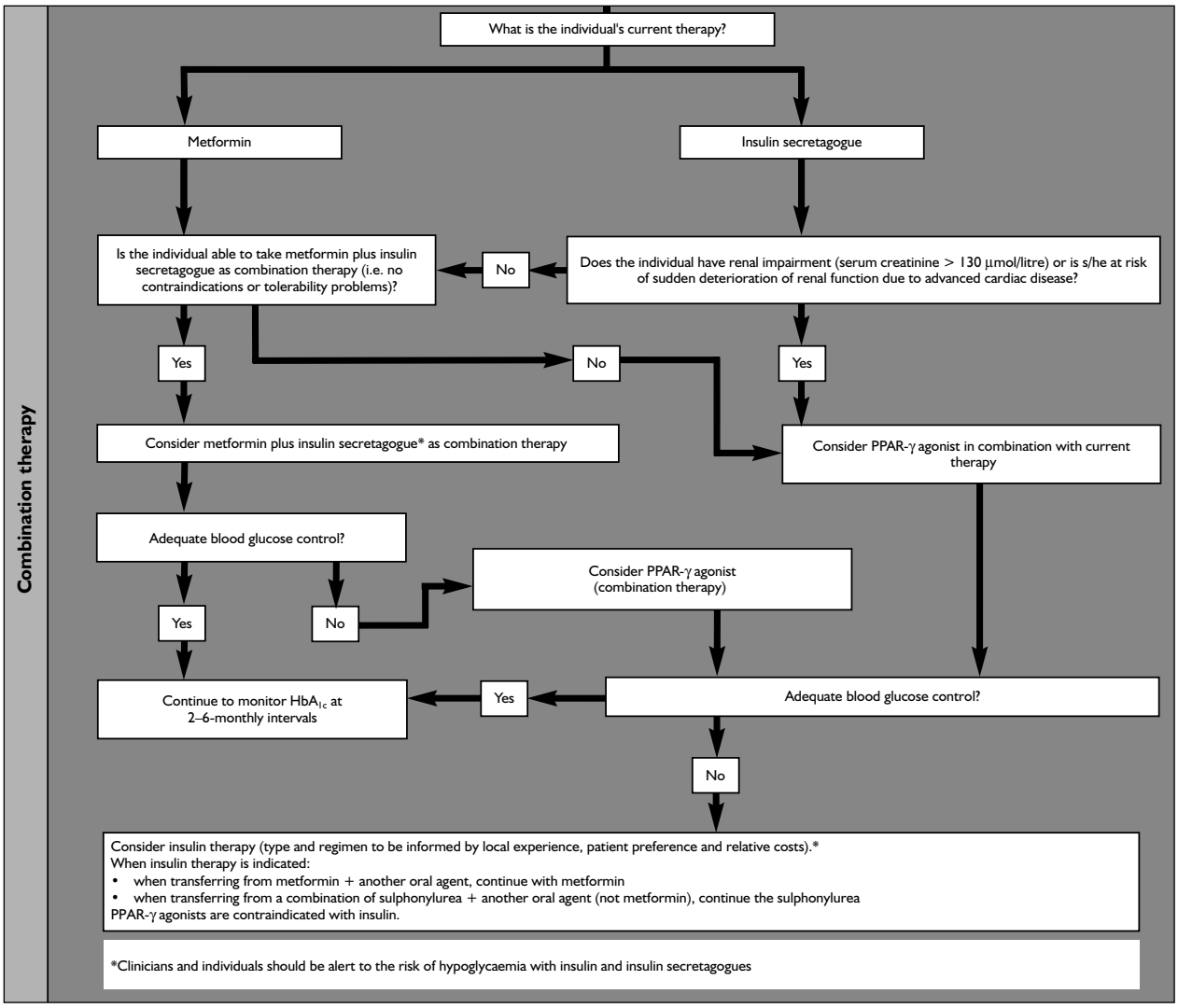

FIGURE 4 *Summary of NICE guidelines for the management of type 2 diabetes mellitus. BMI, body mass index; PPAR-γ, peroxisome proliferator-activated receptor-γ. National Institute for Clinical Excellence. Algorithm for the management of blood glucose in adults with type 2 diabetes, from Inherited Clinical Guideline G:* Management of type 2 diabetes: management of blood glucose*. London: NICE; 2002. URL: www.nice.org.uk/page.aspx?o=36737. Reproduced with permission.*

Alternative insulin treatment options

As a result of the limitations with existing insulin regimens there has been a search for alternatives and, in particular, for a delivery mechanism that avoids the need for injections, and an insulin absorption profile that more closely reflects the natural insulin response. Inhaled insulin has been considered for some time and provides a mechanism of delivery that avoids mealtime injections.

Drugs have been given by inhalation in other conditions, most notably asthma. Most corticosteroid and bronchodilator drugs are given by inhalation, and there is a wide variety of devices, reviewed by Peters and colleagues.[33] (It should be noted that the site of action of asthma drugs is in the larger airways, to reduce bronchoconstriction, whereas insulin has to penetrate farther, into the alveoli, from where it is absorbed.) Although the concept of giving insulin by the respiratory tract, either nasally or via the lung, is not new, it is only recently that adequate delivery devices have been developed. The only inhaled insulin marketed in the UK is Exubera®, the product of a joint development programme between Pfizer and Sanofi-Aventis, in collaboration with Nektar Therapeutics. Two other products, the AERx® insulin diabetes management system (AERx iDMS), being jointly developed by

Novo Nordisk and the Aradigm Corporation, and human insulin inhalation powder (known as HIIP), being developed by Lilly and Alkermes, are further from market and are not covered by this review. Other devices are being developed; see Cefalu (2004) for a review.[4]

Currently, inhaled insulin is restricted to a short-acting profile and for almost all patients would not completely remove the need for injection. A study by Rave and colleagues[34] compared the time-action profile of one inhaled insulin, Exubera, with that of a subcutaneously injected insulin analogue, lispro, or regular human soluble insulin in healthy volunteers. Inhaled insulin was found to have a faster onset of action than regular insulin, but was comparable to lispro. The duration of action for inhaled insulin was longer than lispro and comparable to regular. Hence, it can be an alternative to injected short-acting insulins.

The lung in patients with diabetes mellitus

Lung function in diabetes mellitus

Delivering insulin into the lung is novel, and there is a need to consider possible harms. However, it is important to be aware of changes in the lung in diabetes before any insulin is inhaled, so that any changes seen after inhaled insulin can be set in context. This is done in detail in Appendix 1, and summarised here. In brief:

- Diabetes reduces the elasticity of the lung, making it a little stiffer to inflate and deflate. The pulmonary function tests which measure the ability to breathe out rapidly [forced expiratory volume in one second (FEV_1) and the volume of air expelled after a deep breath – forced vital capacity (FVC)] show some reduction.
- There are changes in small blood vessels, similar to those seen in the kidney, but less marked.
- The diffusion capacity is slightly reduced. This is usually measured by diffusion of carbon monoxide (DLCO).

However, pulmonary effects are slight and usually subclinical (not noticed by patients). This may be because of the size of the vascular bed in the lungs (if the lung surface were spread out, it would roughly equate to the size of a tennis court).

That there are changes to the lung, due to diabetes itself, needs to be borne in mind when considering the evidence of side-effects of inhaled insulin. Some of the lung changes appear to be related to control, so if inhaled insulin improved control, it might have beneficial effects on the lung as well as adverse ones.

Lipohypertrophy and the lung

A hypothetical complication in the lung is lipohypertrophy. At the site of insulin injection, lipohypertrophy occurs as a result of a cellular response of the adipocytes. Susceptibility varies possibly reflecting the role of immunological factors. A review by Chowdhury and Escudier[35] notes that in children and young adults with type 1 diabetes mellitus the titres of insulin antibodies correlated with the degree of lipohypertrophy. Adipocytes are also present in the lung and so there are theoretical risks of lipohypertrophy there. However, at present there is little evidence to indicate the effect of inhaled insulins on these cells, in either animal or human studies.

Conclusions

NICE guidelines for the management of type 1 diabetes mellitus indicate that the insulin regimen should be tailored to suit the needs of the individual. A basal–bolus approach was favoured as best practice or, where appropriate, continuous infusion (i.e. after failed basal–bolus regimen in someone able and committed enough to use the regimen effectively). While biphasic insulin given twice a day was one option considered by NICE, it was only recommended where the number of injections was a major quality of life concern, or where delivery of the lunchtime dose of insulin creates logistical or compliance problems.

In type 2 diabetes mellitus, the NICE guidelines highlighted the lack of evidence about the optimal insulin regimen, indicating the need to consider patient preferences and circumstances as well as clinical disease control. The guidelines indicated that insulin should only be considered after diet, weight reduction and oral therapies (used in combination) had failed.

Inhaled insulin provides a potential alternative to short-acting injected insulin in the management of type 1 and type 2 diabetes mellitus. For most, it would be used in combination with a long-acting injected insulin. In all, it would require blood sugar monitoring and education about the effective management of diabetes.

Key questions to be addressed by this review

Type 1 diabetes mellitus

- Is inhaled insulin clinically effective in people with type 1 diabetes mellitus as an alternative to short-acting injected insulins?
- In people wishing to minimise the number of injections a day, would inhaled insulin (in combination with once-daily long-acting insulin) be clinically effective compared with continuous subcutaneous injection infusion?

Type 2 diabetes mellitus

- Is inhaled insulin clinically effective in people with type 2 diabetes mellitus failing on maximal oral therapy, as an alternative to other injected insulin regimens?
- Is inhaled insulin clinically effective in people with type 2 diabetes mellitus failing on single long acting insulin (in combination with oral therapy), as an alternative to intensification by short-acting injected insulin? There may be groups of people for whom additional injections create logistical issues for administration that could be solved by a different method of insulin delivery.
- Would inhaled insulin have a place in people failing on their current regimens where the number of injections causes substantial issues in terms of quality of life and impacting on compliance with therapy?

Cost-effectiveness

- Does inhaled insulin provide marginal benefits in terms of control of diabetes, reduction in hypoglycaemic episodes, patient preference or quality of life, sufficient to make it a cost-effective alternative?

Chapter 2

Clinical effectiveness

Introduction

From the previous discussion, a number of groups of patients can be identified who may have the potential to benefit from inhaled insulin. These are summarised in *Table 1*. The column 'Potential clinical benefit' includes various benefits alleged in the literature to be possible benefits of inhaled insulin. The evidence for each of these will be examined later.

In people with type 2 diabetes mellitus, it is not standard practice in the UK to consider insulin therapy as an alternative to oral therapy where oral therapy is providing adequate glycaemic control. We do not believe that inhaled insulin differs in this respect to other insulins. Therefore, *Table 1* does not include the use of inhaled insulin in people who are adequately controlled on oral therapy. The oral therapy should be as recommended in the NICE guidelines, with conversion to insulin only considered when maximally tolerated doses of at least two oral agents, combined with reinforcement of lifestyle advice such as weight loss and exercise, have failed to provide satisfactory control of blood glucose levels.

Methods for reviewing effectiveness

The a priori methods for the review were outlined in the research protocol sent to NICE and

TABLE 1 *Groups that may have the potential to benefit from inhaled insulin (INH)*

Patient group	Potential clinical benefit	Comments or conditions to be met
Type 1 diabetes mellitus		
Existing or new users of basal–bolus regimens	Reduction in injections. More natural profile of insulin in bloodstream?	If INH is clinically equivalent (or better) and cost-effective
Existing or new users of basal–bolus regimens who are poorly compliant with injections because of mealtime injection (inconvenience, fear, quality of life, unpredictability of work, etc.)	Improved control because of improved compliance? Better quality of life?	Would apply if compliance with inhaled was better than with short-acting injections; or if the availability of inhaled insulin made it easier to persuade those on conventional regimens, such as twice daily premixed, to move to intensified regimens. CSII would be another option here, especially for people with unpredictable activity and mealtimes
Type 2 diabetes mellitus		
Those failing on maximal oral therapy and requiring conversion to insulin treatment, usually starting on once-daily long-acting insulin	INH an alternative to injections? More natural profile of insulin in bloodstream?	If mealtime INH was clinically equivalent (or better) and cost-effective, compared with once-daily long-acting insulin (now usually glargine or detemir)
Existing users on once-daily long-acting insulin who require intensification of treatment by the addition of mealtime insulin	Fewer injections than with injected mealtime insulins	If INH was clinically equivalent and cost-effective compared with adding short-acting injected insulins
Existing users of basal-bolus regimens who are poorly compliant with injections because of mealtime injection (inconvenience, lack of flexibility, fear, quality of life, work, etc.)	Improved control because of better compliance? Better quality of life?	As for the second group in type 1 diabetes, except that NICE does not currently recommend CSII for type 2 diabetes

CSII, continuous subcutaneous insulin infusion.

presented at the meeting with consultees. The methods are summarised below.

Preliminary searches identified that the main comparators in trials to date have been with various injected insulin regimens and against oral combination therapy. As outlined above, inhaled insulin was considered to be an alternative to continued oral therapy in patients with type 2 diabetes only for individuals who were not controlled on oral therapy, and required some sort of insulin regimen. Therefore, this review was interested in comparisons of inhaled short-acting insulin, versus any injected insulin regimen, or with insulin injected by CSII. Studies in people with diabetes requiring insulin therapy, whether type 1 or type 2, were included.

Only randomised controlled trials (RCTs) with parallel groups and controlled cross-over trials were considered eligible. Blinding in trials of this nature would be extremely difficult owing to the need to adjust dosage, and while theoretically possible, is impractical. As HbA_{1c} is an objective measure, this outcome should not be affected by lack of blinding. However, outcomes such as patient satisfaction and quality of life are vulnerable to bias as a result of the lack of blinding and any differences must be interpreted with caution. Another caveat might be that patients volunteering for trials of inhaled insulin might be those most disenchanted with injections.

The minimum trial duration considered eligible was 10 weeks, based on the time taken for HbA_{1c} to reflect reliably changes in glycaemic control.[36] For patient acceptability, longer trial duration is desirable (say adherence at 12 months), but results from shorter durations were included as preliminary searches showed that data from longer periods were not available. For long-term pulmonary effects an uncertain period, probably of at least several years, would be required.

Glycaemic control, as a proxy for long-term complications of diabetes, was taken as the primary outcome of interest. Information was also sought about patient satisfaction, quality of life, hypoglycaemia, weight change and other adverse events.

The search strategy is summarised in Appendix 2 and included electronic databases (MEDLINE, EMBASE, Science Citation Index, BIOSIS, Web of Science Proceedings), the National Research Register, Cochrane Library, Current Controlled Trials and handsearching of recent issues of relevant diabetes journals. The websites of the ADA and the European Association for the Study of Diabetes (EASD) were searched for recent meeting abstracts.

Pfizer helpfully provided copies of posters of studies for which abstracts had been identified from the search; the posters gave much more detail. One study, cited in the manufacturer's submission (Trial 217-1022), is ongoing and the data (interim 12-month data) are not currently published. Its primary outcome is lung function change and, therefore, it has been summarised in the relevant section as 'additional information'.

All retrieved titles and abstracts were reviewed independently by two researchers. Full papers were retrieved and reviewed by two reviewers independently, using a predefined data extraction form, if the information given suggested that the study:

- included diabetic patients treated with insulin (either type 1 or type 2)
- compared inhaled insulin with insulin injected subcutaneously
- assessed one or more relevant clinical outcomes.

Quality assessment of the trials was done using the methods described in the manual of the Centre for Reviews and Dissemination, for RCTs and controlled clinical trials, and by Jadad and Spitzer.[37–39]

Results of effectiveness review

Quantity and quality

From a total of 213 articles identified as potentially relevant, full review of the articles (where available) or abstracts identified nine trials of inhaled insulins with appropriate comparators. Seven studies: Cappelleri (2002),[40–42] Heise (2004),[43] Hollander (2004),[44,45] Quattrin (2004)[46–48] Skyler (2001),[49,50] Skyler (2005)[51,52] and Dumas (2005)[53] used Exubera inhaled insulin (sponsored by Pfizer). One study, Hermansen (2004)[54,55] used the AERx iDMS (sponsored by Novo Nordisk), and one, Garg (2005),[56] used the Lilly/Alkermes system. These two studies were not included in any further analysis in this review. One of the studies[53] was only available in poster or abstract form.

Some trials had been reported in duplicate, as abstracts from both EASD and ADA conferences, and some gave little detail of location of the

co-authors or study groups, thus making it quite difficult to collate all the reports based on any one trial. Abstracts from the same study sometimes had no authors in common.

A further 12 studies were identified, but excluded because the comparators used were not felt to be relevant to clinical practice in the UK (e.g. inhaled insulin versus oral therapy). These excluded studies are listed in Appendix 3.

Details of the characteristics of the included studies are shown in Appendix 4, along with the data extraction of outcomes. *Table 2* summarises the characteristics of the seven included studies. Overall, there were 1355 participants in the seven trials; 1005 had type 1 and 350 had type 2 diabetes mellitus.

The reporting of the methods in some trials was poor, hence it was not possible adequately to assess their quality, particularly those published only in abstract form. We did not exclude any trials on the basis of quality, but planned to assess impact of quality by sensitivity analysis of any positive primary outcomes. *Table 3* summarises the quality assessment.

Comparators and diabetic status at treatment initiation

Type 1 diabetes

The study participants had type 1 diabetes mellitus in five studies.[43,46,50,51,53] *Table 2* summarises the inclusion criteria regarding diabetes control and the treatment regimens compared. All studies included people who were stable on their current insulin regimens and used at least two injections of insulin per day. No studies included only people who were failing on their current insulin regimen (entry HbA_{1c} ranged from 5 to 11%).

Once randomised, participants in the control arm received either once- or twice-daily basal injections and short-acting insulin at mealtimes (*Table 2*). No trials comparing inhaled insulin regimens with continuous subcutaneous insulin infusions were found. None of the trials compared inhaled insulin with intensified regimens currently used (i.e. long-acting analogue insulin once per day plus three injections of short-acting insulin) and none compared regimens using rapid-acting insulin analogues. This is a weakness, as discussed later.

Type 2 diabetes

Participants had type 2 diabetes in two studies.[40,44] *Table 2* summarises the inclusion criteria regarding diabetes control and the treatment regimens compared. In both studies participants were stable on injected insulin regimens involving at least two injections per day. None of the participants was failing on oral therapy, none was failing on single basal injections plus oral therapy, and none was in people starting insulin. HbA_{1c} at entry ranged from 6 to 11%, so again not all participants were failing on their current injection regimen.

Participants in the control arm of both of the studies continued on their current regimen of insulin.

Basal insulin regimens

Only two studies[43,51] used the same basal insulin in both groups. Details of the basal insulins used were unclear in Cappelleri[40] and Dumas.[53] The other three studies[44,46,50] used a different basal insulin in each group, preventing a direct comparison between inhaled and soluble insulin.

Assessment of outcomes

Three main outcomes were used to assess effectiveness:

- HbA_{1c} (as a surrogate for long-term complication control, as none of the trials was of sufficient duration to assess long-term outcomes): HbA_{1c} has been shown to be closely linked to long-term outcomes[7–10]
- patient preference and quality of life: these outcomes are important if inhaled insulin is demonstrated to have clinical equivalence in terms of HbA_{1c} and adverse events, since other aspects may then determine which should be used
- adverse events, including hypoglycaemia, lung effects and weight gain.

Glycosylated haemoglobin

Two measures of glycaemic control were reported: change from baseline and proportion of participants achieving a target HbA_{1c} of less than 7%. For both type 1 and type 2 diabetes mellitus, inhaled insulin provided equivalent control of HbA_{1c} to injected insulin regimens (*Table 4*).

Type 1 diabetes

Change from baseline

All five trials in patients with type 1 diabetes mellitus showed equivalence in terms of diabetes control, as reflected in HbA_{1c}. Two trials[43,50] provided data in a format to allow a meta-analysis. This was done using the differences between baseline and the end-point for each group (*Figure 5*). Again, this analysis shows equivalence

TABLE 2 *Summary of characteristics of included studies*

Trial	Participants	Duration	Intervention
Type 1 diabetes mellitus			
Dumas, 2005[53]	Little reported in abstract Mean age: range 12–65 years	12 weeks	*n* = 226 INH combined with once- or twice-daily intermediate or long-acting insulin versus injected short-acting insulin, combined with once- or twice-daily intermediate- or long-acting insulin
Heise, 2004[43]	Inclusion: stable insulin regimen involving at least two daily injections and a dose ⩽150 U/day, HbA_{1c} 5–9% Mean age: INH 37.6; SC 35.9 years Duration of diabetes (mean years): INH 16.6; SC 18.0	24 weeks	*n* = 23 Premeal INH + NPH s.c. twice daily versus *n* = 22 premeal injected regular insulin + NPH s.c. twice daily (two withdrew before treatment)
Quattrin, 2004[46–48]	Two or more injections of insulin a day, for previous 2/12; HbA_{1c} 6–11% Mean ages: INH 33.5; SC 34.0 Duration of diabetes (mean years): INH 16.2; SC 16.5	24 weeks	*n* = 169 INH before meals + bedtime ultralente versus *n* = 165 NPH + regular insulin before breakfast, regular insulin before dinner, second NPH before dinner or bedtime
Skyler, 2001[49,50]	Stable insulin schedule for >2 months involving two or three injections/day, HbA_{1c} 7–11.9% Mean ages: INH 35.4; SC 39.7 Duration of diabetes (mean years): INH 14.6; SC 14.4	12 weeks	*n* = 35 INH three times/day plus single-dose s.c. ultralente at bedtime versus *n* = 37 s.c. injections two or three times/day (no rapid-acting analogues) and human NPH before breakfast and bedtime
Skyler, 2005[51,52]	HbA_{1c} levels 6–11%; stable insulin regimen (two or more injections daily for >2 months) Mean ages: 29.5 (14.6); range 12–65 years Duration of diabetes: 13.8 years	24 weeks	*n* = 163 INH before meals plus a morning and bedtime dose of NPH versus *n* = 165 premeal regular s.c. insulin, plus a morning and bedtime dose of NPH
Type 2 diabetes mellitus			
Cappelleri, 2002[40–42]	Inclusion: HbA_{1c} 7–11.9%; stable insulin regimen (two or three injections/day) Mean ages: INH 51.1; SC 53.6 Duration of diabetes (mean years): 11 (INH 11.2; SC 11.5)	12 weeks	*n* = 26 INH before meals plus single ultralente s.c. insulin injection at bedtime versus *n* = 25 injected insulin: usual regimen of split/mixed insulin, two or three injections/day
Hollander, 2004[44,45]	Stable SC insulin schedule: two or three injections/day for ⩾2 months before study; not receiving OHA; HbA_{1c} 6–11% inclusive Mean ages: INH 58.7 (9.5); SC 56.2 (11.1) years Duration of diabetes (mean years): INH 13.8; SC 13.2	24 weeks	*n* = 149 INH before meals plus single ultralente injection at bedtime versus *n* = 150 At least two daily injections of s.c. insulin (mixed regular insulin/NPH)

SC, subcutaneous injection.

TABLE 3 *Quality assessment of included studies*

Study	Random	Allocation concealment	ITT	Sample size[a]	Withdrawals
Type 1 diabetes mellitus					
Dumas, 2005[53]	Unclear	Unclear	Unclear	Not reported	Inadequate
Heise, 2004[43]	Adequate	Unclear	Inadequate	Not reported	Adequate
Quattrin, 2004[46–48]	Unclear	Unclear	Inadequate	Not reported	Adequate
Skyler, 2001[49,50]	Adequate	Unclear	Adequate	Adequate	Adequate
Skyler, 2005[51,52]	Unclear	Unclear	Inadequate	Adequate	Adequate
Type 2 diabetes mellitus					
Cappelleri, 2002[40–42]	Unclear	Unclear	Inadequate	Adequate	Inadequate
Hollander, 2004[44,45]	Adequate	Adequate	Inadequate	Not reported	Adequate

[a] Sample size reported as adequately powered for the primary outcome measure, HbA_{1c}.
Blinding: all studies were open label. Blinding would have been impractical.
ITT, intention-to-treat analysis.

TABLE 4 *Summary of the HbA_{1c} results*

Trial	Mean ± SD change from baseline	
	INH	Injected
Type 1 diabetes mellitus		
Dumas 2005[53]	–0.4%	–0.5%
Heise 2004[43]	–0.06 ± 0.42%	–0.08 ± 0.77%
Quattrin 2004[46–8]	–0.2%	–0.4%
Skyler 2001[49,50]	–0.64 ± 0.98%	–0.83 ± 0.92%
Skyler 2005[51,52]	–0.3%	+0.1%
Type 2 diabetes mellitus		
Cappelleri, 2002[40–42]	–0.7 ± 0.7%	–0.7 ± 0.7%
Hollander, 2004[44,45]	–0.7%	–0.6%

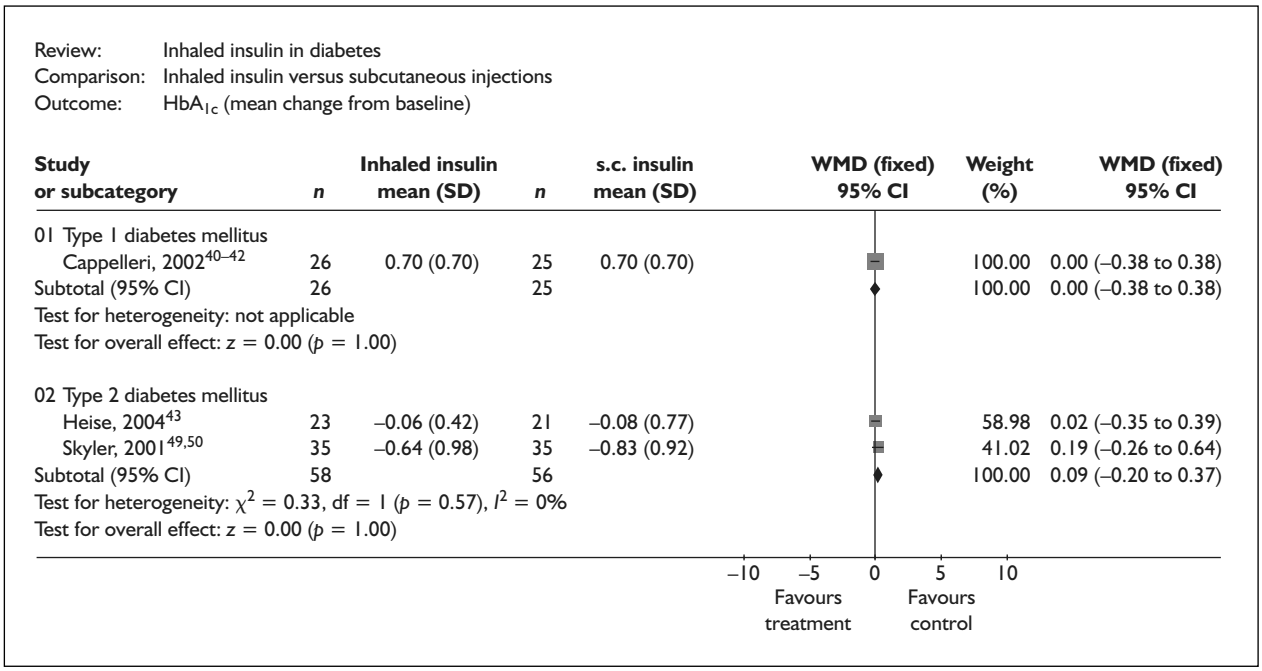

FIGURE 5 *Meta-analysis of HbA_{1c} in type 1 and type 2 diabetes mellitus. WMD, weighted mean difference; CI, confidence interval.*

between inhaled insulin and basal–bolus injected insulin regimens.

Percentage of patients achieving HbA_{1c} levels of below 7%

This outcome was reported by two trials. The percentage of patients achieving HbA_{1c} levels of below 7% was comparable for inhaled and subcutaneous groups. In Quattrin (2004),[46] the figures were: inhaled insulin 15.9% and subcutaneous injected insulin 15.5%; the adjusted odds ratio (OR) was 0.92 (95% CI 0.40 to 2.10), but different basal insulins were used. In Skyler (2005),[51] which did use the same basal, the percentages were again similar: inhaled insulin 23.3% and subcutaneous injected insulin 22.0% (OR 1.53, 95% CI 0.75 to 3.14).

Type 2 diabetes

Change from baseline

Both trials in patients with type 2 diabetes mellitus[40,44] showed equivalence in terms of diabetes control, as reflected in HbA_{1c}. These trials included patients who were 'stable' on an injected insulin regimen before the study, although the mean HbA_{1c} at baseline was 7.9–8.7%, suggesting that control on this regimen was not ideal. The control arm did not receive a change to their therapy regimen, but dose was titrated and advice was given about diet and so on. Similar improvements to inhaled insulin were achieved in the control arm as in the inhaled insulin groups.

Percentage of patients achieving HbA_{1c} levels of below 7%

Hollander (2004)[44] reported that significantly more patients in the inhaled group than the subcutaneous group achieved target HbA_{1c} levels below 7% (inhaled insulin 46.9%, subcutaneous injected insulin 31.7%); the odds ratio was 2.27 (95% CI 1.24 to 4.14). However, different basal insulins were used, so the regimens differed in more than inhaled versus injected.

In conclusion, the trials show that using inhaled insulin in place of short-acting injected soluble insulin gives similar control of blood glucose in the groups studied. Unfortunately, only two of the trials[43,51] used the same basal insulins in both groups.

Patient satisfaction

Five trials reported patient satisfaction, four in type 1 and one in type 2 diabetes patients. Patient satisfaction was measured using the Patient Satisfaction with Insulin Therapy (PSIT) questionnaire[57] (scale 0–100). This consisted of a survey of 15 patient-administered questions, which covered attributes of satisfaction with both injected and inhaled insulin therapy. The items were derived from five qualitative research studies that consisted of one-to-one interviews conducted in the USA. Responses to each item were ranked on a five-point Likert scale, ranging from 'strongly agree' to 'strongly disagree'.

All five trials showed statistically significantly greater satisfaction with the inhaled insulins (*Table 5*). Importantly, the studies were not blind to treatment allocation and patients were, therefore, aware if they received the 'new intervention'; therefore, their reporting of satisfaction may be prone to bias. In two trials[40,50] it was noted that the subcutaneous group also showed an increase in satisfaction levels.

Blinding was impractical, and this could introduce a bias in favour of inhaled insulin for patient satisfaction, which is the key outcome. Patients' views on injections will influence their satisfaction. Inhaled insulin may be particularly useful in the very small proportion of insulin-treated patients with injection phobia. However, there may be a much larger group who have some anxiety about injections. Zambanini and colleagues,[58] reported that 42% (our calculations give 95% CI 33 to 51%) of a group of 116 patients had some anxiety about increasing the number of injections.

Whether and how much inhaled insulin would help this group is not known, since anxiety about intensification of insulin regimens could be due to other factors such as fear of hypoglycaemia or reluctance to increase blood glucose self-monitoring, rather than the injections themselves.

The trials used syringes and needles rather than the much more convenient insulin pens, which creates another bias.

Quality of life

Three trials[44,46,51] reported quality of life. In all three trials the overall quality of life showed statistically significant improvement in the inhaled insulin group compared with the subcutaneous insulin group. However, only Skyler (2005)[51] used the same basal insulin and none of the studies reported the baseline and final (or mean change) in quality of life assessment scores, so the scale of the improvement and clinical relevance could not be assessed. The changes in satisfaction in the control group were sometimes statistically significant for small changes; it is

TABLE 5 *Summary of patient satisfaction and quality of life*

Trial	Measures of satisfaction	Quality of life
Type 1 diabetes mellitus		
Dumas, 2005[53]	Not stated	Not stated
Heise, 2004[43]	Not stated	Not stated
Quattrin, 2004[46–48]	OSSS improved significantly for INH (57.7 to 74.1) ($p < 0.001$) and decreased for SC (58.0 to 56.4) ($p < 0.03$, but clinical significance of difference doubtful)	OQLS and subscales showed more favourable improvements for inhaled vs SC ($p < 0.05$).
Skyler, 2001[49,50]	OSSS: increase in satisfaction from baseline greater in INH (35.1% improvement) vs SC (10.6% improvement). Difference in improvement = 24.5% (95% CI 6.6 to 42.5%, $p < 0.01$) Convenience/ease of use: increase from baseline significantly greater in INH (41.3%) vs SC (11.2%). Difference in improvement = 30.1% (95% CI 10.7 to 49.5%, $p < 0.01$) Social comfort: no statistically significant difference between INH (28%) and SC (18%). Difference in improvement 10% (95% CI –14.6 to 34.6%, $p = 0.42$)	Not stated
Skyler, 2005[51,52]	OSSS improved significantly for INH (62.1 to 74.5) ($p < 0.001$) and decreased for SC (62.8 to 64.3) ($p < 0.05$, but clinical significance doubtful). All subscales showed similar improvement	OQLS and subscales of behavioural and emotional control, general and hyperglycaemic symptom distress, overall cognition, mental acuity and awareness also improved more favourably for INH vs SC (all $p < 0.01$ to 0.05)
Type 2 diabetes mellitus		
Cappelleri, 2002[40–41]	OSSS: improvement from baseline INH 31% (95% CI 14 to 50%); SC 13% (95% CI 7 to 19%). Geometric mean % improvement statistically significantly greater in INH group ($p < 0.05$)	Not stated
Hollander, 2004[44,45]	OSSS INH group reported increased satisfaction (59.3 to 76.3); SC group reported decreased satisfaction (60.1 to 58.8). Difference $p < 0.001$	OQLS: showed favourable improvements for INH vs SC ($p < 0.05$) (no data)

OSSS, overall satisfaction summary score; OQLS, overall quality of life score.

probably better to regard them as unchanged in clinical terms.

Patient preference

At the end of the trial period, two studies considered patient preference for treatment, asking whether patients would prefer to remain on current therapy or to switch. In both cases the results showed that patients preferred to continue with inhaled insulin rather than subcutaneous insulin. Cappelleri[40] reported that patients in the inhaled insulin group (all with type 2 diabetes) were significantly more likely (71%) to wish to continue their assigned regimen than patients who had to inject short-acting subcutaneous insulin ($p < 0.05$).

Skyler (2001)[50] reported that significantly more patients in the inhaled insulin group than in the subcutaneous insulin group agreed with the statement: 'I would like to continue to take insulin the way I took it during the study' ($p < 0.01$).

Uncontrolled follow-up studies (extension studies and patient preference cross-over, for up to 12 months after the 3-month RCTs) where patients choose which form of therapy to continue with support these findings, but should be interpreted with caution[59,60]

Rosenstock[60] determined patient satisfaction in patients with type 1 or type 2 diabetes receiving an

inhaled insulin or a subcutaneous insulin regimen, as assessed by pooled analysis of two 12-week parent studies[40,50] and 1-year extension studies.

In the 1-year extension studies, patients were allowed to select either treatment regimen. It was found that of the 60 patients who received inhaled insulin during the parent studies, 85.0% ($n = 51$) chose to continue treatment, 13.3% ($n = 8$) switched to subcutaneous insulin and 1.7% ($n = 1$) did not continue. Of the 61 patients who received subcutaneous insulin, 21.3% ($n = 13$) chose to continue treatment, 75.4% ($n = 46$) switched to inhaled insulin and 3.3% ($n = 2$) did not continue. From baseline to 1 year, HbA_{1c} reductions of 0.8% were sustained, and greater improvements were observed in the inhaled insulin group compared with the subcutaneous insulin group in terms of overall satisfaction (37.9 versus 3.1%, $p < 0.01$) and ease of use (43.2 versus –0.9%, $p < 0.01$).

However, the results from this cohort study should be treated with caution, since patients were not randomised to their respective groups, but chose their treatments, and hence the results are potentially subject to bias.

The preference results are consistent, and appear to refute any suggestion that the inhaled insulin regimens were cumbersome and difficult to use.

Adverse events

Hypoglycaemic episodes

Total hypoglycaemic episodes

This outcome was reported in six trials. It should be noted that all compared inhaled insulin with soluble insulin rather than short-acting analogues. Four trials[43,44,46,51] reported a lower rate of total hypoglycaemic events in the inhaled insulin group than in the subcutaneous insulin group; in three of these trials[44,46,51] this difference was statistically significant but only just so, and in one trial[43] it was not reported whether the difference was significant. In the other trial[53] the rate of overall hypoglycaemic events was statistically significantly higher in the inhaled group (*Table 6*).

Skyler (2001)[50] reported frequencies of mild to moderate hypoglycaemic episodes with the inhaled insulin group of 5.5 events per month, and for the subcutaneous insulin group 5.3 events per month. There was no significant difference between treatment groups.

Serious hypoglycaemic events

This outcome was reported in all seven trials. Rates were higher in the inhaled insulin group in two trials,[43,51] equivalent in four trials[40,44,46,50] and less in one trial[53] (*Table 7*).

Weight change

Four trials[40,46,50,51] reported that there was no statistically significant difference between the groups in terms of weight gain. In one trial,[44] the inhaled insulin group body weight remained stable at 90.5 kg at 24 weeks, whereas the subcutaneous group displayed a small increase (89.2–90.6 kg). The adjusted mean group difference was –1.29 kg (95% CI –1.98 to –0.59). Dumas[53] did not report weight change in the published abstract.

Pulmonary function tests

Six trials reported on this outcome. In three trials[40,44,50] there were no significant differences between groups. Three trials[46,51,53] reported a statistically significantly greater mean decrease in

TABLE 6 *Overall hypoglycaemic events*

Trial	Hypoglycaemia (total)		
	INH	**Injected**	**Comment**
Type 1 diabetes mellitus			
Dumas, 2005[53]	6.8 events/subject-month	5.5 events/subject-month	RR 1.24 (90% CI 1.17 to 1.31)
Heise, 2004[43]	7.8 events/subject-month	9.4 events/subject-month	
Quattrin, 2004[46–48]	8.6 events/subject-month	9.0 events/subject-month	RR 0.96 (95% CI 0.93 to 0.99)
Skyler, 2001[49,50]	NR		
Skyler, 2005[51,52a]	9.3 events/subject-month	9.9 events/subject-month	RR 0.94 (95% CI 0.91 to 0.97)
Type 2 diabetes mellitus			
Cappelleri, 2002[40–42]	0.8 events/subject-month	1.1 events/subject-month	No significant difference
Hollander, 2004[44,45]	1.4 events/subject-month	1.6 events/subject-month	RR 0.89 (95% CI 0.82 to 0.97)

NR, not reported; RR, relative risk.

TABLE 7 *Severe hypoglycaemic events*

Trial	Hypoglycaemia (severe)		
	INH	**Injected**	**Comment**
Type 1 diabetes mellitus			
Dumas, 2005[53]	0.053 events/subject-month	0.103 events/subject-month	RR 0.52 (90% CI 0.30 to 0.86)
Heise, 2004[43]	4 events	2 events	
Quattrin, 2004[46–48]	5.5 events/100 subject-months	4.7 events/100 subject-months	RR 1.16 (95% CI 0.76 to 1.76)
Skyler, 2001[49,50]	0.08 events /subject-month	0.1 events/subject-month	"Not significant"
Skyler, 2005[51,52a]	6.5 events/100 subject-months	3.3 events/100 subject-months	RR 2.0 (95% CI 1.28 to 3.12)
Type 2 diabetes mellitus			
Cappelleri, 2002[40–42]	None	None	
Hollander, 2004[44,45]	0.5 events/100 subject months	0.1 events/100 subject-months	

[a] Four patients accounted for ~50% of severe hypoglycaemia events. One patient took unprescribed insulin doses and another was reported to be unaccustomed to having glucose in a more 'normal' range and was thought to be experiencing hypoglycaemic symptoms when glucose was still acceptable clinically.

TABLE 8 *Summary of pulmonary function results*

Trial	Pulmonary function		
	INH	**Injected**	**Comment**
Type 1 diabetes mellitus			
Dumas, 2005[53]	–0.070 L (FEV_1) and –0.973 mL/min/mmHg (DLCO)	–0.027 L (FEV_1) and –0.246 mL/min/mmHg (DLCO)	Adjusted difference, FEV_1, –0.043 L; DLCO, –0.727 mL/min/mmHg
Quattrin, 2004[46–48]	–0.065 L (FEV_1) and –1.685 mL/min/mmHg (DLCO)	+0.02 L (FEV_1) and –0.031 mL/min/mmHg (DLCO)	Adjusted difference, FEV_1, –0.031 L; DLCO, –1.218 mL/min/mmHg
Skyler, 2001[49,50]	–2.17 L (FEV_1) and –5.78 mL/min/mmHg (DLCO)	–1.02L (FEV_1) and –7.71 mL/min/mmHg (DLCO)	No statistically significant difference
Skyler, 2005[51,52]	–0.0016 L (FEV_1) and –0.75 mL/min/mmHg (DLCO)	+0.008 L (FEV_1) and –0.229 mL/min/mmHg (DLCO)	Adjusted difference: FEV_1, –0.037 L; DLCO, –0.791 mL/min/mmHg
Type 2 diabetes mellitus			
Cappelleri, 2002[40–42]	No significant difference between groups in pulmonary function tests, but no data were reported		
Hollander 2004[44,45]	No significant change in FVC, FEV_1, TLC and DLCO		

TLC, total lung capacity.

DLCO in the inhaled insulin group. Details of results of the pulmonary functions for each trial are given in *Table 8*.

Cough

Four trials[44,46,51,53] reported this. In all four trials the frequency was greater in the inhaled insulin group, but appeared to be mild and to decrease over the study period. Details of the studies are given below.

Other adverse events

Adverse event reporting other than those detailed above was sparse. Two studies gave more, albeit limited, information.

In Quattrin,[46] with the exception of cough and overall hypoglycaemic events, the frequency and nature of other adverse events were comparable between treatment groups. No further details were reported. Skyler (2005)[51] reported that the overall

frequency and nature of adverse events were comparable between groups. No details were given apart from cough.

Insulin doses

Few trials gave full details of doses.

Skyler (2005)[51] reported that insulin dosages were comparable at baseline and increased slightly over the study period. Inhaled insulin doses were given in milligrams, and injected insulin in international units. For example, at week 24 the prebreakfast doses were 3.3 mg with inhaled and 8.9 units with injected insulin. The authors state that 1 mg is the equivalent of 2–3 units of subcutaneous insulin insulin.

Cappelleri[40] reports that patients receiving inhaled insulin were given 14.6 ± 5.1 mg of inhaled insulin and 35.7 ± 18.4 units of ultralente daily by the end of the study, compared with before the study, where doses were 19 units of regular insulin and 51 units of long-acting insulin.

Additional studies

Notes are given below on some other studies, including some of the exclusions, for completeness, and because some of these studies may be used by others as evidence in favour of inhaled insulin.

This review is concerned only with the replacement of short-acting injected insulin by inhaled insulin. However, some trials have found that in patients with type 2 diabetes who are poorly controlled on oral agents, control can be improved either by adding inhaled insulin to oral agents, or by stopping the OHAs and replacing them with inhaled insulin. These trials are summarised below, but are not included in the review because all they show is that inhaled insulin is effective; injected insulin would have achieved the same. The default position in this review is that the NICE treatment guidelines should be followed.

Rosenstock[61] recruited patients with inadequate control on two OHAs (the combination of an insulin secretagogue and an insulin-sensitiser) and randomised them to inhaled insulin alone, inhaled insulin plus the previous OHAs, or continuation on OHAs alone. HbA_{1c} did not change on the OHA continuation, but improved in the inhaled insulin groups. However, all this really tells us is that insulin reduces blood glucose levels. Injected insulin would have done the same.

Defronzo[62] randomised type 2 diabetes patients inadequately controlled on diet and exercise, but not on any hypoglycaemic agents, to premeal inhaled insulin (Exubera, one or two inhalations of 1 or 3 mg) or to rosiglitazone 4 mg twice daily. A larger drop in HbA_{1c} was seen with inhaled insulin (2.3%) than with rosiglitazone (1.4%). More patients achieved the HbA_{1c} target of below 8% with inhaled insulin (83%) than with rosiglitazone (56%). Weight gain was greater with inhaled insulin (1.9 kg) than with rosiglitazone (0.8 kg), although this was not statistically significant.

Hypoglycaemic episodes were more common with inhaled insulin than rosiglitazone (0.7 and 0.05 events per person-month). This trial is not relevant to this review because going from diet and exercise direct to insulin is not standard practice in the UK, and not in keeping with the stepped care approach recommended by the NICE guidelines.

Testa and colleagues[63] recruited 470 type 2 patients who had failed to achieve good control with metformin monotherapy, and randomised them to additional therapy with glibenclamide or inhaled insulin for 24 weeks, with treatment titrated aiming at a fasting plasma glucose of 80–140 mg/dl. In those with initial HbA_{1c} between 9.5 and 12%, it fell by 2.9% with inhaled insulin and 2.5% with glibenclamide. In those with HbA_{1c} 8–9.5 at baseline, falls were 1.5 and 1.6%, respectively. Quality of life gains were reported as greater with inhaled insulin, but only in those with high initial HbA_{1c} levels, and absolute differences were not great.

Testa and colleagues,[64] in a similar trial, recruited 423 people with type 2 diabetes poorly controlled (HbA_{1c} 8–12%) on sulphonylurea monotherapy, and randomised them to have additional inhaled insulin before meals or metformin for 24 weeks. Overall end-study HbA_{1c} was 7.6% for inhaled insulin and 7.8% for metformin. Quality of life and overall satisfactions were similar, but there was greater dissatisfaction with side-effects with inhaled insulin, mainly weight gain and hypoglycaemia. The trial is reported as showing superiority of inhaled insulin, but the differences seem marginal.

In the Weiss study,[65] 68 patients inadequately controlled (HbA_{1c} 8.1–11.9%) despite a sulphonylurea and/or metformin (36 of the 69 were on both metformin and a sulphonylurea), were randomised to continue on their previous OHA(s) or to have inhaled insulin added. There

was no change in the OHA-alone group, but a drop of 2.3% in the insulin group. Again, all this tells us is that insulin lowers blood glucose; injected insulins would have done the same. In addition, about half the group were on only one OHA.

Barnett[66] (Exubera Phase III study group) reports the 24-week extensions (i.e. to 52 weeks) of what look like the Testa studies above (it is not clear from the abstract), which compared the glycaemic effect of adding, in type 2 diabetes mellitus patients inadequately controlled on a single OHA, either inhaled insulin or another OHA. The primary purpose was to examine pulmonary safety. HbA_{1c} at 52 weeks was similar in the inhaled insulin and OHA groups (7.6% and 7.8%). No differences in DLCO were found among groups.

These studies all compared inhaled insulin to oral regimens which are less than maximal, and usually only monotherapy, and are therefore not relevant in terms of assessing clinically relevant scenarios.

In the Freemantle study,[67] patients with type 2 diabetes failing to achieve target glycaemic control on diet and/or OHA therapy were randomised to receive information only about existing treatment options (OHAs and subcutaneous insulin, although it is not stated whether CSII was an option), or to receive that information plus information on the risks and benefits of inhaled insulin too. Patients then made theoretical choices about whether to use inhaled or other therapy. In the group offered information in which inhaled insulin was an option, 43% would choose to start insulin, whereas in the group where that was not an option, only 16% would opt for (subcutaneous) insulin. However, the preference would be influenced by the information provided, and no details of this were published. The study was funded by Pfizer and Aventis, manufacturers of Exubera, who have provided a copy of the information, which seems to give a balanced approach with no obvious bias in favour of inhaled insulin.

The study provides useful information on the reluctance to move to insulin; 50% of the physicians considered that the patients should start insulin, but only 16% did (inhaled insulin was not available). Hence, the authors argue that the availability of inhaled insulin might make it easier for physicians to persuade those failing on non-insulin therapies to move to an insulin-containing regimen. It must be noted that this was a hypothetical study and because inhaled insulin was not available, the true uptake remains uncertain.

The study also restricted the population to type 2 diabetes mellitus failing on oral agents or diet, so nothing is known from this about the impact on choosing insulin regimens in type 1 diabetes mellitus, or intensification of insulin regimens in type 2 diabetes mellitus already on some form of insulin. Those with experience of injecting insulin probably see it as less of a problem than those who have never experienced it.

In Skyler, 2004[68] open-label inhaled insulin therapy was offered to patients who had completed any of three 3-month, randomised, controlled clinical trials (type 1, insulin-treated type 2 or type 2 diabetes uncontrolled on oral agents). It is not clear from the abstract which trials these were. A total of 204 patients entered the extension, with 159 choosing to stay on inhaled insulin or switch to it, and 89 patients received at least 4 years of inhaled insulin therapy. Mean ± SD HbA_{1c} was 8.23 ± 1.21% after 4 years in inhaled insulin patients, compared with 8.71 ± 1.49% at the start of inhaled insulin treatment. Inhaled insulin dose increased slightly from 0.15 mg/kg after 3 months of treatment to 0.18 mg/kg after 4 years. The rate of overall hypoglycaemia decreased from 2.58 episodes per subject-month (first 4 weeks of inhaled insulin treatment) to 1.50 after 4 years (final 6 months). Hence glycaemic control was sustained. The small changes seen in lung function did not progress, and indeed decreased slightly over time.

Cefalu and Sedarevic-Pehar[69] gave 2-year follow-up data from three trials in type 2 diabetes, all with Exubera. The abstract does not say which trials these were, but they do not appear from the descriptions to have been trials in which inhaled insulin was compared with injected, and are hence not inclusions in this review. Changes in lung function parameters were similar among all groups. Insulin antibody levels rose, but were not associated with changes in glycaemic control or adverse events in any of the studies.

The manufacturer's submission also provided interim results from an ongoing trial (217–1022) of inhaled insulin versus injected insulin in 580 patients with type 1 diabetes mellitus. At 12 months, interim analysis reported less reduction in HbA_{1c} with inhaled (HbA_{1c} –0.04% versus –0.31%), although more people on inhaled achieved an HbA_{1c} of below 7%, and more people withdrew from the inhaled group than injected (53

versus 42). Pulmonary function at 12 months was similar between the two treatment groups (measured by DLCO), but one patient in the inhaled group withdrew due to breathlessness. Weight gain was less in the inhaled group (0.21 versus 1.56 kg).

Bioavailability issues

The summary of product characteristics (SPC) for Exubera states that the relative bioavailability of Exubera compared with subcutaneous fast-acting insulin is approximately 10%. A review by Valente and colleagues[70] notes that relative biopotency is between 10 and 12%, which is that about eight to ten times as much as must be inhaled as injected. The word 'inhaled' here is used as short-hand for 'emitted from the inhaler' because much of the insulin will not reach the alveoli in the lungs from which it is absorbed. Some will coat the mouth and throat and be swallowed; some will reach the lungs, but only as far as the bronchi from where it will be expelled; some will be breathed out again.

The impact of smoking on inhaled insulin

Himmelmann and colleagues[71] reported that absorption was faster and peak plasma insulin concentration was greater in smokers, although immediately after smoking, absorption was slower. This study was done in non-diabetic subjects and used low doses of insulin, but it does imply that smoking could affect absorption.

Asthma and inhaled insulin

Henry and colleagues[72] reported that in non-diabetic subjects, those with asthma had poorer absorption, and more variable absorption, than non-asthmatics. Hence, diabetic patients with asthma may need to inhale more insulin than patients with normal respiratory function to achieve similar glycaemic control. In practice, short-term variations in airways resistance and hence in insulin absorption may be more of a problem. Inhalers are used very successfully in asthma, but it should be noted that the target sites are the bronchi, not the alveoli.

Influence of acute upper respiratory tract infection on the absorption of inhaled insulin

McElduff and colleagues[73] reported that upper respiratory tract infections (URTIs) did not affect absorption, and hence that the need for dose adjustments will not differ from subjects with an acute URTI who are receiving subcutaneous insulin. This study was done in non-diabetic people, because of the logistical difficulties of finding a group with diabetes who had URTIs when needed.

Absorption and bioavailability

Patton and colleagues[74] reviewed studies of the pharmocokinetics and pharmacodynamics of different versions of inhaled insulin, usually glucose clamp studies, and concluded that serum insulin concentrations peaked earlier and decayed more rapidly following inhalation, compared with subcutaneously administered regular insulin. Intrapatient variability in the pharmacokinetics and pharmacodynamics of inhaled insulin was low, and is similar to (or perhaps less than) that with subcutaneous insulin. Absorption is only about 10% of that experienced with subcutaneous insulin. Most of the losses are in the device/atmosphere, mouth and throat, with approximately 30–50% of the insulin deposited in the lungs being absorbed.

Kim and colleagues[75] (probably the full version of a 2002 abstract included in the Patton review[74]) also concluded that inhaled insulin was as reliably absorbed, in terms of predictability of bioavailability, as subcutaneous. Kapitza and colleagues[76] also found that intrasubject variability was comparable between patients receiving inhaled insulin and subcutaneous insulin.

Variability from day to day in the absorption of inhaled insulin has been reported to be similar to[77] or less than that of subcutaneous insulin.[78,79] Unpublished data provided by Novo Nordisk, admittedly from a small study with only 17 participants with type 1 diabetes, suggest that there is less variation in the bioavailability of inhaled insulin than there is with short-acting subcutaneous insulin. In a recent study of 15 patients with type 2 diabetes, Perera[80] found no greater intrapatient variability of effect between inhaled and subcutaneous administration. A review[77] of the literature on comparative bioavailability concluded that the intra-individual variability remained a problem irrespective of route of administration.

There may be differences between young and elderly patients in insulin doses required. Henry and colleagues[72] compared the pharmacokinetics, pharmacodynamics and safety of inhaled insulin delivered by one of the inhaled insulin systems not included in this review, AERx iDMS, in 27 young (18–45 years) and 28 elderly (65 or over) patients with type 2 diabetes. Results in terms of lung function and plasma insulin levels, and variability of effect, were similar in young and old, but the elderly group had significantly less glucose reduction, indicating that they may be more insulin resistant. Elderly diabetic patients may

need to inhale more insulin than young patients to achieve similar glycaemic control.

Implications of bioavailability on cost of insulin therapy

As mentioned above, much more insulin has to be inhaled than injected to achieve the same effect. This will have implications for the cost.

There are varying figures quoted. Skyler (2001)[50] quotes studies giving a range of 10–30% of the inhaled dose being absorbed into the bloodstream. Gerich[3] quotes other studies suggesting 15% bioavailability for inhaled versus 19% for subcutaneous, presumably for powder forms, but a ten-fold difference for aerosol forms. With the powder form, most (White and Campbell[81] report 95%) of what is inhaled is drug, whereas with the aerosol forms, 98% is water.

Weerakhady and colleagues[82] estimated that seven times as much insulin has to be given by mouth as by injection for the same effect.

Insulin antibodies

Inhaled insulins have been reported to cause higher levels of insulin antibodies than subcutaneous. The higher antibody levels observed in the inhaled insulin groups in the trials did not result in any apparent clinical change.

Fineberg and colleagues[83] pooled insulin antibody data from Phase II/III trials and from a 24-month extension of the Phase III studies. Antibody levels were higher after inhaled, but this seemed to have no adverse clinical consequences.

Generalisability

It is difficult to comment on generalisability because some of the studies give few or no details of the patients recruited. The average age of the type 2 patients in the studies was 56 years, which may be representative of type 2 patients who are treated with insulin. The generalisability of the results is reduced by the large number of exclusion criteria. It should be noted that one of the main reasons for exclusion is asthma, which has been reported in Europe to be less common in people with type 1 diabetes than in the general population.[84] There does not appear to be any evidence of increased risk of harm in people with both diabetes and asthma, and their exclusion is presumably only on the grounds of caution. However, the bioavailability of inhaled insulin might well be unpredictably affected if asthma led to bronchoconstriction, and this would need to be assessed. Smokers have also been excluded; it has been shown that smokers show a greater absorption of inhaled insulin,[85] and once patients had worked out the appropriate dosage at mealtimes, it might be necessary to ensure that people did not vary their smoking habits around the time of inhaling insulin.

In the trials considered acceptable for inclusion, patients were already taking insulin; no trials studied those starting it.

As always, one cannot say how typical patients who participate in trials are of all insulin-treated patients.

Conclusions from clinical effectiveness review

In type 1 diabetes, there is good evidence that inhaled insulin has the same level of effectiveness in controlling HbA_{1c} as injected soluble insulin. The trials did not use insulin analogues, which would have been a more logical comparator with faster onset and shorter duration of action, and would have provided slightly tougher competition to inhaled. Nor was there any comparison with continuous subcutaneous insulin infusion, which requires only one injection every 3 days. There is some evidence that both of these treatment options perform better in terms of HbA_{1c} than soluble insulin.

In type 2 patients, the evidence is that inhaled insulin gives similar HbA_{1c} results to soluble insulin. Again, there are no trials comparing inhaled insulin with short-acting analogues or with continuous subcutaneous insulin infusion. No trials have compared injected to inhaled insulin in type 2 diabetes mellitus failing on oral therapy, or failing on single basal injection regimens. There is evidence that inhaled insulin improves control in those not currently controlled on OHAs, but a similar reduction would be expected in HbA_{1c} with injected insulin in these groups.

Weight gain and other adverse events appear to be similar between inhaled and injected insulins. There were consistent differences in patient preference. One problem with that is that the control arms used syringes to inject, rather than pen injectors which are more convenient; that might have reduced the patient satisfaction difference.

There is no evidence of any harm to the lung, at least up to 3–4 years of use.

While potential benefits may exist for specific groups where number of injections is a major issue in quality of life, compliance or administration of insulin, no studies were found where these groups were specifically considered.

Patient satisfaction and reported quality of life were greater in the inhaled insulin groups, compared with injected insulin, but it should be noted that satisfaction also increased in some control patients, presumably due to the effects of being in a trial. The trials were not blinded; therefore, these self-reported measures are subject to bias.

Chapter 3

The industry submission

This chapter provides a commentary on selected aspects of the industry submission, and in particular on issues where we agree, or disagree, with the industry view.

The EAGLE model

The industry submission uses the Economic Assessment of Glycaemic Control and Long-term Effects (EAGLE) model. Diabetes is a complex disease on which to do economic modelling because of the variety of outcomes, timescales and treatments. The treatments often change over time, especially in type 2 diabetes, because of the progressive nature of the disease.

A number of well-developed models already exists in diabetes, of which EAGLE is one. There is a forum in which the designers and users of the models can demonstrate them, by feeding the same data sets from clinical trials into each model. This forum is known as the Mount Hood Challenge. EAGLE has been presented at this meeting on at least two occasions, including the most recent, and is regarded as a reputable model.

In brief, EAGLE has two modules, an epidemiological one and a health economics one. The epidemiological one takes data from high-quality published studies such as the DCCT and UKPDS, and uses the data to generate risk equations, for example derived from outcomes at different HbA_{1c} levels. The users can then feed in assumptions about HbA_{1c} levels in response to treatments (or other parameters such as blood pressure) and assess the effect on the frequency of outcomes. It is, as expected, driven largely by changes in control as measured by HbA_{1c}. The health economics module then quantifies the costs and cost-effectiveness (taking quality of life into account).

Pfizer provided an executable copy of EAGLE for inspection and use, with accompanying documentation. The model is still commercial in confidence; it is sponsored by Pfizer and Aventis. An account of its development and validation has been published.[86] We considered it to be a high-quality model and have used it in our own economic analysis, thereby allowing direct comparison of the effects of various assumptions with those in the industry submission.

Further details of the model need not be given here. In most health technology assessments, it is the assumptions fed into the models that affect the results, rather than the model structure itself.

The industry submission

The approach and methods described in the industry submission's review of clinical effectiveness were clearly described. No additional studies that met the inclusion criteria were identified.

We are in broad agreement with many of the points in the industry submission, including:

- Many people with diabetes are not achieving good control of blood glucose and so are at risk of the long-term complications.
- Poor adherence is associated with poor control.
- Many people with type 2 diabetes, inadequately controlled on oral agents, are reluctant to switch to insulin treatment.
- Inhaled insulin is effective in controlling blood glucose.

Our conclusions on efficacy are similar, except that we excluded trials that were not considered relevant because of inappropriate comparators, such as the use of inhaled insulin in patients not well controlled on diet and exercise, or oral monotherapy alone. The industry submission meta-analysis included 'any comparator' and so included trials that we did not consider relevant to standard clinical practice,[61–65] as described in the section 'Additional studies' (p. 20). Two of these trials[62,65] compared inhaled insulin to single oral therapy, whereas the standard step would be to add a second OHA. Unsurprisingly, inhaled insulin improved diabetic control in these trials compared with continued oral therapy. Such a meta-analysis is inappropriate given the heterogeneity of the studies. In addition, some of the trials used different basal insulins in the two arms, making direct comparison difficult.

The industry meta-analysis of weight gain suggests less with inhaled insulin, but the studies included in this analysis do not compare like with like. Meta-analysis of the two comparable studies (Skyler[49,50] and Heise[43]) would show no difference in terms of weight gain.

The submission included some unpublished data, including from an ongoing trial (217-1022), but none of this affected the results. In particular, the findings on adverse events were similar to our conclusions: there is no evidence of any safety problems, although without large-scale use and long-term follow-up one cannot be entirely sure that no lung damage will occur; perhaps it may occur only in a few people.

Given the findings from the review of the clinical evidence comparing inhaled with injected insulin – no difference in diabetic control or hypoglycaemic events; little difference in anything except for patient preference; the need for much greater doses of insulin by inhaler than by injection and hence much higher cost – how does the manufacturer argue the case for inhaled insulin?

The industry submission places considerable weight on the patient preference aspects, and argues that the availability of inhaled insulin would improve outcomes by either improving compliance with basal–bolus regimens (in those already on insulin), or making it easier for those currently poorly controlled on OHAs to switch to insulin. It provides six scenarios in which inhaled insulin may make a difference, which will be dealt with below.

The submission examines the barriers to the initiation of insulin treatment in patients with type 2 diabetes mellitus, in order to make the case later that reducing the number of injections would reduce patient reluctance. However, some of the evidence cited is not relevant. For example, the submission notes that 27% of patients randomised to (injected) insulin in the UKPDS initially refused. This is not relevant. The UKPDS was a randomised study with informed consent, and patients being randomised were aware that for them (by definition from their inclusion in a trial), insulin treatment was of unproven benefit.

The submission cites the Diabetes Attitudes, Wishes, and Needs (DAWN) study as evidence that 55% of patients who have never had insulin treatment are anxious about its being required. However, this citation is to an early report published in a journal supplement; the full report was published too recently to be included in the submission, but has now appeared. In it, Peyrot and colleagues[27] review previous studies of patient attitudes contributing to resistance to insulin therapy. They note that these involve beliefs that:

"taking insulin:
- Leads to poor outcomes including hypoglycaemia, weight gain and complications
- Means that the patient's diabetes is worse and that the patient has failed
- Means life will be more restricted and people will treat the patient differently
- Will not make diabetes easier to manage."

It is worth noting that pain on injection does not feature on this list. Most of these attitudes would apply to using any kind of insulin, including inhaled.

The submission also cites Polonsky and colleagues: "A recent survey reported that 43.8% of insulin-naïve respondents are unwilling or only slightly willing to take insulin should it be prescribed in the future". The reference cited is a conference abstract.[87] The full study[88] has been published (again, too late to be included in the industry submission) and gives more details. *Table 9* shows the attitudes for those unwilling and willing to take insulin (by injections; inhaled was not an option).

Most of the attitudes causing reluctance are not about injection pain. Inhaled insulin would resolve only one of them. Most subjects reported several reasons for avoiding insulin. The study was a hypothetical one, with no data on how many patients, willing or unwilling, would have taken insulin if the need arose. It is also worth noting that they had no experience of injecting, and probably overestimated the pain. Modern needles for injecting insulin are very fine and sharp. Patients whose only experience of needles is when having blood tests would not be aware of that.

The submission also considers barriers to adherence such as the need to adjust timing and type of meals; and the self-motivation required to manage a complex regimen. However, such factors would apply to inhaled as well as injected. For example, there would be no difference in the need for self-monitoring of blood glucose.

Great weight is placed on the study by Freemantle and colleagues[67] (already mentioned in Chapter 2). It is worth restating that that was a purely hypothetical study in patients who had never

TABLE 9 *Attitudes for those unwilling and willing to take insulin*

	Unwilling	Willing
Illness severity: taking insulin means my diabetes will become a more serious disease	47%	35%
Restrictiveness: insulin therapy would restrict my life	56%	42%
Lack of fairness: I've done everything I was supposed to; if I had to do insulin therapy, it wouldn't be fair	42%	22%
Anticipated pain	51%	30%
Problematic hypoglycaemia	49%	38%
Low self-efficacy: not confident could handle demands of insulin therapy	58%	40%
Personal failure: insulin therapy would mean I had failed	55%	34%
Permanence: once you start insulin, you can never quit	53%	43%

From Polonsky *et al.* (2005) (figures rounded).[88]

injected insulin, and who may overestimate the painfulness of injections. In our experience (three of the authors of this report have changed patients from oral treatment to insulin), and that of clinical colleagues, reluctance to start insulin is in practice seldom a great problem if the reasons are explained.

The figures from the Freemantle study are used in the Pfizer scenarios in *Table 10*, assuming that with inhaled insulin available 35% will switch to insulin immediately, compared with only 15% if only injected is available.

We considered whether to carry out modelling exercises on all the six groups, using EAGLE to assess impact on changes in HbA_{1c}. Our conclusions were as follows.

Subgroup A: type 1 uncontrolled on twice-daily premix

There are no data on whether there is benefit here. Trials show no difference in HbA_{1c} or hypoglycaemic episodes. It is possible that some patients may shift to basal–bolus more readily if inhaled is available for the mealtime doses, but there is no evidence for this. The 35% and 15% from the Freemantle study do not apply here since these patients are long-term insulin users. The Skyler (2005) study,[51] where patients were stable on two or more injections, is the only one relevant, if one allows twice-daily NPH to be classed as basal. The current best basal option would be a long-acting analogue (glargine or detemir at present); older insulins such as ultralente are being phased out. So, any modelling around HbA_{1c} would be speculative.

Conclusion: No modelling.

Subgroup B: type 1 already on basal–bolus

There is no evidence of benefit in this group. Skyler (2005)[51] used twice-daily NPH as basal (see above) and found no difference in HbA_{1c}. Garg[56] used glargine as basal and compared inhaled and injection boluses; again, there was no difference. The industry submission suggests that inhaled would lead to 100% becoming compliant and well controlled, compared with 100% of those left on injected being uncontrolled. They produce no evidence on compliance to support this. These patients are already experienced insulin users for whom injections are probably not a problem. Other aspects of diabetes control such as blood glucose testing may be more of a burden. Other options for this group include CSII pumps and the education package Dose Adjustment For Normal Eating (DAFNE), already approved by NICE.[6,89]

Conclusion: No modelling around HbA_{1c} because the evidence shows no difference.

However, for both of the above groups, a comparative cost analysis follows.

Subgroup C: type 2 uncontrolled on two or more OHAs

The industry submission envisages that the options for this group are:

- to stay uncontrolled on two OHAs for 4 years then start insulin
- to add inhaled insulin but continue with the two OHAs
- to start basal subcutaneous insulin and continue with two OHAs
- to start twice-daily premixed insulin (a mixture of short-acting and intermediate-acting insulins).

TABLE 10 *Treatment options with and without Exubera by subgroup in patients uncontrolled (>7.4% HbA1c) on their existing treatment, as envisaged in the industry submission*

Population	Treatment alternative(s) with Exubera	Treatment alternative(s) without Exubera
Subgroup A Patients with type 1 diabetes currently uncontrolled on subcutaneous premix insulin regimens	35% start basal–bolus treatment with Exubera immediately and continue for 20 years AND 65% remain uncontrolled on premix for 4 years and then switch to basal–bolus treatment with Exubera for the remaining 16 years	15% start basal–bolus treatment with subcutaneous insulin immediately and continue for 20 years AND 85% remain uncontrolled for 4 years and then switch to basal–bolus treatment with subcutaneous insulin for the remaining 16 years
Subgroup B Patients with type 1 diabetes currently uncontrolled on subcutaneous basal–bolus regimens	100% start a subcutaneous basal and inhaled bolus regimen immediately and continue for 20 years. All the patients are compliant and thus achieve control with this regimen	100% remain uncontrolled on the existing subcutaneous basal–bolus treatment for 20 years
Subgroup C Patients with type 2 diabetes currently uncontrolled on two or more oral antidiabetic therapies	35% start a bolus (+ two orals) treatment with Exubera immediately and continue for 20 years AND 65% remain uncontrolled on two oral drugs for 4 years and then switch to bolus treatment with Exubera (+ two orals) for the remaining 16 years	15% start a subcutaneous basal regimen (+ two orals) immediately and continue for 20 years AND 85% remain uncontrolled on two oral drugs for 4 years and then move to a subcutaneous basal regimen (+ two orals) for the remaining 16 years OR 15% start a subcutaneous premix regimen immediately and continue for 20 years. AND 85% remain uncontrolled on two oral drugs for 4 years and then move to a subcutaneous premix regimen for the remaining 16 years
Subgroup D Patients with type 2 diabetes currently uncontrolled on a subcutaneous basal regimen	35% start a subcutaneous basal and inhaled bolus treatment immediately and continue for 20 years AND 65% remain uncontrolled on a subcutaneous basal regimen for 4 years and then switch to a subcutaneous basal and inhaled bolus treatment for the remaining 16 years	15% start a subcutaneous premix regimen immediately and continue for 20 years AND 85% remain uncontrolled on a subcutaneous basal regimen for 4 years and then start a subcutaneous premix regimen for the remaining 16 years OR 15% start a subcutaneous basal–bolus regimen immediately and continue for 20 years AND 85% remain uncontrolled on a subcutaneous basal regimen for 4 years and then start a subcutaneous basal–bolus regimen for the remaining 16 years
Subgroup E Patients with type 2 diabetes currently uncontrolled on a subcutaneous premix regimen	35% start a subcutaneous basal and inhaled bolus treatment immediately and continue for 20 years AND 65% remain uncontrolled on a subcutaneous premix regimen for 10 years and then switch to a subcutaneous basal and inhaled bolus treatment for the remaining 10 years	15% start a subcutaneous basal–bolus regimen immediately and continue for 20 years AND 85% remain uncontrolled on a subcutaneous premix regimen for 10 years and then start a subcutaneous basal–bolus regimen for the remaining 10 years
Subgroup F Patients with type 2 diabetes currently uncontrolled on a subcutaneous basal–bolus regimen	100% start a subcutaneous basal and inhaled bolus regimen immediately and continue for 20 years. All the patients are compliant and thus achieve control with this regimen	100% remain uncontrolled on the existing subcutaneous basal–bolus treatment for 20 years

The submission envisages that the availability of inhaled insulin would increase the proportion starting insulin at once, from 15% if only injected insulin is available to 35% if inhaled insulin is available. After 4 years, it is assumed that further deterioration in control occurs, and all patients start insulin. Since it is unlikely that there would be much change in symptoms from an average rise of about 0.8% in HbA_{1c}, the only change over this period would be in the advice given by doctors to patients. The industry hypothesis is presumably that as HbA_{1c} rises, so does the pressure from doctors to start insulin.

This seems a very reasonable hypothesis, but given the modern emphasis on tight control, and the targets in the GP contract, one might expect pressure to be applied sooner than 4 years. The 4-year period is based on unpublished data from the Doctors' Independent Network Patient Database (DINLINK), from primary care records. These data do not say how many patients are looked after only by GPs. The DAWN study noted that specialists were much more likely to advocate an early switch to insulin than non-specialists. So, one option for dealing with reluctance would be for poorly controlled patients with type 2 diabetes mellitus not attending hospital clinics to be referred there. Specialist advice might carry more weight.

Another issue is that the relative preference for inhaled insulin will almost certainly vary according to the injected regimen: from once-daily long-acting analogue, to twice-daily mixtures, to basal plus mealtimes with four injections. CSII with an insulin pump involves one injection every 3 days.

Studies on the relative contributions of preprandial and postprandial hyperglycaemia (see Chapter 1) show that the higher the HbA_{1c}, the greater the contribution of fasting and other preprandial hyperglycaemia. In the early stages of elevation of HbA_{1c}, postprandial is relatively more important, but over time preprandial becomes the main contributor (as expected, because people spend more of the 24 hours in a preprandial state).[14] So, in subgroup C, preprandial will be a more important cause of poor control than postprandial. In that situation, it would be more logical to start with a basal insulin such as glargine. It might be argued that by allowing the pancreas to rest for most of the day, it would be more able to cope with mealtime demands. Conversely, it might be argued that three mealtime doses on inhaled insulin would allow the pancreas to cope better with basal secretion of insulin. Both arguments are speculative, and a trial would be needed of basal long-acting analogue plus metformin versus thrice-daily inhaled insulin plus metformin. The Exubera regimen proposed for subgroup C is not supported by evidence.

Therefore, assuming that these patients have had full educational and dietetic support [the results of the trial of the Diabetes Education and Self-Management for Ongoing and Newly Diagnosed (DESMOND) educational package are awaited], and are still failing on OHAs, the usual next step would be to start them on once-daily long-acting insulin while continuing an insulin-sensitising OHA such as metformin. There might be a case for adding a meglitinide to boost postprandial insulin production, and the incretin mimetics such as exenatide or a dipeptidyl peptidase IV (DPP IV, an enzyme that degrades glucagon-like peptide) inhibitor will also enter the picture in future.

The Freemantle figures are more relevant to this group, as well as the DINLINK data showing that in practice it was taking 4 years of poor control to convert people failing on OHAs to insulin. The DINLINK data may not reflect current practice post-UKPDS. Two years may be more appropriate now, assuming that first there are a couple of clinic visits characterised by exhortations and hope about weight loss and exercise. However, in the modelling analyses which follow, both 2 years and 4 years are used.

Some of the things done in the industry submission are odd, such as taking the baseline HbA_{1c} from one study and that achieved after inhaled insulin from another. This exaggerates benefit. The Janka trial[29] is relevant here. Patients poorly controlled on OHAs were randomised either to twice-daily premixed insulin, or to continue on OHAs with the addition of basal glargine. It shows a bigger reduction in HbA_{1c} with basal than in the older Yki-Jarvinen study used in the industry submission: 19% versus 7.4%.

Modelling has been done, because this subgroup can gain from conversion to insulin, and they are more akin to those interviewed for the Freemantle study. The modelling assesses the effect of conversion to good control with insulin 2 years earlier, with a sensitivity analysis with a 4-year assumption.

It is important to note that insulin treatment is not just about injections, but a whole package of care

including dietary adjustments, home blood glucose testing and self-adjustment of insulin doses. It is likely that for most people, insulin injections are less troublesome than blood testing. Just changing to basal–bolus does not mean that control will improve. Unpublished data from the Lothian audit show that the average HbA_{1c} in type 2 diabetes mellitus patients on insulin is about 8.5% (McKnight J: personal communication, presented at the Royal College of Physicians of Edinburgh conference, September 2005; available on www.rcpe.ac.uk). The average for those with type 2 diabetes mellitus on OHAs is 7.5%, which implies that there is no longer, at least in Lothian, a large proportion poorly controlled on OHAs.

Conclusion: Modelling included.

Subgroup D: patients with type 2 currently uncontrolled on basal

This group is composed of patients with type 2 diabetes mellitus currently uncontrolled on a basal regimen. So, the 35% and 15% figures used in the submission will not apply; they are already injecting and will almost certainly regard it as less troublesome than the subjects in the Freemantle study. We have no data on them.

The submission envisages the following options for this group:

- basal injected and mealtime inhaled
- basal injected and mealtime injected
- twice-daily injected premixed
- remaining uncontrolled for 4 years, then starting insulin.

One important option is missing from the industry submission – the addition of metformin to basal insulin. All people with type 2 diabetes mellitus not controlled on diet alone should be on metformin if they tolerate it and if there are no contraindications, as per the NICE guideline. There is one study of adding metformin to premixed.[90] The drop in HbA_{1c} there was 0.9%, but with a single basal injection the drop may be less (because metformin is acting as an insulin sensitiser) – for modelling purposes 0.5% was assumed. Only 90% might tolerate metformin. The other 10% might benefit from a glitazone, but these drugs are not licensed in that situation (although they might still be used). The comment above about the whole package of insulin treatment applies. Simply adding short-acting insulin may not change anything.

One subgroup within this group may need separate consideration: people such as the elderly on once-daily basal insulin given by a district nurse. Adding three mealtime injections would be a logistical problem, but they may not be able to cope with inhaled insulin either, especially if they have visual loss.

Conclusion: Modelling included, assuming that the drop from adding metformin is 0.5%, to 8.0%; that adding inhaled gives HbA_{1c} 7.5%; that those left on basal have HbA_{1c} 8.5% (although in reality all groups would have rising HbA_{1c} over time, in line with UKPDS 16: about 0.2% a year).

Subgroup E: patients with type 2 uncontrolled on twice-daily premix of short-acting and intermediate insulins

The Freemantle figures do not apply to this group, who are already injecting twice a day. There is no evidence of any gain in HbA_{1c}, so no modelling around that is justified.

The Cappelleri[40] and Hollander[44] studies are relevant to this subgroup: "stable on 2–3 injections per day but HbA_{1c} 7–12%"; interestingly, the control arms, who were failing injected regimens but continued on them, improved as much as those who changed to inhaled insulin. So, is there a role for 'education and support', as provided via the attention given to participants in trials? The DAFNE education package would be an option here.

Conclusion: No modelling.

Subgroup F: patients with type 2 uncontrolled on basal–bolus

The industry submission makes an unsupportable assumption here: that 100% are compliant and controlled on bolus inhaled versus 100% uncontrolled on injected bolus. There is no evidence to support this. The study that comes nearest is Hermansen[54] (boluses plus bedtime isophane insulin), which found no difference in HbA_{1c}.

Other options include DAFNE and insulin pumps.

Conclusion: No modelling.

The industry submission has no modelling of inhaled against intensive education such as DAFNE, which has been shown to improve control in type 1 diabetes. A similar package for type 2 diabetes is being trialled at the time of writing.[91]

There have been no trials of CSII pumps against inhaled insulin-containing regimens. While more relevant to people with type 1 diabetes mellitus, CSII pumps could be an option in type 2 diabetes mellitus patients who require a basal–bolus regimen. The annual cost of CSII pumps lies within the dose-related range for inhaled insulin.

One of the key assumptions in the submission is that patients poorly controlled on OHAs will be allowed to continue for 4 years before being finally persuaded to switch to insulin. This is based on data from DINLINK, provided in the submission. The data are disappointing in that they show that many patients are poorly controlled, although many are still on only one OHA; the next step there should be to add a second. Those on two or three OHAs had a higher chance of insulin being started, presumably because their doctors were keener to achieve better control. Of those with HbA_{1c} over 7.5% and on two OHAs, 40% were on insulin by 5 years; of those on three OHAs at baseline, 60% were on insulin by 5 years, and 23% by 1 year.

Data were not given separately for those with poorer levels of control, such as an HbA_{1c} of 8.5% or over. The impression gained is that most clinicians would not hurry to start insulin for those just over 7.5%.

By 4 years, almost half of those with initial HbA_{1c} over 7.5% were on insulin, but this may reflect further rises over time. The UKPDS showed an average decline of 0.2% a year, so the average patient would rise from 7.5% to 8.3% by 4 years. Others might have much slower rises. Figure 2c of the DINLINK paper shows that the number switching to insulin reached 50% by year 5 and then levelled off. A year after starting insulin, 72% of patients had an HbA_{1c} of over 7.5% and 44% had a level of over 8.5%. So, switching to insulin did not achieve target in most patients.

The industry submission assumes that all patients entering the model are free of complications. This is unrealistic in type 2 diabetes for two reasons. First, many people with type 2 diabetes mellitus have complications at diagnosis (UKPDS 6).[92] Secondly, to reach the stage of poor control as in the subgroups cited, patients will have had at least several years of treatment, and complications increase with duration of poor control.

The aims of intensification of treatment are:

- to achieve good control and prevent complications in those who have none, perhaps aiming at an HbA_{1c} of 7.5% or less, as in the NICE guidelines
- in those who do have complications, to improve control and reduce the risk of progression. In patients who already have evidence of harm from diabetes, much tighter control may be aimed for, such as an HbA_{1c} of 6.5%.

Quality of life

This is a separate and generic issue across all subgroups. There is good evidence of patient preference. The industry submission argues that the preferences translate to a utility gain of 0.05, which if the cost is £1000 a year, gives a rough cost per quality-adjusted life-year (QALY) of £20,000. However, DAFNE is much cheaper, improves quality of life (NICE guidance) and has some effect on HbA_{1c} (0.5% at 12 months).

Other submissions

In addition to the industry submission, two other submissions were received, from Diabetes UK (who were also part of the peer-review process) and from the Royal College of Nursing (RCN) (written by two diabetes nurse specialists).

The Diabetes UK position can probably be summarised by two quotations: "Diabetes UK believes that people with diabetes should have equal access to the best diabetes care" and "be able to choose the treatment that gives them best control of their diabetes and the best quality of life".

However, Diabetes UK is aware of the likely cost constraints, and identified two groups as those being the highest priority for inhaled insulin; "a core of patients with type 1 diabetes mellitus with poor control who would benefit from more frequent insulin but who do not want more injections because of convenience or needle phobia" and "those on multiple daily injections who have lipohypertrophy or hardening of injection sites".

The RCN submission made a number of useful points about the practicalities of inhaled insulin, especially for people with visual impairment or problems with manual dexterity. They also noted that for those patients who had once-daily insulin given by the district nurse, a switch to inhaled insulin would cause increased workload. They noted the convenience of 'dial a dose' pen injectors and the less convenient administration with inhalers, requiring five steps for each blister taken; each mealtime might require several blisters. However, the patient preference data from

the trials suggest that in practice, inconvenience was not a problem. The RCN submission supports the view that injections are much less painful than blood testing: "Many people are 'needle anxious' when starting insulin, but this usually resolves after the first few injections, especially with the modern short fine needles available for all pen devices. They often compare the ease and pain of using insulin favourably to those of self blood glucose monitoring."

Chapter 4

Economics: preferences, quality of life, modelling and cost-effectiveness

Introduction

In this chapter we examine further how the industry submission has made a case for cost-effectiveness. We also use the industry model to provide an assessment of cost-effectiveness and the strengths and limitations of the model and assumptions.

It is clear that insulin therapy with Exubera will be more expensive than the regimens it may replace. As a consequence, for Exubera to be cost-effective requires that it results in sufficiently greater patient health-related quality of life (HRQoL) to compensate for its increased cost.

This may arise from a simple patient preference for the Exubera regimen. For instance, within the EuroQol 5 Dimensions (EQ-5D) it is conceivable that the avoidance of an injection may affect some patients' scoring of the usual activities dimension, or perhaps the pain/discomfort dimension. Possible patient preference for Exubera and the HRQoL that may arise from this are examined in the following two sections.

The use of Exubera may also affect patient HRQoL through patient management of blood glucose levels. Two possibilities present themselves:

- Any patient preference for Exubera-based insulin therapy may lead to some patients beginning insulin therapy at an earlier, more appropriate date.
- Once on insulin therapy, any greater convenience arising from Exubera-based insulin therapy may lead to better compliance with therapy and better overall blood glucose control if adopted within a package of insulin treatment.

Either of the above would be anticipated to affect the likelihood of complications arising from diabetes in the short term, the long term or both. These complications would affect the downstream patient HRQoL. However, Chapter 2 has outlined how there is no evidence that different forms of insulin delivery result in different blood glucose control. As a consequence, the cost-effectiveness section will restrict itself to consideration of the effects that may arise from Exubera in (1) involving an HRQoL increment from its own use, and (2) encouraging more patients to begin insulin therapy at an earlier, more appropriate date, so affecting the downstream complications rate. These will be explored through the use of modelling using the EAGLE modelling package. This is the subject of the subsequent third section.

Patient preference for inhaled insulin against injected insulin

Several studies of patient satisfaction with, and preference for, inhaled insulin have been conducted. Although these do not provide a simple means of assessing the quality of life benefit of Exubera, they are summarised below.

Some of these studies use the PSIT questionnaire (© Pfizer Inc.), as reported in Cappelleri.[57] This was developed to assess novel forms of insulin therapy, specifically to assess patient preference for inhaled/injected regimens as against injected only, previous rating scales being deemed insufficiently sensitive or unsuited to this assessment. It comprises 15 questions:

1.	I find it easy to take insulin the way I take it now	C
2.	I have no discomfort taking insulin the way I take it now	C
3.	I find it convenient to take insulin the way I take it now	C
4.	I am self conscious about taking insulin away from home	S
5.	I find it easy to take all the doses of insulin my doctor recommends	C
6.	I find the time it takes for each dosing acceptable	C
7.	I find that my eating schedule can be flexible with few problems	C
8.	I prefer to stay at home rather than take insulin away from home	S

9.	I do not mind measuring my blood glucose before each meal	C
10.	I feel good about my current insulin treatment schedule	C
11.	I find it difficult to take every dose of insulin my doctor recommends	S
12.	I find it difficult to take insulin away from home	S
13.	I would find it difficult to take insulin four times a day	S
14.	I find it easy to travel for a few days and take all my doses of insulin	C
15.	Overall, I am satisfied with my current way of taking insulin	C

The agreement or disagreement of subjects with the above questions is assessed on a five-point Likert scale ranging from strongly agree to strongly disagree. The PSIT questionnaire is broken down into the two subscales of convenience/ease of use (C) and social satisfaction (S). With suitable adjustment for positive and negative questions (e.g. question 3 and question 4), the Likert scores for all 15 questions can be summed to give an overall satisfaction score, ranging from 15 to 75.

While the PSIT is undoubtedly sufficiently sensitive to pick up differences in patient satisfaction that may arise from novel forms of insulin therapy, it should be noted that there does appear to be a degree of repetition within the questionnaire (e.g. questions 5 and 11). The degree of bias, if any, within the questionnaire as to its identifying aspects of treatment therapy that may be affected by the use of inhaled insulin coupled with injections as against the use of injections alone is difficult to assess. Unfortunately, there is no ready read across to more generic measures of HRQoL.

It also appears to be solely intended as a measure of patient preference, and not to imply any necessary impact upon patient health.

Twelve-week follow-up

Gerber and colleagues[49] (sponsored by Pfizer) use the PSIT to assess patient satisfaction with insulin therapy in 69 type 1 American diabetics. A 4-week lead-in phase during which patients continued their usual therapy was followed by randomisation to either Exubera plus one pre-bedtime injection or the continuation of two or three injections. At baseline there were no statistically significant differences between the two arms. Among those responding to all 15 questions of the PSIT, at 12 weeks those on Exubera/injected scored a significantly greater average increase than those remaining on injections alone (35% versus 11%). The improvement in the convenience subset of questions was significantly greater among the Exubera group (41% versus 11%), and while the social comfort subscale was not statistically significantly different the estimate of the mean remained higher for Exubera (28% versus 18%).

Cappelleri and colleagues[40] (sponsored by the Inhaled Insulin Phase II Study Group and Inhale Therapeutic Systems), in a study of 51 type 2 American diabetics, likewise compare Exubera before meals plus a single bedtime injection with the alternative of two or three daily injections. Patient satisfaction is assessed through the PSIT. Forty-seven patients responded to all 15 questions of the PSIT at baseline and week 12. Significantly greater improvements for Exubera/injected compared with injections alone ($p < 0.03$) were observed for the first three questions of the PSIT when evaluated by the log percentage change in score:

- I find it easy taking insulin the way I take it now
- I have no discomfort taking insulin the way I take it now
- I find it convenient to take insulin the way I take it now.

When assessed by the probability of increased satisfaction under Exubera, with 50% being the break-even score favouring neither Exubera nor injected, these three items scored around the 70% level.

Average scores for all questions favoured Exubera/injected over injected alone, although no others were statistically significant. An additional question: "I would like to take insulin the way I took it during the study", was also asked at week 12, with a significantly higher score in the Exubera/injected group, again at roughly the 70% level.

Six-month follow-up

A similar study by Quattrin and colleagues[46] (sponsored by Pfizer and Aventis) of Exubera/injected against injected alone was conducted among 416 type 1 American and Canadian diabetics, over 6 months. While it appears to have been mainly motivated to investigate clinical efficacy in terms of glucose control, it also assessed patient satisfaction. It appears not to have used the PSIT, but is unclear as to what questionnaire was used. It reports a significant improvement in the OSSS occurring

TABLE 11 *Summary of change in PSIT score at 12 weeks and 1 year*

Average change in PSIT score[a]	12 weeks	1 year
Ease of use		
Exubera then Exubera	+50%	+50%
Exubera then injected	+50%	+ 5%
Injected then Exubera	+18%	+35%
Injected then injected	+18%	– 8%
Social comfort		
Exubera then Exubera	+35%	+45%
Exubera then injected	+35%	+10%
Injected then Exubera	+12%	+30%
Injected then injected	+12%	+ 9%
Overall satisfaction		
Exubera then Exubera	+40%	+42%
Exubera then injected	+40%	+10%
Injected then Exubera	+12%	+32%
Injected then injected	+12%	– 4%

[a] Figures read from graph.

among those using Exubera and a significant decrease with those remaining on injections alone. Unfortunately, the values associated with these reported patient satisfaction effects are not reported. The reason for the decline or negative pseudo-placebo effect is unclear, but the study reports that the questions underlying the OSSS displayed a similar pattern. The negative effect in the group whose treatment did not change may have been due to dissatisfaction at being allocated to the 'old' treatment, rather than reflecting any real decline in utility.

In an almost identical study parallel to Quattrin, of 520 type 2 American and Canadian diabetics, Hollander and colleagues[44] (sponsored by Pfizer and Aventis) report a significant mean overall improvement in the OSSS of the Quality of Life and Treatment Satisfaction Questionnaire within the Exubera group. Hollander and colleagues also report a worsening in the OSSS among the injected group.

Unfortunately, again paralleling Quattrin, Hollander and colleagues do not report the values associated with these reported changes.

One-year follow-up

In a study of 70 patients with type 1 and 51 patients with type 2 diabetes, Rosenstock and colleagues[60] (sponsored by Pfizer) evaluated patient satisfaction with Exubera through a pooled analysis of two 12-week parent trials and 1-year extension studies. Within the parent studies following a lead-in period of 4 weeks during which patients continued to receive their usual regimen of two or three injections per day, patients were randomly assigned to receive either pre-meal Exubera coupled with a single bedtime injection, or a conventional regimen of two or three injections per day.

Those completing the 12-week parent studies were given the option to continue either treatment for the 1-year extension studies. It is not clear which if any of the 12-week parent trials are included within the surveys summarised above.[40,49,60]

At the end of the two 12-week parent trials, 60 patients randomised to Exubera and 61 patients randomised to injections were eligible. Of those using Exubera/injected, 13.3% chose to switch to injected alone, while 75.4% of those using injected alone chose to switch to Exubera/injected. When measured by the PSIT questionnaire, those on Exubera/injected typically showed an increase in overall satisfaction within the 12-week parent trials (pooled data), maintaining or improving this over the year-long extension studies. Those on, or switching to, injected alone showed an initial although less marked improvement in overall satisfaction within the 12-week parent trials, but this tended to drop back to around starting values over the period of the 1-year extension trials. Similar patterns were seen in the convenience and social subscales of the PSIT (*Table 11*).

The studies reported above indicate a general patient preference for inhaled insulin over injected insulin, although some questions as to elicitation methods may remain. But none of the above indicates the strength of this patient preference, or the possible effects that adopting inhaled insulin instead of injected insulin might have upon HRQoL. As a consequence, the above studies do not provide the estimate of HRQoL that would be necessary to assess the direct effect that treatment with Exubera has upon cost-effectiveness and the cost per QALY. This is the subject of the next section.

Patient HRQoL from treatment options

While not a study of inhaled insulin and Exubera per se, Gerber and colleagues[93] surveyed the willingness to pay (WTP) for treatment options that involved a reduction in the number of injections, together with differing levels of glucose control among 952 Americans with type 2 diabetes. Unfortunately, they do not indicate what proportion was already taking injected insulin. Three possibilities were presented as treatments: one injection coupled with oral agents, two injections, and three injections.

Similarly, three possibilities were presented for blood glucose control: optimal with 90–120 mg/dl fasting plasma glucose (FPG) and below 7% HbA_{1c}, medium with 70–170 mg/dl FPG and 7–8% HbA_{1c}, and poor with above 170 mg/dl FPG and above 8% HbA_{1c}. Annual out-of-pocket expenses were varied between US$600 (approximately £330) and US$2400 (£1330). Each respondent completed a series of 12 state preference questionnaires.

The average value placed upon going from poor to medium control was an annual US$360 (£200), while the value placed upon going from medium to optimal control was US$2220 (£1230). The average annual value placed upon going from three to two injections was US$336 (£200), while the average annual value placed upon going from two injections to one injection plus oral was US$720 (£400). The natural comparison for these WTP figures would be the cost of Exubera, depending on the injection regimen being displaced. But given the modelling results as described, in particular the cost-effectiveness in terms of reducing downstream complications, this comparison is similar in an arithmetic sense to inferring an HRQoL value for the direct treatment utility impact arising from the reduced number of injections. This can be used as an aid to interpretation of the modelling results. With a threshold of £20,000 per QALY, the effect of going from three to two injections would imply an HRQoL effect of around 0.01. Likewise, the HRQoL can be inferred for going from two injections to one injection plus orals at around 0.02. However, it should be stressed that this method of inference is not routinely applied, and rests upon a series of untested assumptions. Furthermore, even if the method is applicable the values reported for WTP may encompass some patient preferences that would not typically be measured within generic HRQoL scale, and may be outside the elements that the NHS would wish to pay for. To the extent that this is the case, the inferred HRQoL effects would be overestimates.

A similar study of 936 Canadians with type 2 diabetes by Hauber and colleagues[94] found that patients place value upon reducing the number of daily injections from two to one plus oral tablets of a mean of Can$612 (£290) per annum. As with the Gerber study,[93] an HRQoL of between 0.01 and 0.02 can be inferred for this reduction if the WTP per QALY is £20,000. Similar considerations as outlined above for the Gerber paper apply to the paper by Hauber and colleagues. Note also that Hauber and colleagues do not indicate the proportion of patients currently taking insulin.

Within the manufacturer's submission the effect of inhaled insulin on patient HRQoL has been estimated within a sample of 132 type 1 and 212 type 2 adult diabetics, recruited through telephone sampling. Both time trade-off (TTO) and EQ-5D were used; the dimensions and levels of EQ-5D reported in Dolan are shown in *Table 12*.

Before being interviewed for the purpose of utility elicitation, respondents were given background information as to the inhalation device and shown an example of it. They were also briefed on the comparator pen device for injections. The current treatment regimens of respondents were as shown in *Table 13*.

For the utility ratings exercise, respondents were first asked to rate their current health status by both TTO and EQ-5D. They were then asked to rate the pairs of scenarios shown in *Table 14*, type 1 patients being presented with the first two pairs, type 2 patients with the latter three pairs.

Within this exercise, for each scenario and method, a percentage of respondents stated that

TABLE 12 *Dimensions and levels of EQ-5D*

EQ-5D dimension	Level 1	Level 2	Level 3
Mobility	No problems	Problems walking	Bedridden
Self care	No problems	Problems washing/dressing	Unable to wash/dress
Usual activities	No problems	Some problems	Unable
Pain/discomfort	None	Some	Extreme
Anxiety/depression	None	Moderate	Extreme

TABLE 13 *Respondents' current regimens*

	Type 1 (*n* = 112)	Type 2 (*n* = 212)	All (*n* = 344)
Diet and exercise only	0.8%	12.3%	7.9%
Tablets only, no injection	1.5%	70.7%	44.2%
Tablets and twice-daily injections	10.6%	6.6%	8.1%
Twice-daily injection	30.3%	4.7%	14.5%
Other, involving insulin	56.8%	5.7%	25.3%

TABLE 14 *Scenarios used to elicit utility ratings*

Scenario[a]	Injected	Exubera
1 (A)	Basal o.d. and bolus before meals, typically t.d.s.	Basal injection o.d. + inhalation before meals, typically t.d.s.
2 (B)	Remain on basal o.d. and bolus before meals, typically t.d.s. Improve monitoring, adjust dosage and timing as necessary	Basal injection o.d. + inhalation before meals, typically t.d.s. Improve monitoring, adjust dosage and timing as necessary
3 (E)	Basal o.d. and bolus before meals, typically t.d.s.	Basal injection o.d. + inhalation before meals, typically t.d.s.
4 (C)	Oral (review and adjust) + basal o.d.	Oral (review and adjust) + inhalation before meals, typically t.d.s.
5 (D)	Basal o.d. and bolus before meals, typically t.d.s. (*n* = 89), so four injections a day OR Premixed injections b.d.; discontinue oral (*n* = 123) = two injections a day	Basal injection o.d. + inhalation before meals, typically t.d.s.; discontinue oral

[a] Letters in parentheses refer to the treatment options in *Table 10*.

they anticipated that they would prefer injections instead of Exubera. The gains in HRQoL from the use of Exubera reported from this exercise among those stating that they would prefer to use Exubera were as below. These values are combined in the study with the disutility values from those who would prefer injected to yield an average HRQoL gain from Exubera among the entire respondent group, as also outlined in *Table 15*.

Immediately striking within the TTO HRQoL figures are the large increments that are anticipated to arise from the use of Exubera among those preferring it over injections. As Exubera would only be used by those who prefer it, it is these HRQoL figures that should be used in any modelling, provided that they are credible. The values are large when compared with the disutilities from the complications arising from diabetes, such as amputation, dialysis and blindness, and it is an open question whether unintended upward bias may have crept into the study.

Should such upward bias have crept into the TTO estimation of HRQoL effects, it would also be anticipated that this might have occurred with EQ-5D responses as regards the anticipated effect of Exubera relative to injected within the scenarios. Within the EQ-5D results reported, the overall utility levels under each scenario appear to have been calculated using the results of Dolan

TABLE 15 *Average gains in HRQoL from using inhaled insulin*

Scenario	TTO			EQ-5D		
	Those preferring		Average	Those preferring		Average
	Exubera	Injected		Exubera	Injected	
Type I						
1 (A)	0.144 (70%)	–0.060 (30%)	0.074	0.055 (70%)	–0.013 (30%)	0.043
2 (B)	0.131 (78%)	–0.089 (22%)	0.076	0.047 (77%)	–0.001 (23%)	0.029
Type II						
3 (E)	0.126 (85%)	–0.093 (15%)	0.088	0.045 (86%)	–0.026 (14%)	0.037
4 (C)	0.128 (69%)	–0.112 (31%)	0.053	0.055 (70%)	–0.050 (30%)	0.020
5 (D)	0.100 (71%)	–0.089 (29%)	0.043	0.031 (72%)	0.008 (28%)	0.021

Figures in parentheses: percentage stating preference for Exubera or injected.

and Roberts.[95] This is based on calculating the incremental effect on individual utilities of moving from one health state to another. This calculation requires individual-level patient data, which were not available within Appendix H of the industry submission. A more commonly applied approach is that of Dolan,[96] which simply seeks to provide an absolute valuation for individual health states.

Within both the Dolan methodologies, any experience of the worst state in any of the five dimensions of EQ-5D has a major negative impact on the calculation of the utility for the associated health state. Given this non-linearity, respondent error may result in a downward bias. It is also questionable whether once patients have switched to either Exubera or injected insulin, any difference in level 3 scores within some or all of the dimensions of EQ-5D would be anticipated, or whether this may have been an artefact of the utility elicitation study in much the same way as the TTO HRQoL values appear to be rather large.

The percentages of those reporting an anticipated difficulty in level 3 EQ-5D scores within the study, and the net difference between those under Exubera relative to under injected are shown in *Table 16*. These figures are across the whole group. The results for those preferring inhaled and those preferring injected are not disaggregated.

The impact that these reported level 3 changes have on the average EQ-5D estimated HRQoL can be estimated by assuming that there is no net effect on level 3 EQ-5D scores and amalgamating these respondents into the level 2 responses for their respective dimensions. This results in the HRQoL effects shown in *Table 17*. Within this, it is assumed that not all patients will be at full health, and the constant terms have consequently been uniformly applied. As the study was hypothetical and the questions were about inhaled versus injected, it may have failed to pick up general health problems. If the constant term is applied only to the maximum percentage, the net effect of Exubera increases slightly, to 0.028, 0.028, 0.021, 0.006 and 0.009.

Based on the respondents' anticipation of EQ-5D scores within the HRQoL study of the industry submission, these differing methods of calculation result in a range of estimates for the HRQoL benefit from the use of Exubera against injected insulin (*Table 18*). This illustrates the large impact that the relatively small number of respondents anticipating level 3 EQ-5D problems arising and these being mitigated through the use of Exubera has on the overall average EQ-5D estimated HRQoL values.

The base case of the industry submission uses the TTO values reported above. If these HRQoL values applied, the quality of life gain from the use of Exubera would be sufficient in many cases to justify its extra cost. This is doubly so if the TTO HRQoL values among respondents preferring Exubera are applied, as is the logical use of the

TABLE 16 *Reported EQ-5D scores*

(a) Type 1

	Scenario 1			Scenario 2		
Level 3 EQ-5D	**Exubera**	**Injected**	**Net**	**Exubera**	**Injected**	**Net**
Mobility	2.27%	0.76%	1.51%	0.00%	0.00%	0.00%
Self-care	0.76%	0.76%	0.00%	0.76%	0.76%	0.00%
Usual activities	1.52%	0.00%	1.52%	1.52%	1.52%	0.00%
Pain/discomfort	4.55%	3.79%	0.76%	6.06%	5.30%	0.76%
Anxiety/depression	2.27%	2.27%	0.00%	3.03%	3.03%	0.00%

(b) Type 2

	Scenario 3			Scenario 4			Scenario 5		
Level 3 EQ-5D	**Exubera**	**Injected**	**Net**	**Exubera**	**Injected**	**Net**	**Exubera**	**Injected**	**Net**
Mobility	1.42%	0.47%	0.95%	0.47%	0.94%	–0.47%	0.00%	0.00%	0.00%
Self-care	0.94%	0.94%	0.00%	0.47%	0.47%	0.00%	0.00%	0.00%	0.00%
Usual activities	4.72%	2.36%	2.36%	1.42%	1.42%	0.00%	2.19%	1.46%	0.73%
Pain/discomfort	4.72%	4.72%	0.00%	5.19%	4.25%	0.94%	2.19%	2.92%	–0.73%
Anxiety/depression	8.02%	5.66%	2.36%	4.72%	2.83%	1.89%	5.84%	4.38%	1.46%

study TTO data. However, estimates from EQ-5D valuations are somewhat lower. They are considerably lower under the plausible assumption that there is unlikely to be much if any difference in level 3 EQ-5D scores arising through the use of Exubera.

These quality of life values should also be compared to the estimates of the HRQoL impact taken from the literature and used within the industry submission. For type 1 diabetics, blindness in one eye and diabetic foot syndrome result in utility losses of 0.074 and 0.076, respectively. Within the submission, the TTO method estimates that a similar utility loss would apply transferring from Exubera with injections to injections alone. Indeed, among those who anticipate preferring Exubera, the anticipated utility losses transferring from Exubera with injections to injections alone would be somewhat greater. This seems implausible; either the disutility from blindness in one eye or diabetic foot syndrome is a serious underestimate, or the estimate of the direct HRQoL benefit from the use of Exubera is an overestimate. The losses from blindness in one eye and diabetic foot syndrome for type 2 diabetics are estimated as 0.074 and 0.099, respectively. Amputation is estimated as resulting in a loss of 0.28. The TTO method suggests that this could be compensated for in aggregate by moving around four type 1 diabetics onto Exubera, or between three and six type 2 diabetics onto Exubera. Again, it is not intuitively clear that the use of Exubera would be sufficient alone to result in these parallel HRQoL effects.

EQ-5D estimation results in somewhat lower HRQoL gains from Exubera. Estimates based on assuming any difference in problems between Exubera/injections and injections alone being restricted to differences in level 2 of the dimensions of EQ-5D are more in line with what might be anticipated in the light of the WTP studies of Gerber and Hauber, reported above.[93,94]

It should be noted that all the above studies reported within the industry submission are entirely based upon hypothetical scenarios presented to patients. No actual quality of life data are available as regards the use of Exubera with injections against injections alone. Within type 2 diabetes, Coffey and colleagues[97] estimate a quality of life detriment from insulin therapy of –0.034 compared with a detriment from oral antidiabetic agents of –0.023: a net effect of –0.011. Intuition suggests that the HRQoL gain from Exubera insulin therapy over injected insulin is likely to be less than the difference between oral and injected insulin therapy within the groups as Exubera does not usually eliminate the need for injections and is in itself likely to be less convenient than oral therapy. Bagust and Beale[98] also report utility detriment estimates from EQ-5D data for oral therapy and insulin therapy among type 2 diabetics from the Europe-wide CODE-2 survey. Using the visual analogue scale (VAS) score

TABLE 17 *HRQoL effects based on assumption of no net effect on level 3*

Cohort of 100 patients		Dolan tariff	Scenario 1: type 1				Scenario 2: type 1				Scenario 3: type 2				Scenario 4: type 2				Scenario 5: type 2			
			Injected		Exubera		Injected		Exubera		Injected		Exubera		Injected		Exubera		Injected		Exubera	
			No.	Utility	No.	Utility	No.	Utility	No.	Utility	No.	Utility	No.	Utility	No.	Utility	No.	Utility	No.	Utility	No.	Utility
Constant		–0.081		–8.10		–8.10		–8.10		–8.10		–8.10		–8.10		–8.10		–8.10		–8.10		–8.10
Mobility	L2+L3	–0.069	24.24	–1.67	21.21	–1.46	25.00	–1.73	22.73	–1.57	28.31	–1.95	27.83	–1.92	26.41	–1.82	27.83	–1.92	29.93	–2.07	27.01	–1.86
Self-care	L2+L3	–0.104	12.12	–1.26	15.91	–1.65	16.67	–1.73	15.91	–1.65	20.75	–2.16	18.39	–1.91	15.09	–1.57	15.56	–1.62	17.52	–1.82	19.71	–2.05
Usual activities	L2+L3	–0.036	28.04	–1.01	28.03	–1.01	28.79	–1.04	25.00	–0.90	34.91	–1.26	32.08	–1.15	28.31	–1.02	27.84	–1.00	30.66	–1.10	29.20	–1.05
Pain/discomfort	L2+L3	–0.123	44.70	–5.50	28.79	–3.54	43.18	–5.31	32.57	–4.01	46.70	–5.74	40.10	–4.93	36.79	–4.53	33.97	–4.18	42.34	–5.21	35.04	–4.31
Anxiety	L2+L3	–0.071	37.12	–2.64	34.09	–2.42	35.61	–2.53	32.58	–2.31	45.28	–3.21	40.09	–2.85	35.85	–2.55	33.49	–2.38	39.42	–2.80	34.31	–2.44
Total cohort of 100				79.82		81.81		79.57		81.46		77.57		79.13		80.42		80.80		78.90		80.19
Average QoL				0.798		0.818		0.796		0.815		0.776		0.791		0.804		0.808		0.789		0.802
Difference						**0.020**				**0.019**				**0.016**				**0.004**				**0.013**

QoL, quality of life.

TABLE 18 *Comparison of impact on HRQoL using different assumptions*

Scenario	TTO	EQ-5D: Manufacturer	EQ-5D: Only level 2
Type 1 diabetics			
1 (A)	0.074	0.043	0.020
2 (B)	0.076	0.029	0.019
Type 2 diabetics			
3 (E)	0.088	0.037	0.016
4 (C)	0.053	0.020	0.004
5 (D)	0.043	0.021	0.013

the detriment from tablets is estimated as –0.025, while that for insulin therapy is –0.060: a net effect of –0.035. Using EQ-5D social tariff scores, the detriment from insulin therapy is estimated as –0.049. Note that Redekop and colleagues[99] perform a similar analysis to Bagust and Beale for the subsample of Dutch patients within the CODE-2 survey, arriving at a detriment of –0.134. However, as the Redekop cohort is a non-UK subsample of the CODE-2 data, the results of Bagust and Beale would seem preferable. Care must also be taken in interpreting these scores and applying them to the situation of Exubera versus injected, as:

- a range of insulin therapies will be being evaluated
- orals will be more convenient than both Exubera and injected insulin therapy.

The direct effect of Exubera on HRQoL within this section will relate in large part to lifestyle. As a coda to this, it should perhaps be noted that within the literature Coffey and colleagues[97] estimate the HRQoL impact from being obese with a BMI greater than 30 as a decrement of –0.021. The effect on lifestyle of obesity of BMI greater than 30 should perhaps be borne in mind when assessing the value of reducing the number of injections required for insulin therapy. Whether patients would prefer to reduce their injections per day by one, or have their BMI reduced to non-obese levels is a moot question.

Quality of life and complications from diabetes mellitus

A diverse number of HRQoL measures specifically designed for people with diabetes have emerged within the literature. However, being disease specific they are of limited generalisability for cost-effectiveness modelling purposes. In line with the NICE guidance, this section briefly reviews the four main papers within the literature that provide estimates of the HRQoL impact of complications from diabetes using recognised generic measurements of HRQoL:

- Bagust and Beale[98]
- Clarke and colleagues[100]
- Redekop and colleagues[99]
- Coffey and colleagues[97]

Bagust and Beale[98] use EQ-5D data from 4641 European type 2 diabetics from the CODE-2 survey to model the impact that diabetic complications have on both the VAS score of EQ-5D and the TTO social tariff as developed by Dolan and colleagues and reported in Dolan.[96] However, the TTO scores developed by Dolan are over a closed interval with a negative minimum of –0.594; that is, there are states worse than death, which renders direct comparison with other scores difficult. As a consequence, Bagust and Beale[98] transform the TTO scores by the addition of 0.6 and division by 1.6 to ensure that scores lie on the scale [0,1]. Multiplication by 100 gives a direct comparison over the scale [0,100]. The effects of the various complications on these VAS and modified TTO tariff scores are explored through basic ordinary least squares (OLS) modelling. In addition to these, Bagust and Beale[98] explore a compound effects mode, but as the compound modelling components are not readily applicable to the modelling undertaken within the EAGLE package, these are not considered in the following. The values for the VAS and TTO modelling are summarised in *Table 19*, normalising HRQoL values over the scale [0,1].

Paralleling Bagust and Beale,[98] Clarke and colleagues[100] use EQ-5D data from 3192 British people with type 2 diabetes from the UKPDS 62 survey to model the impact that diabetic complications have on both the VAS of EQ-5D and the TTO social tariff as reported by Dolan.[96] Clarke and colleagues[100] did not modify the TTO values, but did apply Tobit modelling in an attempt to reduce bias that might result from a significant proportion of respondents reporting themselves as being in full health. Clarke and colleagues[100] also distinguish between the effect of a complication in the year it is reported and the effect of a complication in subsequent years. As with Bagust and Beale,[98] they also explore some compound effects modelling, but for the same reasons as for Bagust and Beale this is not considered in what follows. The values for the VAS and TTO modelling are summarised in *Table 19*.

Redekop and colleagues[99] provide a similar analysis of EQ-5D social tariff scores for the Dutch subsample of the CODE-2 survey. As the CODE-2 survey is analysed in detail by Bagust and Beale,[98] and the Redekop group is not a British subsample, it has not been considered further.

In slight contrast to Bagust and Beale,[98] Redekop[99] and Clarke,[100] Coffey and colleagues[97] use the Quality of Well Being index – Self Administered (QWB-SA) to calculate health utility scores among a sample of 784 type 1 and 1257 type 2 Americans with diabetes. The QWB-SA

TABLE 19 *Summary of the values for the VAS and TTO modelling*

	Bagust and Beale:[98] type 2		Clarke et *al.*:[100] type 2 (Tobit)				Coffey et *al.*[97]		Sub-mission
	VAS	TTO	VAS		EQ-5D		QWB-SA		
			Year 1	Year 1+	Year 1	Year 1+	Type 1	Type 2	Type 2
Base QoL	0.814	1.027	0.683	0.683	0.814	0.683	0.672	0.689	0.814
Patient characteristics									
Age per 10 years	–0.009	–0.024	0.000	0.000	0.000	0.000			
Female	–0.035	–0.093	–0.063	–0.063	–0.148	–0.148	–0.033	–0.038	
Diabetes duration per 10 years	–0.021	–0.016	0.000	0.000	–0.001	–0.001			
Diabetic treatment									
Tablets	–0.025						0	–0.023	
Insulin	–0.060	–0.049					0	–0.034	
Complications									
Myocardial infarction			–0.106	–0.045	–0.129	–0.078	–0.018	–0.044	–0.055
Coronary heart disease	–0.036	–0.028	–0.112	–0.044	–0.205	–0.132			–0.090
Heart failure			–0.003	–0.095	–0.121	–0.181	–0.058	–0.052	–0.108
Stroke	–0.060	–0.115	–0.096	–0.073	–0.181	–0.269	–0.018	–0.044	–0.164
Stroke with residual							–0.105	–0.072	
Hypertension							–0.032	–0.011	
Nephropathy									
Proteinuria	–0.032	–0.048					–0.017	–0.011	
Dialysis							–0.023	–0.078	–0.078
End–stage renal disease	–0.139	–0.175							–0.011
Transplantation									–0.078
Lower extremity disease									
Neuropathy	–0.036	–0.084					–0.055	–0.065	–0.065
PVD	–0.041	–0.061							–0.065
Neuropathy + PVD	–0.051	–0.085							
Foot ulcers	–0.080	–0.170					–0.076	–0.099	–0.099
Amputation	–0.087	–0.272	–0.116	–0.140	–0.538	–0.412	–0.116	–0.105	–0.280
Retinopathy									
Retinopathy	–0.023								
Blindness	–0.027	–0.057							
Blindness in one eye			–0.093	–0.041	–0.094	–0.112			–0.074
Blindness in two eyes									
Obesity per 1 BMI > 25	–0.003	–0.006							
Obesity BMI > 30							–0.016	–0.021	–0.021
Depression	–0.090	–0.202							

PVD, peripheral vascular disease.

includes three separate scales: mobility, physical activity and social activity. There is an additional list of 58 symptoms or problems, any of which may be highlighted by the respondent as having affected them in the past 3 days. These data are then weighted by the preferences of an independent sample of judges to arrive at an overall utility score. Unfortunately, Coffey and colleagues[97] do not provide any reference or information as to this independent sample of judges. Results are as summarised in *Table 19*.

The final column of *Table 19* shows the base-case values used within the manufacturer's submission. Given the heterogeneity of the results of the main papers, the values assumed by the manufacturer reflect this uncertainty. While some values could not be confirmed from the quoted sources, it does appear that the manufacturer may have been unduly harsh on itself within its modelling for some utility decrements, for example myocardial infarction, end-stage renal disease, blindness in one eye.

For others, unduly optimistic decrements in terms of establishing the cost-effectiveness of Exubera may have been assumed, for example, minor amputations are assumed to have the utility

TABLE 20 *Drug costs and related costs*

(a) Scenario A	
Drug	**Cost**
All initially	
Metformin 2 g/day	£37.54
Gliclazide 160 mg/day	£66.31
Monitoring strips 1	£109.50
	£213.35
switching to	
Option A 1	
Metformin 2 g/day	£37.54
Gliclazide 160 mg/day	£66.31
Glargine 0.4 U/kg/day	£318.86
Monitoring strips 1	£109.50
	£532.22
or	
Option A 2	
Metformin 2 g/day	£37.54
Premix mixtard	£219.44
Monitoring strips 2	£219.00
	£475.99
or	
Option A 3	
Metformin 2 g/day	£37.54
Exubera 0.15 mg/kg/day	£1067.98
Spirometer test	£25.00
Monitoring strips 3	£328.50
	£1459.02

(b) Scenario B	
Drug	**Cost**
All initially	
Metformin 2 g/day	£37.54
Glargine 0.4 U/kg/day	£318.86
Monitoring strips 1	£109.50
	£465.91
switching to	
Option B 1	
Metformin 2 g/day	£37.54
Glargine 0.2 U/kg/day	£159.43
Lispro humalog 0.2 U/kg/day	£120.43
Monitoring strips 4	£438.00
	£755.41
or	
Option B 2	
Metformin 2 g/day	£37.54
Premix mixtard	£219.44
Monitoring strips 2	£219.00
	£475.99
or	
Option B 3	
Metformin 2 g/day	£37.54
Glargine 0.2 U/kg/day	£159.43
Exubera 0.075 mg/kg/day	£533.99
Spirometer test	£25.00
Monitoring strips 4	£438.00
	£1193.96

decrement of –0.280. While this is a reasonable average of the values listed, it is not clear that a minor amputation would necessarily be this serious.

Cost-effectiveness simulations

Cost-effectiveness modelling uses the model of the industry submission: EAGLE. It is felt that there are two scenarios where Exubera might be anticipated to have an effect:

- scenario A (relates to industry subgroup C): simulation of moving from being poorly controlled on metformin and gliclazide to:
  - metformin and Exubera; or
  - metformin, gliclazide and basal subcutaneous glargine; or
  - metformin and premix basal bolus in the form of mixtard 30.
- scenario B (relates to industry subgroup D): simulation of moving from being poorly controlled on metformin and glargine to:
  - metformin, glargine and exubera; or
  - metformin, glargine and subcutaneous lispro; or
  - metformin and premix.

The direct costs assumed for these are shown in *Table 20*.

The basic underlying assumption is that those on insulin therapy require the same dose of insulin, 1 mg of Exubera being approximately equivalent to 2.75 international units (IU). Note that in the manufacturer's submission, the parallel modelling to scenario B in the above assumes that the switch to basal–bolus also involves an intensification of insulin therapy. This appears to assume a continued need for 0.15 mg/kg/day of Exubera in addition to the basal dose. Within scenario B applying, this increase in the bolus dose across options B1, B2 and B3 while retaining the basal dose as above would further increase the absolute difference in cost between the Exubera option B3 and the subcutaneous options B1 and B2.

This would tend to worsen the cost-effectiveness ratios under scenario B which, given the modelling assumptions as outlined below, would see incremental cost-effectiveness ratios (ICERs) for scenario B probably similar to or possibly worse than those of scenario A.

There is no obvious source of data that outlines the age and duration distributions for patients transferring, or being advised to transfer to insulin therapy or an intensification of insulin therapy. As a result, the modelling will for simplicity broadly retain the assumptions and values of the manufacturer submission with regard to patient characteristics and downstream costs of complications, but will

- discount costs and health impacts at a common rate of 3.5% per annum
- simulate for discrete illustrative patient population groups:
  - age 40 with 5-year diabetes duration
  - age 50 with 8-year diabetes duration
  - age 60 with 12-year diabetes duration.

The first modification brings the analysis into line with the current NICE guidance, and parallels the sensitivity analysis J.2.7 of the manufacturer submission. The latter is felt to ease interpretation of results, stripping out one level of complexity within the modelling. Note, however, that these groups are illustrative rather than representative. For a 60-year-old transferring to or intensifying insulin treatment, an assumed duration of diabetes of 12 years may be unrepresentatively long. To address this, a sensitivity analysis of the base case with age 60 but only 5 years' duration will be modelled to assess the impact that duration of diabetes has on the results of the modelling.

Note that the base-case assumptions and parameter values adopted from the manufacturer submission are applied to the different cohorts age 40, 50 and 60. In practice, it appears likely that there may be some worsening of some parameter values within the older cohorts. This has not been accounted for within the modelling. Note also that were a population age distribution modelled rather than discrete cohorts as appears to be the case within the manufacturer submission, there is no obvious means within EAGLE of implementing any of the possible covariances implied.

While the groups modelled are illustrative rather than representative, it should be borne in mind that the cost-effectiveness modelling outlined above is attempting to model those being newly offered insulin therapy. It is not attempting to model the introduction of insulin therapy across the diabetic population; thus, the application of population and duration of diabetes distributions from surveys such as UKPDS would be inappropriate. Rather, the groups modelled are intended to reflect a range of relative extremes in terms of age and duration of diabetes before being pressed to go onto insulin therapy.

Cost-effectiveness of Exubera within these two scenarios could arise from three sources:

- HRQoL gains arising solely from the difference in insulin delivery modality
- greater and earlier acceptance of insulin therapy, leading to earlier control of HbA_{1c}
- greater clinical effectiveness in terms of control of HbA_{1c}.

As noted above, the clinical effectiveness section found no evidence that Exubera as an alternative means of insulin delivery results in greater control of HbA_{1c} than other means of insulin delivery. As a consequence, cost-effectiveness modelling will be restricted to considering the first two bullet points above. In the light of the clinical evidence it is assumed that the mode of insulin delivery in conjunction with the overall clinical advice as to exercise and diet result in identical HbA_{1c} control.

As a consequence, those poorly controlled will be assumed to have an HbA_{1c} of 8.5%, while those switching to an insulin therapy or a more intensive insulin therapy will be assumed to achieve an HbA_{1c} of 7.5%. This is probably unduly optimistic: the Lothian audit data show that type 2 patients on insulin achieve an average HbA_{1c} of 8.6% (McKnight J, Western General Hospital, NHS Lothian: personal communication, February 2005; abstract available on www.rcpe.ac.uk).

Concentrating on the first two points, if the gain in quality of life that arises from treatment alone is above a certain value, Exubera will be cost-effective even if it does not result in any earlier adoption of insulin therapy. As a consequence, there is little point in modelling scenarios where this direct treatment quality of life gain would automatically result in low ICERs. In the light of the section on patient preferences and quality of life, direct utility increments arising solely from treatment with Exubera over other treatments of 0.00, 0.02 and 0.04 will be modelled. However, it should be noted that for scenario B, given the relative difference in treatment costs, a direct utility increment of 0.04 from Exubera treatment

still results in automatic cost-effectiveness, even if there is no impact upon the progression of diabetes and its complications.

It is our opinion that any direct HRQoL impact from Exubera is likely to be restricted to differences in level 2 problems within EQ-5D. It is not felt probable that the use of Exubera alone will result in many, if any, patients experiencing differences in level 3 problems within EQ-5D (e.g. being bedridden or extremely depressed). As a consequence, it seems that the direct HRQoL benefit from the use of Exubera is more likely to lie in the 0.00–0.02 range than in the 0.02–0.04 range.

In line with the hypothetical study of Freemantle,[67] it will be assumed that 35% of those poorly controlled and offered Exubera insulin therapy will accept, compared with 15% of those poorly controlled and offered subcutaneous insulin therapy.

For scenario A and those poorly controlled on orals alone, this seems a reasonable assumption. For scenario B, given that this patient group is already injecting, this assumption is questionable. It would be anticipated that this group would be more likely to intensify their insulin therapy, with the adoption of mealtime insulin. It would also be anticipated that the difference in adoption rates of these boluses would be less marked between Exubera and subcutaneous users, as this group is already injecting. As a consequence, for scenario B a sensitivity analysis of 50% early adoption of the bolus among the Exubera group and 40% early adoption of the bolus among the subcutaneous group will be undertaken.

The base case will assume that those not among the early adopters will switch to insulin therapy or an intensification of their insulin therapy after 2 years, since the DINLINK data upon which Freemantle is based appear slightly dated. However, we add a sensitivity analysis lengthening of this period to 4 years, as assumed by the manufacturer.

Within the EAGLE package it is not possible to differentiate the utility decrement for different complications by their first and subsequent years, as in the study by Clarke and colleagues.[100] It does, however, permit conditions to be defined as chronic or non-chronic. As a consequence, if using the utility estimates of Clarke and colleagues, within the modelling a decision has to be made as to frontloading the utility decrement or applying a modified utility decrement and assuming a chronic condition. Base-case modelling uses the utility decrements shown in *Table 21*.

TABLE 21 *Utility decrements for base-case model*

Diabetes complications	Decrement	Chronic
	–0.186	Yes
Myocardial infarction	–0.055	No
Coronary heart disease	–0.090	Yes
Heart failure	–0.100	Yes
Stroke	–0.100	Yes
Nephropathy		
Dialysis	–0.078	Yes
End-stage renal disease	–0.140	Yes
Transplantation	–0.078	No
Lower extremity disease		
Neuropathy	–0.065	Yes
PVD	–0.050	Yes
Foot ulcers	–0.100	Yes
Amputation (minor)	–0.100	Yes
Amputation (major)	–0.280	Yes
Retinopathy		
Blindness in one eye	–0.094	Yes
Obesity BMI > 30	–0.021	Yes

While it is recognised that myocardial infarction does have long-term quality of life implications, the work of Clarke and colleagues[100] suggests that the utility decrement in subsequent years may tail off sharply. As a consequence, rather than applying a modified utility decrement over the time-horizon of 20 years, a modified utility decrement has been applied.

Note also that, in line with the manufacturer's submission, the prevalence of complications such as myocardial infarction, stroke and neuropathy will be assumed to be zero at the start of modelling. This may be unrealistic, in that the diagnosis of diabetes will in some cases arise from the patient presenting with a complication of diabetes. Similarly, after 5, 8 or 12 years' duration a degree of prevalence of complications would be anticipated. Zero complication rates have been assumed for simplicity. Also, to the extent that this is unrealistic it is likely slightly to favour Exubera. However, given the results of the modelling as outlined in the next section, this is not felt to be a serious bias in terms of the decision-making process.

Within EAGLE, patients are also defined by their activity level and smoking status. For 40- and 50-year-olds it was assumed that the split between low and medium activity levels was 60:40, with none being highly active. For 60-year-olds this split between low and medium activity levels was

revised to 70:30. As Exubera is contraindicated among smokers, smokers have been excluded from the analysis. The split between former smokers and those who had never smoked was assumed to be 35:65.

The time-horizon of the modelling in the base case is taken as 20 years. Given that this relies on some extrapolation, a sensitivity analysis of only 10 years will also be applied.

Another uncertainty within the modelling is the conversion rate of Exubera into available insulin. The base case in line with the manufacturer and some trial evidence suggests a conversion rate of 2.75 IU per 1 mg of Exubera. It is unclear whether this effectiveness will pertain in the non-trial situation. As a consequence, a conversion rate of 2.00 and 3.50 IU will be modelled within the sensitivity analyses. Note that as this will have no impact on the direct HRQoL impact from the adoption of Exubera or on the downstream complications rate, this sensitivity analysis is equivalent to changing the price of Exubera on a pro rata basis.

Results

The full results of all modelling are presented in Appendix 5.

Base cases

Base case: scenario A

For scenario A, the modelling of a move from being poorly controlled on orals to either metformin plus Exubera, orals plus glargine or metformin plus premix results in a relatively minor reduction in downstream complications. Over 20 years, this reduction in downstream complications results in a total average gain of around 0.011–0.012 QALYs per patient aged 40 or 50 years, rising to around a total average gain of 0.018 QALYs per patient aged 60 years. Downstream cost savings ranged between £60 and £120 per patient. These savings were dwarfed by the increase in treatment costs of between £7800 and £11,500 as against subcutaneous basal insulin, and between £8200 and £12,200 as against premix subcutaneous insulin.

If there is no direct HRQoL gain from Exubera over orals plus glargine, this results in ICERs of around £1,077,000, £908,000 and £440,000 per QALY for those aged 40, 50 and 60 years, respectively. The parallel figures for the ICERs of Exubera over premix for those aged 40, 50 and 60 years are, respectively, £1,140,000, £961,000 and £466,000 per QALY. These large cost-effectiveness ratios arise owing to the minor gains in terms of HRQoL and slight savings from mooted reductions in downstream complications being far from sufficient to offset the much higher treatment cost of Exubera. The ICERs are clearly well above those that would normally be considered cost-effective.

For Exubera to be cost-effective in the base case requires that, in addition to the downstream clinical effect in terms of the very slight lessening of complications, Exubera must have some additional direct HRQoL impact from treatment alone. Such HRQoL effects could result in the data shown in *Table 22*.

TABLE 22 *Modelling results: base case for scenario A*

Exubera utility increment	ICER	
	Exubera vs basal	Exubera vs premix
Age 40, 5-year diabetes duration		
0.00	£1,076,854	£1,139,562
0.02	£44,661	£47,262
0.04	£22,803	£24,131
Age 50, 8-year diabetes duration		
0.00	£907,859	£960,823
0.02	£44,095	£46,668
0.04	£22,596	£23,914
Age 60, 12-year diabetes duration		
0.00	£440,353	£465,561
0.02	£42,180	£44,595
0.04	£22,151	£23,419

Base case: scenario B

For scenario B, the modelling of a move from being poorly controlled on subcutaneous glargine to Exubera plus glargine, glargine plus lispro humalog bolus or premix relies on the same underlying clinical assumptions. As a consequence, over 20 years this results in the same downstream savings from reduced complications and QALY gains as for scenario A.

Where the simulations differ is in their assumptions as to treatment costs. For Exubera the net treatment cost as against subcutaneous basal–bolus was between £3750 and £5500 over the 20-year time-horizon, while against premix it was between £5950 and £8829. These differences in treatment cost relative to simulation A above arise from only half as much Exubera being required within simulation B, the remaining required insulin being supplied through standard subcutaneous basal insulin. Injections are still required with the Exubera regimen. What effect this requirement for continued injections has on any likely direct HRQoL effect from Exubera treatment alone is uncertain, although the responses to the hypothetical patient preference and QoL survey sponsored by the manufacturer suggest a greater HRQoL impact under this scenario than under scenario A.

If there is no direct HRQoL gain from Exubera over the subcutaneous basal bolus combination, this results in ICERs of around £561,000, £429,000 and £210,000 per QALY for those aged 40, 50 and 60 years, respectively. The parallel figures for the ICERs of Exubera over premix for those aged 40, 50 and 60 years are, respectively, £903,000, £693,000 and £335,000 per QALY. As in simulation A, minor HRQoL gains and savings from a slight reduction in downstream complications are not sufficient in themselves to offset the higher cost of Exubera, despite this higher cost being roughly between one-quarter and two-thirds that of simulation A, owing to the continued inclusion of subcutaneous basal insulin within the Exubera regimen.

As before, for Exubera to be cost-effective requires some additional direct HRQoL benefit from treatment with Exubera alone, over and above that which arises from any reduction in downstream complications (*Table 23*).

The cross-over into cost-effectiveness for a utility increment for Exubera of 0.04 arises almost entirely from an annual additional 0.04 QALYs arising from treatment being sufficient to justify the additional annual cost of Exubera treatment. The contribution from the HRQoL increment from fewer downstream complications is slight.

Sensitivity analyses

Sixty-year-old only having 5 years' duration of diabetes

The simulations have taken the three patient groups: age 40 with 5 years' duration of diabetes, age 50 with 8 years' duration of diabetes and age 60 with 12 years' duration of diabetes, as illustrative examples of possible patient subgroups. The latter is of some concern in terms of the assumed duration of diabetes, given UKPDS data as to the progression of HbA_{1c} control within diabetes. An assumption of 12 years' duration of diabetes before initiating or switching insulin

TABLE 23 *Modelling results: base case for scenario B*

Exubera utility increment	ICER	
	Exubera vs basal–bolus	Exubera vs premix
Age 40, 5-year diabetes duration		
0.00	£560,954	£903,312
0.02	£21,307	£34,312
0.04	£10,860	£17,488
Age 50, 8-year diabetes duration		
0.00	£428,942	£692,814
0.02	£20,834	£33,650
0.04	£10,676	£17,244
Age 60, 12-year diabetes duration		
0.00	£209,533	£335,126
0.02	£20,070	£32,101
0.04	£10,540	£16,857

TABLE 24 *Modelling results: shortened duration*

(a) Simulation A		
Exubera utility increment	**ICER**	
	Exubera vs basal	**Exubera vs premix**
Age 60, 5-year diabetes duration		
0.00	£545,138	£576,207
0.02	£43,146	£45,605
0.04	£22,462	£23,742
(b) Simulation B		
Exubera utility increment	**ICER**	
	Exubera vs basal–bolus	**Exubera vs premix**
Age 60, 5-year diabetes duration		
0.00	£260,652	£415,446
0.02	£20,630	£32,881
0.04	£10,740	£17,118

therapy may be too long. Shortening this to only 5 years results in the HRQoL impact being reduced from 0.018 to 0.014 QALYs. Downstream savings are correspondingly lessened, resulting in the ICERs shown in *Table 24*.

From the above it is clear that within the modelling the duration assumed for diabetes has some impact on the modelling for the 60-year-old cohort within each scenario. This is particularly the case for the simulations within which no additional utility is assumed from the treatment with Exubera. In these simulations, the relatively slight HRQoL gain from reduced downstream complications is affected, as already noted, falling from 0.018 to 0.014 QALYs. There is a proportionate impact on ICERs.

For simulations assuming a utility increment from treatment with Exubera, the slight HRQoL impact from reduced downstream complications becomes less important. The greater the utility increment assumed for Exubera, the less important are the downstream effects and as a consequence the less is the effect on the ICERs of reducing the assumed duration of diabetes. However, for the underlying modelling of the clinical condition, the duration of diabetes assumed has some impact on the clinical impact and HRQoL. For this reason, the cohort of 60-year-olds with an assumed duration of diabetes of 12 years may be seen as a slightly extreme example given UKPDS data as to progression, and possibly an example within the current modelling more likely to favour the use of Exubera.

Scenario A: additional sensitivity analyses

A brief summary of the sensitivity analyses is presented below. For a fuller presentation of the results the reader is referred to Appendix 5.

A 4-year delay in late adoption of insulin therapy

The base case assumes that 35% of those offered Exubera and 15% of those offered subcutaneous insulin adopt insulin therapy immediately. The remainder are assumed to adopt insulin therapy with a 2-year delay. Lengthening this delay to 4 years results in a slight increase in the HRQoL gains from Exubera to 0.018, 0.023 and 0.032 among 40-, 50- and 60-year-olds, respectively. This also results in increased savings from a reduction in downstream complications of between £110 and £180. These are still relatively minor when weighed against the increased cost of Exubera, and the ICERs are shown in *Table 25*.

Ten-year time-horizon

The modelling has adopted a 20-year time-horizon in order to explore the long-term effects of initial changes to the numbers adopting insulin therapy. As in all modelling, the accuracy of long-term extrapolations can be questioned, and it is prudent to explore the impact of this through a shorter time-horizon of only 10 years. While this does not alter the underlying structure of the model, it can reveal any unwarranted or disproportionate compounding within the model. The adoption of a 10-year time-horizon sees utility gains arising from the reduction in downstream

TABLE 25 *Modelling results: 4-year delay in starting insulin*

Exubera utility increment	ICER	
	Exubera vs basal	Exubera vs premix
Age 40, 5-year diabetes duration: 4-year treatment delay		
0.00	£568,810	£600,537
0.02	£43,320	£45,737
0.04	£22,517	£23,773
Age 50, 8-year diabetes duration: 4-year treatment delay		
0.00	£402,424	£424,805
0.02	£41,785	£44,109
0.04	£22,036	£23,262
Age 60, 12-year diabetes duration: 4-year treatment delay		
0.00	£212,019	£223,385
0.02	£38,447	£40,508
0.04	£21,140	£22,273

complications being reduced to 0.007, 0.009 and 0.012 for the 40-, 50- and 60-year-old cohorts, respectively. Given the 20-year time-horizon of the base-case modelling, when coupled with discounting these reductions do not seem disproportionate and result in not dissimilar ICERs, although there is a slightly curious non-linearity with age, which appears primarily to be due to the shortening of the time-horizon from 20 years to 10 years affecting the age 60 cohort relatively little. Overall, there is no evidence that the adoption of a 20-year time-horizon unreasonably compounds effects.

Lower Exubera cost

The base-case assumption is that 1 mg of Exubera is approximately equivalent to 2.75 IU. There is a degree of uncertainty over this in clinical practice, and as a consequence a conversion rate of 1mg being equivalent to 3.5 IU can be used for a sensitivity. This is entirely equivalent to the price of Exubera being reduced by about one-quarter. This results in a reduced net cost from Exubera treatment of between £6000 and £8000 relative to subcutaneous basal insulin, and between £6400 and £8700 relative to subcutaneous premix insulin. While this does not render Exubera cost-effective in terms of the HRQoL gain from the reduction in downstream complications alone, if it is associated with an annual treatment utility increment of 0.04 over the 20 years the ICERs begin to look more favourable (*Table 26*).

Higher Exubera cost

As in the sensitivity analysis above, the conversion rate and cost of Exubera are subject to some uncertainty. Reducing the conversion rate of Exubera to 1 mg being equivalent to 2.00 IU, or increasing its cost by about one-quarter, results in the ICERs shown in *Table 27*.

Scenario B: additional sensitivity analyses

A 4-year delay in late adoption of revised insulin therapy

Similar to simulation C, the assumed delay in adoption of a more intensive insulin regimen among dissenters for scenario D can be lengthened from 2 years to 4 years. Just as for simulation A, this results in increased HRQoL gains in total over the 20 years from reduced downstream complications among 40-, 50- and 60-year-olds of 0.018, 0.023 and 0.032 QALYs, respectively, as against 0.010, 0.011 and 0.018 QALYs under the base case. This results in the ICERs shown in *Table 28*.

Greater absolute adoption and lower relative adoption of insulin therapy

The hypothetical results of Freemantle[67] refer to insulin-naive patients envisaging their use and adoption of insulin therapy. It is from this that the initial rates of adoption of 35% for Exubera and 15% for subcutaneous insulin are drawn. However, within scenario B patients are already using a subcutaneous basal insulin regimen. It may be anticipated that these patients would be less reluctant to switch to a basal–bolus regimen, and given that they are already injecting and used to injections any relative advantage of Exubera over subcutaneous might be less. As a consequence, a sensitivity analysis of 50% of those offered Exubera within a basal–bolus regimen and 40% of

TABLE 26 *Modelling results: lower cost of Exubera*

Exubera utility increment	ICER	
	Exubera vs basal	Exubera vs premix
Age 40, 5-year diabetes duration		
0.00	£747,515	£810,223
0.02	£31,002	£33,603
0.04	£15,829	£17,157
Age 50, 8-year diabetes duration		
0.00	£698,263	£751,226
0.02	£33,915	£36,487
0.04	£17,379	£18,697
Age 60, 12-year diabetes duration		
0.00	£339,347	£364,556
0.02	£32,505	£34,920
0.04	£17,070	£18,338

TABLE 27 *Modelling results: higher cost of Exubera*

Exubera utility increment	ICER	
	Exubera vs basal	Exubera vs premix
Age 40, 5-year diabetes duration		
0.00	£1,720,752	£1,789,469
0.02	£65,362	£67,973
0.04	£33,314	£34,644
Age 50, 8-year diabetes duration		
0.00	£1,326,073	£1,379,037
0.02	£64,408	£66,981
0.04	£33,005	£34,324
Age 60, 12-year diabetes duration		
0.00	£641,891	£667,100
0.02	£61,485	£63,900
0.04	£32,289	£33,557

TABLE 28 *Modelling results: 4-year delay in starting insulin in scenario B*

Exubera utility increment	ICER	
	Exubera vs basal–bolus	Exubera vs premix
Age 40, 5-year diabetes duration		
0.00	£271,696	£429,766
0.02	£20,692	£32,731
0.04	£10,755	£17,013
Age 50, 8-year diabetes duration		
0.00	£190,964	£302,473
0.02	£19,828	£31,406
0.04	£10,457	£16,563
Age 60, 12-year diabetes duration		
0.00	£101,356	£157,983
0.02	£18,379	£28,648
0.04	£10,106	£15,752

TABLE 29 *Modelling results: varying rates for switching to insulin*

Exubera utility increment	ICER	
	Exubera vs basal–bolus	Exubera vs premix
Age 40, 5-year diabetes duration		
0.00	£1,585,801	£2,565,615
0.02	£21,928	£35,476
0.04	£11,040	£17,861
Age 50, 8-year diabetes duration		
0.00	£1,095,718	£1,770,815
0.02	£21,817	£35,259
0.04	£11,018	£17,807
Age 60, 12-year diabetes duration		
0.00	£266,035	£430,064
0.02	£20,402	£32,981
0.04	£10,607	£17,148

TABLE 30 *Modelling results: lower cost of Exubera in scenario B*

Exubera utility increment	ICER	
	Exubera vs basal–bolus	Exubera vs premix
Age 40, 5-year diabetes duration		
0.00	£425,460	£767,818
0.02	£16,161	£29,165
0.04	£8,237	£14,865
Age 50, 8-year diabetes duration		
0.00	£324,144	£588,015
0.02	£15,743	£28,560
0.04	£8,067	£14,635
Age 60, 12-year diabetes duration		
0.00	£209,533	£335,126
0.02	£20,070	£32,101
0.04	£10,540	£16,857

those within a purely subcutaneous basal–bolus regimen accepting, with the remainder adopting it after 2 years, can be performed.

This reduces the incremental average total downstream benefits that would be anticipated over the 20 years from Exubera to 0.003, 0.004 and 0.014 QALYs for 40-, 50- and 60-year-olds, respectively, significantly worsening the ICERs (*Table 29*). Given these extremely small downstream gains, any direct quality of life increment from treatment comes to dominate the analysis.

Lower Exubera cost

As for simulation A, the base-case assumption is that 1 mg of Exubera is approximately equivalent to 2.75 IU. There is a degree of uncertainty over this in clinical practice, and as a consequence a conversion rate of 1 mg being equivalent to 3.5 IU can be used for sensitivity. As in the sensitivity analysis for simulation A this is entirely equivalent to the price of Exubera being reduced by about one-quarter. This results in a reduced net cost from Exubera treatment of between £3700 and £4200 relative to subcutaneous basal–bolus insulin, and between £5900 and £7500 relative to subcutaneous premix insulin. While this does not render Exubera cost-effective in terms of the HRQoL gain from the reduction in downstream complications alone, utility increments from treatment can help to render the ICERs more favourable (*Table 30*).

TABLE 31 *Modelling results: higher cost of Exubera in scenario B*

Exubera utility increment	ICER	
	Exubera vs basal–bolus	Exubera vs premix
Age 40, 5-year diabetes duration		
0.00	£625,536	£967,894
0.02	£23,761	£36,765
0.04	£12,110	£18,738
Age 50, 8-year diabetes duration		
0.00	£478,893	£742,764
0.02	£23,260	£36,076
0.04	£11,919	£18,487
Age 60, 12-year diabetes duration		
0.00	£233,605	£359,197
0.02	£22,376	£34,406
0.04	£11,751	£18,068

TABLE 32 *Change in insulin dose with age*

	Age range (years)		
	15–18	18.1–22	22.1–25
Insulin dose/kg	1.13	0.93	0.88
SD	0.46	0.29	0.32

Higher Exubera cost

As in the sensitivity analysis above, the conversion rate and cost of Exubera are subject to some uncertainty. Reducing the conversion rate of Exubera to 1 mg being equivalent to 2.00 IU, or increasing its cost by about one-quarter, results in the ICERs shown in *Table 31*.

Insulin doses and costs

Insulin dosage varies with factors such as type of diabetes, age and level of insulin resistance. Someone with type 2 diabetes, starting insulin as a supplement to oral agents, may take only 0.2 IU/kg/day. Another person with type 2 diabetes failing on oral agents, with a long duration of diabetes (and hence β-cell depletion; UKPDS 17),[101] and who is obese and insulin resistant, may need well over 1 IU/kg/day.

Type 1 diabetes

In type 1 diabetes, dosage varies with age. Acharya and colleagues,[102] reporting on three groups of younger patients, noted that insulin dose fell with age (*Table 32*).

When the daily dose is split between basal and bolus, the relative proportions vary. In the Exubera trials, the percentage given as basal at baseline was around 40% in type 1.[46,50,51] In the two type 2 trials, the percentages were 27%[40] to 41%.[44]

However, the basal agent used was mainly NPH. None of these trials used long-acting analogues, with which less may be given as basal. With NPH, some may in effect be providing some mealtime cover.

Experience with DAFNE in type 1 patients in Aberdeen (Robertson A, Aberdeen Royal Infirmary, NHS Grampian: personal communication, August 2006) has been that the dose of basal glargine is often reduced after the DAFNE intervention. The DAFNE approach assumes dosage of about 0.5–0.8 IU/kg/day, with a 50:50 split between bolus and basal, or about 1 unit of basal drug per hour. However, experience shows that many people need less basal drug than 24 IU/day.

The total cost of insulin therapy includes the insulins, the means of administration (more often pens than syringes; needles) and monitoring of blood glucose levels.

Details of costs are given in Appendix 5, but a comparison of annual costs for injected basal–bolus with injected basal and inhaled bolus, for an 84-kg patient on 0.07 IU/kg/day, and assuming a 50:50 split between basal and bolus, is shown in *Table 33*.

The approximate figures for other daily insulin requirements, again assuming a 50:50 basal–bolus split, are shown in *Table 34*. The last two columns

TABLE 33 *Comparative costs*

Injected basal and bolus		Inhaled bolus and injected basal
	Glargine £279 Pen £7.33 Needles £31.28	
	Monitoring strips £438	
Lispro £211 Pen £4.90 Needles £31.28		Exubera £1017 Spirometer testing £25
Total cost (rounded) £1003		£1798
	Marginal cost of inhaled £795	

TABLE 34 *Comparative costs for type 1 diabetes*

Daily dose (IU/kg/day)	SC cost p.a.	INH cost p.a.	Difference	Utility required at £20,000/QALY	Utility required at £30,000/QALY
0.4	£793	£1424	£631	0.03	0.02
0.5	£863	£1464	£601	0.03	0.02
0.6	£933	£1758	£825	0.04	0.03
0.7	£1003	£1798	£795	0.04	0.027
0.8	£1073	£2092	£1019	0.05	0.034
0.9	£1143	£2132	£989	0.05	0.033
1.0	£1212	£2426	£1213	0.06	0.059
1.1	£1282	£2466	£1184	0.06	0.039

TABLE 35 *Comparative costs for type 2 diabetes*

Daily dose (IU/kg/day)	SC cost	INH cost	Difference	Utility required at £20,000/QALY	Utility required at £30,000/QALY
0.4	£533	£1625	£1092	0.055	0.036
0.5	£613	£1879	£1266	0.063	0.042
0.6	£693	£2133	£1441	0.072	0.048
0.7	£772	£2388	£1615	0.081	0.054
0.8	£852	£2642	£1790	0.089	0.060
0.9	£932	£2896	£1964	0.098	0.065
1.0	£1012	£3151	£2139	0.107	0.07
1.1	£1091	£3405	£2314	0.116	0.077
1.2	£1171	£3659	£2488	0.124	0.083

show the utility gain required for the difference in cost of the regimens to become cost-effective in terms of quality of life and hence costs per QALY, at two cost per QALY thresholds.

Type 2 diabetes

The relative costs for type 2 diabetes will depend on the comparator regimen. Examples are given in Appendix 6. *Table 35* shows costs based on a comparator regimen on basal glargine and gliclazide, for an 84-kg patient, at a range of different dosages per kilogram per day.

Table 35 assumes that patients on inhaled insulin would have a basal long-acting insulin. However, if one assumed that many patients with type 2 still had a fair bit of residual β-cell function, and might only need small amounts of exogenous insulin, then one option might be inhaled insulin at mealtimes without any basal drug. If one assumed that a low dose, say 0.4 IU/kg/day, would suffice as a supplement to basal oral agents (partly because inhaled insulin has some effect on fasting glucose; see DeVries[103] for a review), then costs might be as shown in *Table 36*, for injected and inhaled bolus insulin.

TABLE 36 *Comparative costs: bolus-only regimen*

	Injected		Inhaled			
	Lispro insulin	£240	Exubera	£1,526		
	Pen	£5	Spirometer test	£25		
	Needles	£31	Monitoring	£110		
	Monitoring	£110				
Totals		**£386**		**£1,661**	**Difference**	**£1,275**
Utility required to reach £20,000 per QALY = 0.063; £30,000 per QALY = 0.043.						

Utilities are always averages. Some people may have little or no trouble with injections, whereas others may be more averse. In the latter, utility gain from inhaled rather than injecting insulin may be greater.

Conclusions

The clinical evidence to date shows Exubera insulin therapy to be equally effective as subcutaneous insulin therapy in terms of HbA_{1c} control. As a consequence, modelling has assumed that there is no downstream clinical benefit from the use of Exubera instead of short-acting subcutaneous insulin.

However, the modelling also shows that there could be some theoretical downstream benefits if more patients started insulin therapy at an early and appropriate stage, when offered Exubera compared with when offered subcutaneous insulin. However, provided that all patients adopt insulin therapy within a reasonable period of 2–4 years, it again appears unlikely that the slight benefits that arise with Exubera result in its being cost-effective. The delay would have to be substantially greater than the 2–4 years modelled for any reduction in future complications to cause Exubera to be cost-effective. Cost-effectiveness ratios with regard to the downstream clinical benefits are well in excess of those that would typically be deemed cost-effective in both the base case and all the sensitivity analyses.

Because modelling suggests that any benefits in terms of reduction in complications from the use of Exubera are slight, cost-effectiveness would only be achieved if it conferred a sufficient direct utility increment from the treatment itself, compared with injecting insulin.

The most crucial figure in the above analyses is the utility increment resulting from the switch from injected mealtime to inhaled insulin. While we accept that there is some utility gain, we think that the figure of 0.04 used in the industry submission is too high, and that a lower figure, under 0.02, is more likely. In most analyses, this makes the difference between an ICER that would be considered cost-effective and one that would not.

These figures are averages. There may be some patients who have particular problems with injections, perhaps because they are very thin, whose utility gain may be high enough to give an acceptable ICER. Although in those having particular problems with injections another option is the insulin pump (CSII), which would have similar or lower cost, and involves one injection every few days, those using inhaled insulin would still require basal injections every day.

Chapter 5
Discussion

Main findings

The inhaled insulin, Exubera, is as good as injected short-acting soluble insulin for controlling blood glucose levels. It has not been tested against short-acting analogues, or against CSII using an insulin pump.

In the trials, patient satisfaction was consistently reported to be better with inhaled than with injected insulin. However, the utility gain does not seem to be sufficient to render it cost-effective, because the cost of inhaled insulin is much higher.

There may be patients with particular difficulty with injection sites who may have greater utility gains, in whom it may be cost-effective. One group is those with lipohypertrophy, but it should be remembered that there are adipocytes in the lung. So far, no serious pulmonary side-effects have been seen.

Strengths and limitations of the evidence

There are some weaknesses in the evidence, mentioned in previous chapters, such as having different basal insulins in the inhaled and injected arms of trials, and the lack of comparison with short-acting analogue insulins, and with CSII using insulin pumps.

Overall, we think that clinical effectiveness is confirmed and uncontroversial. However, the evidence is of equivalence rather than superiority.

Issues in cost-effectiveness

The equivalence rather than superiority results have implications for cost-effectiveness analysis. Given the lack of any improvement in glycaemic control, the industry submission has had to emphasise the patient preference aspects, and to argue that these could translate into greater acceptability, leading to earlier conversion to insulin treatment in people with poor control on oral drugs, which is turn is asserted to lead to better control a couple of years earlier, in 20% of patients.

The industry submission relies heavily on the theoretical study by Freemantle and colleagues,[67] which reports that 35% of patients would switch immediately to insulin if inhaled were available, versus only 15% if only injected were available. However, it incorrectly extrapolates the findings to all six scenarios, whereas they really only apply to subgroup C, which is the only insulin-naive group.

The Freemantle study was sponsored by the manufacturers. The published study does not give any data on the relative attractiveness of different injected insulin regimens. For example, once-daily glargine would be expected to be more popular than four-injection basal–bolus. CSII may also be more attractive. In addition, the burden of insulin therapy is not just the injections, but also the self-testing of blood glucose, allowance for diet and exercise, and self-adjustment of doses.

There is no doubt that both clinicians and patients are reluctant to start insulin, but as Peyrot and colleagues[27] describe, there are many reasons for that, of which taking injections is only one. Hence, simply having inhaled insulin available will not overcome all the reluctances to switch. (However, note that Freemantle and colleagues assume that only 35% switch immediately with inhaled insulin.)

Cost rather than effectiveness determines the cost-effectiveness. If inhaled insulin had the same cost as short-acting injected insulin, patients could be given their choice, and the studies suggest that most would choose inhaled. However, the current pricing puts a high premium on inhaled. The industry submission envisages the cost of inhaled insulin to range from £23 to £46 million per annum for England and Wales. Whatever the cost, it would have to be taken away from other forms of care.

Research needs

Current research

The Exubera Real World Classic[104] is a 1-year, open-label outpatient, parallel-group trial

assessing the impact of the availability of inhaled insulin on glycaemic control in patients with type 2 diabetes who are poorly controlled on a minimum of two oral antidiabetic agents.

The aim is to demonstrate that the mean reduction in HbA_{1c} after 52 weeks is greater in patients to whom inhaled insulin is made available than in patients to whom it is not, although they could have injected insulins. It is expected that 1100 patients will be randomised globally.

Other inhaled insulin products continue to progress towards licensing:

- Aradigm and Novo Nordisk initiated a pivotal Phase III study with inhaled insulin formulation in September 2002. This 24-month, 300-patient trial is evaluating inhaled insulin in comparison with insulin aspart. Both medications will be given three times daily before meals in addition to basal insulin administered once or twice daily.[105]
- Eli Lilly and Alkermes have announced a Phase III trial in 400 non-smoking patients with type 1 diabetes. The aim is to show safety and efficacy. It will be a multicentre trial with 70 sites in North America, Europe and India. A second Lilly/Alkermes RCT will recruit 600 type 1 and 2 patients with mild to moderate asthma and chronic obstructive airways disease, again comparing inhaled insulin with subcutaneous injected insulin.[106]

Other developments

Longer-acting forms of inhaled human insulin are in the initial stages of development using a polyethylene glycol (PEG) formulation to provide sustained action. Pegylation is designed to prolong the duration of action and hence create a long-acting inhaled insulin. A trial of inhaled, long-acting Pegylated insulin (Nektar) is being funded by Pfizer. Leach and colleagues[107] report work on a long-acting pegylated insulin, so far only in dogs.

Other delivery routes are being tested. The development of an effective oral insulin has proved difficult in the past owing to the digestion of the protein in the stomach by proteolytic enzymes and its relatively poor absorption from the gastrointestinal tract. However, research has been directed towards overcoming these problems (see references 108–110 for reviews). Cernea and colleagues[111] report preliminary experience with an oral insulin spray. Useful reviews by Cefalu[4] and Gomez-Perez and Rull[112] cover other forms of non-injected delivery, including oral, buccal/sublingual, intranasal, transdermal, rectal and vaginal.

Research needs

Research needs for inhaled insulin can be divided into safety, efficacy and economics.

Safety

Inhaled insulin appears safe so far. However, for complete reassurance on safety, long-term follow-up (i.e. years, not months) is needed of large numbers of patients who use inhaled insulins. Without that, rare but serious lung problems cannot be excluded. Large observational cohort studies would suffice. Because of fears of pulmonary side-effects, most studies to date have excluded all people with diseases such as asthma or chronic bronchitis, and most have excluded smokers. There is no evidence of an increased risk of harm in these patients, although smokers may absorb inhaled insulin more rapidly.

Efficacy

One of the key issues is the choice of comparator. This is straightforward in type 1, where future trials of inhaled insulin should compare it with short-acting analogues, with a long-acting analogue as the basal agent with both inhaled and injected.

However, the situation is more complicated in type 2 diabetes, which is probably seen as the bigger market. The assumption underlying some of the modelling of the place of inhaled insulin seems to be that people failing to achieve adequate control on a combination of oral agents should be considered for insulin therapy. However, perhaps this needs to be challenged and other avenues explored before doing further trials of inhaled insulin in type 2.

What is the optimum treatment for people with type 2 diabetes inadequately controlled on oral agents?

In many of these patients, poor control is associated with overweight or obesity, and trials of intensified dietary advice and exercise are also required.

Time does not permit a full review of all options for people with type 2 diabetes who are 'failing' on oral agents, and so the section that follows aims to illustrate the issues and research needs rather than to provide a systematic review.

It seems clear from the literature that there are differences of opinion on the management

of people with type 2 diabetes who are not adequately controlled on oral agents. A working group drawn from the ADA and the EASD produced a consensus statement in 2006.[113] Some extracts from this statement give an impression of the problems:

> "the availability of the newer agents has provided an increased number of choices for practitioners and patients and heightened uncertainty regarding the most appropriate means of treating this widespread disease. Although numerous reviews on the management of type 2 diabetes have been published in recent years, practitioners are often left without a clear pathway of therapy to follow."

> "The most appropriate target levels for blood glucose, on a day-to-day basis, and HbA_{1c}, as an index of chronic glycaemia, have not been systematically studied."

They noted the different target levels proposed by the various bodies, and reached a consensus that,

> "an HbA_{1c} of over 7% should serve as a call to action to initiate or change therapy"

They recommended that insulin should be initiated with either bedtime intermediate-acting insulin, or once daily long-acting insulin; metformin should be continued.

Goudswaard and colleagues, in a Cochrane review,[114] concluded that combinations of insulin and OHAs should be the starting point for people with type 2 diabetes who required insulin. Their review preceded the studies on long-acting analogues such as glargine and detemir. The oral agents most commonly used in the trials they found were sulphonylureas; only 7% used metformin alone.

Douek and colleagues,[115] from the Metformin Trial Group, carried out an RCT of adding metformin or placebo in people with type 2 diabetes who had been switched to insulin because of poor control. Continuation of metformin resulted in less weight gain, lowered insulin requirement and improved glycaemic control.

Aviles-Santa and colleagues[90] also showed that adding metformin to an insulin regimen in type 2 diabetes reduced HbA_{1c}, by 0.9% compared with placebo. Insulin requirements were 29% lower, and the weight gain seen in the placebo group, of 3.2 kg, was much more than in the metformin group (0.5 kg).

Strowig and Raskin carried out a review of combination therapy with insulin and either metformin or a glitazone, or both.[116] Details of methods are not given and it was probably not systematic. They also concluded that it was worthwhile continuing an insulin sensitiser in type 2 patients switched to insulin. Because metformin and glitazones have different balances of sites of preferential action (acting on glucose production and glucose disposal), they also made the case that triple therapy should also be considered. Bailey also supported combination therapy with metformin and a glitazone for reducing insulin resistance in type 2 diabetes.[117]

Gerstein and colleagues randomised poorly controlled (HbA_{1c} 7.5–11%) patients to continue oral agents or to switch to glargine, in the Canadian INSIGHT study.[118] Those treated with glargine achieved lower HbA_{1c} and non-high-density lipoprotein cholesterol, and greater satisfaction, but more weight gain. However, only 17.5% of patients on glargine reached the target of two or more consecutive HbA_{1c} levels of 6.5% or under. One weakness of the study was that at baseline, about 17% of the patients had not been treated with any oral agent; another 40% were on oral monotherapy.

Hayward and colleagues noted that results from trials of insulin therapy in type 2 showed it to be efficacious, but thought that these results might not be replicated in routine care. In a very large study (8668 patients with type 2 diabetes) they found that "insulin therapy was rarely effective in achieving tight glycemic control".[119] Two years after starting insulin therapy, 60% still had HbA_{1c} levels of 8% of greater, 25% had levels between 8.0 and 8.9%, 20% between 9.0 and 9.9%, and 15% had levels over 10%.

These results are similar to those from the population-based audit from Lothian (*Table 37*).

TABLE 37 *HbA_{1c} levels among people with type 2 diabetes mellitus*

Treatment	Number	Mean HbA_{1c}
Type 2 on insulin	5030	8.5%
Type 2 on oral agents	8007	7.6%
Type 2 on diet alone	2517	6.9%

Source: McKnight J, Western General Hospital, NHS Lothian: personal communication, February 2005; data available from www.rcpe.ac.uk.

The fact that starting insulin in routine care usually fails to give good control in people with type 2 diabetes failing on oral agents is presumably one reason why the physicians in the DAWN study[27] showed considerable resistance to starting insulin therapy in type 2 diabetes; only about half of the physicians thought that insulin would be useful.

Yki-Jarvinen and colleagues came to similar conclusions in people with type 2 diabetes who were obese (defined in this study as BMI over 28.1): insulin did not improve control.[120]

Aas and colleagues tried another approach, randomising patients with poorly controlled type 2 diabetes to insulin or to a lifestyle intervention (exercise and diet counselling).[121] Lifestyle intervention was as effective in glycaemic control, but also resulted in weight loss. In a follow-up study in 2006, we also noted that lowering HbA_{1c} by lifestyle measures had more beneficial effects on adipokine levels than when insulin therapy achieved the same lowering, which may result in a lower cardiovascular risk.[122] However, numbers in this study were small (38 in total), and it needs to be replicated with larger numbers.

Hence research needs include:

- a trial of intensive lifestyle intervention to see whether the results obtained by Aas and colleagues can be replicated with larger numbers
- in those starting insulin, a comparison of a long-acting analogue with inhaled insulin
- a comparison of inhaled insulin with short-acting analogues given by pens.

Economics

For economic analysis, collection of cost and quality of life data needs to be included in future RCTs. The main gain from inhaled insulins is in satisfaction and quality of life. In future trials, the optimum injection methods should be used, including CSII.

However, one issue is whether at the current price, inhaled insulin can ever be cost-effective, because of the need for much larger doses. Are further trials likely to produce any evidence that would improve the cost-effectiveness? If not, they may not be worth doing.

Implications for practice

Inhaled insulin may provide a practical, non-invasive alternative to injections, while achieving comparable glycaemic control and increased patient satisfaction and quality of life. However, it will still not completely eliminate the need for injections, since although inhaled insulin can be substituted for soluble preprandial insulins, the longer acting preparations still require subcutaneous injections. The cost-effectiveness depends on marginal benefits and price, taking into account the dosage required compared with subcutaneous insulin. These marginal benefits hinge around the value attached to patient preference and the impact of preference on quality of life, as well as adherence to the treatment regimen.

Inhaled insulin is much more expensive than injected. This is because it is necessary to use about ten times as much as one would inject, to achieve the same effect. Inevitably, not all the insulin that comes out of the inhaler will reach the part of the lung (the alveoli) where it is absorbed. The inhaler adds to the cost, although as currently formulated this cost is factored into the cost of the insulin inhaled. This reflects both the unit cost of the device and the large capital investment that will have gone into developing it to give a reliable adjustable dose.

The clinical effectiveness evidence shows a clear preference among patients for inhaled insulin over injected, but no other benefit. The manufacturer argues that the availability of inhaled insulin would help to persuade some patients to convert to insulin earlier, which is not unreasonable. However, the benefits of conversion 2 or 4 years earlier would not be considered cost-effective as judged by the threshold band used by NICE. In practice, the patients most at risk of complications, for example because they also had hypertension, or early evidence of retinopathy, for instance, would be subjected to more vigorous persuasion, and so would probably convert earlier to injected insulin, thereby reducing the difference in practice.

So, the cost-effectiveness depends mainly on the utility gain from inhaling rather than injecting. As stated previously, the actual administration of insulin is only part of the package of care: blood glucose testing, self-adjustment of insulin, diet and exercise are all parts of insulin therapy. Cost-effectiveness within the manufacturer's submission arises either from a greater control of blood glucose, for which there is no convincing clinical evidence, or from a large utility gain being assumed for inhaled over injected. We think that the manufacturer's estimate of the

utility gain is an overestimate. However, the average utility gain will conceal individual variations, and some patients with particular problems with injection sites may have more to gain.

Conclusion

For controlling blood glucose, inhaled insulin is as good as, but no better than, short-acting soluble insulin, but is much more costly.

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Contribution of authors

Corri Black (Lecturer in Public Health), Sam Philip (Specialist Registrar) and Norman Waugh (Professor of Public Health) prepared Chapter 1. Corri Black and Pam Royle (Senior Research Fellow) carried out the review of clinical effectiveness. Norman Waugh wrote Chapter 3 on the industry submission, wrote Chapter 5 with contributions from all authors, and carried out the final revisions of the whole report. Ewen Cummins (Health Economist) carried out the economic analyses. Pam Royle carried out the literature searches. Sam Philip wrote the review of lung changes in diabetes (Appendix 1). All authors read and commented on all sections.

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Appendix 1

Lung disease in diabetes mellitus

Introduction

The classification of the chronic complications of type 1 and type 2 diabetes mellitus into microvascular and macrovascular disease emphasises the central role of diabetes-related vascular damage in their pathophysiology. Despite the alveolar–capillary network being the largest microvascular organ (surface area 140 m^2) and receiving the entire cardiac output, the effects of diabetes on the lung are not widely recognised. This may be because pulmonary abnormalities related to diabetes are frequently subclinical, unlike the overt morbidity and mortality associated with other microvascular complications such as retinopathy and nephropathy. A greater functional reserve than other organs for comparable degree of anatomic organ destruction may account for the relative lack of pulmonary symptoms. The lung, with its large exposed surface area, has been recognised as an alternative route for insulin delivery. There is concern that inhaled insulin delivery can have a deleterious effect on lung function and increase the risk of developing other pulmonary pathology such as chronic obstructive lung disease. However, before estimating this risk, it is essential to understand the effects of diabetes per se on the lung.

Schuyler and colleagues[123] were the first to investigate and demonstrate the abnormalities in lung function in young (21–28 years old, non-smokers) patients with type 1 diabetes mellitus, compared with age- and gender-matched normal control subjects. They noted that the elastic recoil at low lung volumes and total lung volumes was significantly less in the diabetics than in the control group. They suggested that the abnormalities in lung elastic behaviour may be manifestations of widespread elastin and collagen abnormalities. A subsequent study by Schernthaner and co-workers[124] could not confirm these findings. However, Sandler and colleagues[125] noted decreased lung elasticity and made additional observations of decreased carbon monoxide transfer capacity (DLCO) with decreased pulmonary capillary blood volume in 40 patients (15–60 years of age) with insulin-dependent diabetes compared with age-matched control subjects, all lifelong non-smokers.

Histopathological studies

Kodolova[126] noted similar, but less severe, microangiopathic changes in the lung than those in the kidney. The changes were most marked in the arterioles and capillaries of the alveolar septae. Vracko and colleagues[127] observed that alveolar epithelial and capillary basal laminae were significantly thicker in diabetics than those in age-matched control subjects. The degree of thickening did not correlate significantly with patient age or with known duration of diabetes. The increase in thickness of the basal lamina in the lungs, although smaller, correlated significantly with thickness of the basal lamina in renal tubules and muscle capillaries.[127] An electron-microscopic study on lung and kidney autopsy samples noted that the thickening of basal lamina was of the same magnitude in lung and kidney in diabetic subjects compared with controls.[128] Hence, in patients with diabetes there is definite histopathological evidence of thickened alveolar epithelial and pulmonary capillary basal laminae, vascular hyalinosis, granulomas, intraseptal nodular fibrosis and emphysema-like septal obliteration.[129–132] Experimental data in mice and hamsters, rendered diabetic by streptozotocin, have shown that hyperglycaemia induces basal laminar thickening, focal nodule formation, and capillary narrowing in both the lung and the glomerulus.[133,134] Animal studies have also suggested possible mechanisms for these changes, such as increased synthesis and degradation of collagen and elastin, altered type 2 pneumocyte morphology, enhanced pulmonary endothelial permeability and structural endothelial changes.[135–137]

Clinical studies of lung function in diabetes

Despite the evidence of microangiopathic changes in the lung, the study of lung function among patients with diabetes has produced inconsistent results. Initial studies noted that asymptomatic young patients with type 1 diabetes mellitus have abnormal lung volumes.[125,138] However, further cross-sectional case–control studies with relatively small numbers of patients have produced

conflicting results. While some have shown significant reduction in lung volumes compared with controls,[139–142] others failed to show significant differences in spirometry between patients with diabetes and normal control subjects,[124,143] differences from normal population-predicted values,[144] or a relationship with diabetes control[145] or duration of disease.[146,147] The nature of pulmonary function abnormalities in patients with diabetes in these studies was also inconsistent. FVC was noted to be low, either in isolation[138,141–143,148–150] or in combination with FEV_1.[139,142] Nirnajan and colleagues noted, in a small case–control study, that chronic maintenance of near-normoglycaemia was associated with improved cardiopulmonary function.[151]

A reduction in pulmonary diffusing capacity has been noticed in most of these studies.[138–140,142,143,150,152] Non-smoking, young, type 1 diabetic patients at rest show a modest (~8%) reduction in average lung diffusing capacity per unit alveolar volume.[125,152] The reduction in resting lung diffusing capacity has been noted to have a correlation with degree of glycaemic control and presence of microalbuminuria in both type 1 and type 2 patients.[153–155] However, other studies have also reported normal lung diffusing capacity in diabetes, especially when corrected for alveolar volumes.[146,148,156] Thus, there seems to be an inconsistency in the reported results. This may be due to differences in patient characteristics or variation in the measurement technique used. Fuso and colleagues reported more milder pulmonary capillary blood volume abnormalities in patients with type 1 diabetes using tests of DLCO transfer capacity and capillary blood volume in both the seated and supine positions.[157] Ozmen and co-workers suggested that their failure to show a relationship between DLCO transfer capacity and microalbuminuria, diabetes duration or glycaemic control was probably due to relative insensitivity of the usual clinical method of measuring DLCO transfer capacity.[145]

Lung function in patients with diabetes: epidemiological studies

In the Copenhagen City Heart Study, cross-sectional subgroup analysis of 284 subjects with diabetes among the 11,763 recruited subjects showed some reduction in pulmonary function among subjects with diabetes. This reduction was more pronounced in those treated with insulin.[158] The average FEV_1 and FVC among insulin-treated patients with diabetes were 239 and 334 ml lower than control subjects, respectively, and 122 and 150 ml lower than individuals with diabetes treated with oral agents.[158] Further longitudinal analysis of participants in the Copenhagen City Heart Study, including 326 subjects with diabetes and 9051 control subjects, demonstrated an association between the new diagnosis of diabetes and impaired pulmonary function;[159] after adjusting for confounders, those individuals who were newly diagnosed with diabetes annually lost 29 ml FVC and 25 ml of FEV_1 more than control subjects. However, the decline in ventilatory function in subjects who had diabetes was not significantly greater than the decline among the non-diabetic subjects during the observation period.

In the Framingham Heart Study cohort, patients with diabetes and those with a higher level of fasting blood glucose had a lower than predicted pulmonary function. The decline was stronger among smokers.[160] Pulmonary function tests showed a restrictive physiology as there was a larger reduction in residual FVC than FEV_1. However, when those with diabetes on treatment were excluded, higher fasting blood glucose levels were associated with an obstructive physiology, as in this group there were larger reductions in FEV_1 than in FVC. No significant association was found between the diagnosis of diabetes and chronic obstructive pulmonary disease (COPD), after adjusting for confounders. This may be due to the relatively small number of participants with an abnormally low FEV_1/FVC ratio. The Cardiovascular Health Study, in determining reference standards for a healthy population, found diabetes to be significantly associated with a decreased FEV_1.[161] Engstrom and colleagues reported an association between lower values of spirometric pulmonary function tests and the incidence of diabetes in middle-aged men in another population-based cohort (Men Born in 1914 study).[162]

The Rancho Bernardo Study examined the link between type 2 diabetes mellitus or plasma glucose level in subjects without diabetes and reduced pulmonary function, with contrasting results. After adjusting for age, height and smoking, pulmonary function was not associated with known or newly diagnosed type 2 diabetes in men or women. While in men with diabetes of 10 or more years' duration, FEV_1 and FVC were reduced and correlated with fasting plasma glucose, no such associations were found in women. The subjects were older (51–95 years) and

the lack of an association of type 2 diabetes with pulmonary function may have been due to survival bias and the small number of subjects with severe diabetes or diabetes of prolonged duration. Owing to differences in the age ranges of the cohorts studied, it is difficult to compare the results of this study with the younger Framingham Offspring Cohort. However, this study does suggest that any effect of glycaemia precedes diabetes.[163]

Association with other complications of diabetes

Epidemiological studies[164,165] have examined the association between simple spirometric pulmonary function tests and either the complications or duration of diabetes after controlling for height, gender, age, BMI and cigarette smoking. In the Fremantle Diabetes Study,[165] patients with type 2 diabetes were found to have spirometric pulmonary function that was below normal for age. Although glycaemic control was not noted to be a significant contributory factor to a reduction in lung function, other factors such as obesity, coronary heart disease and duration of diabetes were associated with decline in lung function. Clinically significant chronic airflow obstruction was noted only in current and ex-smokers. A 7-year follow-up prospective study examined the relationship between diabetes, glycaemic control and spirometric measures in 125 patients with type 2 diabetes. Spirometry showed a reduction of more than 10% in the predicted spirometric values in the whole cohort at baseline. Absolute measures continued to decline at an annual rate of 68, 71 and 84 ml/year and 17 l/minute for FVC, FEV_1, vital capacity and peak expiratory flow (PEF), respectively, in the 125 prospectively studied patients. In this follow-up study, measures of poor glycaemic control such as higher updated mean HbA_{1c}, follow-up HbA_{1c} or follow-up fasting plasma glucose were consistently associated with declining lung function . The severity of pulmonary abnormalities was related to glycaemic exposure and airflow limitation was a predictor of death in type 2 diabetes.

Klein and colleagues[166,167] measured PEF at 10-year follow-up of patients with younger onset diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. They found no association of PEF with progression of retinopathy, incidence of proliferative retinopathy, macular oedema, lower extremity amputation or ulcers, or self-reported cardiovascular disease in univariate analyses. However, on multivariate analysis after adjusting for contributions due to gender, age and BMI, PEF showed an association with a history of cardiovascular disease, pulse rate, HbA_{1c}, end-stage renal disease, lower extremity amputation/ulcer and subsequent 6-year survival. This study suggested that PEF is a predictor of lower extremity complications in patients with long-standing younger onset diabetes.

Conclusions

Thus, the existing literature provides an inconsistent picture of the overall nature of the impairment of pulmonary function among those with diabetes. However, there is considerable evidence showing that diabetes affects the lung. The timing in relation to onset of diabetes, the exact nature of the pulmonary function abnormalities and the progression in the course of the disease need further elucidation. The observation that decreased lung function is associated with level of fasting blood glucose and that this effect appears greater in smokers than non-smokers suggests that diabetes may increase susceptibility to the adverse pulmonary effects of tobacco smoking.[160] This raises a concern as to whether the inflammatory pulmonary infrastructure in the presence of the proinflammatory milieu of chronic hyperglycaemia is at increased risk of adverse reactions to otherwise innocuous agents. Long-term studies using inhaled insulin should shed more light on the effects on lung function.

Appendix 2

Search strategy summary

Searches for studies on clinical effectiveness

Databases searched

The search strategy used in the MEDLINE (Ovid) database, 1993 to August 2005, was:

1. ((inhal$ adj insulin$) or (pulmonary adj insulin$) or exubera).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

There were no language restrictions on this search.

This strategy was adapted as appropriate to the following additional databases:

Embase: 1993 to August 2005
Cochrane Library (all sections): 2005, Issue 3
Science Citation Index, limited to meeting abstracts only: 1993 to August 2005
BIOSIS, limited to meeting abstracts only: 1998 to August 2005
Web of Science Proceedings: 1990 to August 2005
National Research Register: 2005, Issue 2
Current Controlled Trials

Websites searches

The websites of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) were searched for the 2005 meeting abstracts.

Searches for studies on quality of life and diabetes

Databases searched

MEDLINE (Ovid)

1966 to November 2005

1. exp "Quality of Life"/
2. quality of life.tw.
3. qol.tw.
4. (utility or utilities).tw.
5. eq5d.tw.
6. eq-5d.tw.
7. sf-36.tw.
8. sf36.tw.
9. euroqol.tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. diabetes mellitus, type 1/ or diabetes mellitus, type 2/ or diabetes, gestational/
12. 10 and 11
13. limit 12 to (english language and yr="1980 - 2005")

EMBASE (OVID)

1980 to 2005 week 29

1. exp "Quality of Life"/
2. quality of life.tw.
3. qol.tw.
4. (utility or utilities).tw.
5. eq5d.tw.
6. eq-5d.tw.
7. sf-36.tw.
8. sf36.tw.
9. euroqol.tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. insulin dependent diabetes mellitus/ or non insulin dependent diabetes mellitus/ or maternal diabetes mellitus/
12. 10 and 11
13. limit 12 to english language

Appendix 3

Studies excluded from the clinical effectiveness systematic review

TABLE 38 *Excluded studies*

Study	Reasons for exclusion
Barnett, 2004[66]	Wrong comparator: did not give a direct comparison of inhaled and soluble insulin. Compared INH or a second oral agent in poorly controlled type 2 diabetes on oral agent monotherapy
Bergenstal, 2003[168]	Wrong comparator: did not give a direct comparison of inhaled and soluble insulin. Compared INH vs rosiglitazone, both in conjunction with diet and exercise
Bergenstal, 2004[169]	Combined data from three separate trials, all with different comparators
Cefalu, 2002[170]	Wrong comparator: did not give a direct comparison of inhaled and soluble insulin. Type 2 patients previously treated with combination OHAs randomised to: (1) INH monotherapy, (2) INH plus existing OHA, or (3) continued OHA
DeFronzo, 2005[171]	Wrong comparator: did not give a direct comparison of inhaled and soluble insulin. Type 2 patients with suboptimal control on diet and exercise were randomised to treatment with either INH before meals or rosiglitazone twice daily, with diet and exercise
Rosenstock, 2002[61]	Wrong comparator: did not give a direct comparison of inhaled and soluble insulin. Type 2 patients previously treated with combination OHAs randomised to: (1) INH monotherapy, (2) INH plus OHAs, or (3) continued OHA
Rosenstock, 2004[60]	One-year extension study of an RCT where patients were allowed to choose treatment regimen; so cohort study (not an RCT)
Simonson, 2004[172]	Wrong comparator: did not give a direct comparison of inhaled and soluble insulin. Patients were poorly controlled on one oral agent (metformin) and randomised to either INH or glibenclamide. Hence, patients initially only on one drug, so had not failed on OHA
Testa, 2004[173]	Wrong comparator: did not give a direct comparison of inhaled and soluble insulin. Patients were poorly controlled on sulphonylurea monotherapy and randomised to either INH or metformin. Hence, patients initially only on one drug, so had not failed on OHA
Testa, 2004[64]	Duplicate of Testa, 2004[173] (above)
Testa, 2004[63]	Wrong comparator: did not give a direct comparison of inhaled and soluble insulin. Patients poorly controlled on metformin monotherapy and randomised to either INH or glibenclamide. Hence, patients initially only on one drug, so had not failed on OHA
Weiss, 2003[65]	Wrong comparator: did not give a direct comparison of inhaled and soluble insulin. Patients with sulphonylurea and/or metformin randomised either to receive INH in addition to their prestudy OHA therapy (INH + OHA) or to continue taking prestudy OHA alone

Appendix 4

Table of data extraction

TABLE 39 *Data extraction*

Study	Methods	Participants	Interventions	Outcomes	Notes
Cappelleri, 2002[40–42]	*Trial design*: RCT *Randomisation procedure*: *Blinding*: open label *Setting*: multicentre (clinical and outpatient research clinics) *Country*: USA *ITT analysis*: not done for patient satisfaction, no details for HbA_{1c}	*Inclusion criteria*: HbA_{1c} 7–11.9%; age 35–65 years; stable insulin regimen (2–3 injections/day); weight 100–175% ideal; normal chest and pulmonary function *Exclusion criteria*: creatinine >265 μmol/l; major organ disease; smokers; insulin regimen ⩾4 daily doses or 150 U insulin daily, oral hypoglycaemic drugs, on insulin pumps *Type of diabetes*: 2 *Numbers*: 51 (INH 26; SC 25) *Mean ages*: INH 51.1; SC 53.6 *Duration of diabetes (mean years)*: 11 (INH 11.2; SC 11.5) *Gender*: INH 16M/10F; SC 15M/10F *Ethnic groups*: white 53%; black 12%; hispanic 35%	*Intervention*: INH before meals (dry powder aerosol delivery: Inhale Therapeutics via Exubera device) plus single ultralente s.c. insulin injection at bedtime *Control*: s.c. insulin: usual regimen of split/mixed insulin 2–3 injections/day *Duration of trial (weeks)*: 12	**Primary** *HbA1c:* INH: baseline 8.7% (SD 1.4%) to 12 weeks 8.0% (SD 1.4%) SC: baseline 7.9% (SD 0.9%) to 12 weeks 7.1% (SD 0.9%) Mean change in HbA_{1c} from baseline: INH ($n = 26$) –0.7% (SD 0.7%); SC insulin group ($n = 25$) –0.7% (SD 0.7%) **Secondary** *Overall patient satisfaction*: INH 31% (CI 14 to 50%); SC 13% (CI 7 to 19%). Geometric mean % improvement statistically significantly greater in INH group ($p < 0.05$) *Mild to moderate hypos*: INH 0.83 episodes/month; SC 1.1 (ns) *Severe hypos*: none in either group *Average weight loss*: no significant difference *Adverse effects*: none reported for the pulmonary function tests *Losses to follow-up*: 9% for patient satisfaction *Insulin used*: patients receiving INH were given 14.6 ± 5.1 mg of INH and 35.7 ± 18.4 U of ultralente daily by end of study; compared with before study 19 U of regular insulin and 51 U of long-acting insulin	Sponsored by Pfizer Trial powered prospectively for HbA_{1c} values (the primary end-point) and not patient satisfaction

continued

TABLE 39 *Data extraction (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Dumas, 2005[53]	*Trial design*: RCT *Randomisation procedure*: unclear *Blinding*: open *Setting*: ? *Country*: ? *ITT analysis*: ?	*Inclusion criteria*: type 1 diabetes *Exclusion criteria*: ? *Type of diabetes*: 1 *Numbers*: 226 *Mean ages*: range 12–65 years *Duration of diabetes (mean years)*: ? *Ethnic groups*: ?	*Intervention*: INH combined with once- or twice-daily intermediate- or long-acting insulin *Control*: s.c. short-acting insulin, combined with once- or twice-daily intermediate- or long-acting insulin *Duration of trial (weeks)*: 12	*HbA_{1c}*: similar declines from baseline of HbA_{1c} = 7.5% for both groups seen. At week 12 Exubera 7.1%; SC 7.0% *Hypoglycaemia*: overall hypoglycaemic event rates were 6.8 and 5.5 events/subject-month in the Exubera and SC arms (RR 1.24, 90% CI 1.17 to 1.31) Severe hypoglycaemia occurred in 9 (Exubera) and 17 (SC) patients, respectively, corresponding with rates of 0.053 and 0.103 events/subject-month (RR 0.52, 90% CI 0.30 to 0.86) *Pulmonary function tests*: small treatment group differences in lung function occurred within 2 weeks. Mean change from baseline at week 2 in FEV_1 and DLCO, respectively, was: Exubera –0.070 l (FEV_1) and –0.973 ml/minute/mmHg (DLCO); SC –0.027 l (FEV_1) and –0.246 ml/minute/mmHg (DLCO); adjusted difference, FEV_1 –0.043 l; DLCO –0.727 ml/minute/mmHg). Differences remained stable for the rest of the phase and resolved within 2 weeks of Exubera discontinuation *Adverse effects*: overall adverse event profiles for both arms were similar, and the majority was mild to moderate *Cough*: all-causality cough was reported in Exubera 30.9% and SC 7.8% of patients. Cough generally was mild, not productive, and occurred soon after dosing	Sponsored by Pfizer

continued

TABLE 39 *Data extraction (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Heise, 2004[43]	*Trial design*: RCT *Randomisation procedure*: adequate *Blinding*: open *Setting*: ? *Country*: Germany *ITT analysis*: no	*Inclusion criteria*: 18–50 years receiving a stable insulin regimen involving at least two daily injections and a dose ⩽150 U/day; body weight >50 kg; BMI <30 kg/m^2; HbA_{1c} 5–9%; insulin antibodies ⩽20 μU/ml; fasting C peptide ⩽0.3 nmol/l *Exclusion criteria*: smoking; predisposition to severe hypoglycaemia; clinically significant disease; pregnant or lactating; recent blood donation; use of investigational and recreational drugs; glucocorticoid therapy *Type of diabetes*: 1 *Numbers*: 47 (INH 23; SC 22; two withdrew before treatment) *Mean ages*: INH 37.6; SC 35.9 *Duration of diabetes (mean years)*: INH = 16.6; SC = 18.0 *Ethnic groups*: ?	*Intervention*: premeal INH + NPH insulin s.c. twice daily *Control*: premeal s.c. regular insulin + NPH insulin s.c. twice daily *Duration of trial (weeks)*: 24	**Secondary** *HbA_{1c}* INH (n = 23): baseline 6.79 (± 0.70), week 24 6.73 (± 0.87); s.c. insulin (n = 21): baseline 7.13 (± 0.56), week 24 (n = 19) 7.08 (± 0.95); changes from baseline to week 24: INH –0.06 ± 0.42%; SC –0.08 ± 0.77% *Hypoglycaemia (overall)*: hypoglycaemic event rate. Events per subject-month: INH 7.8; SC 9.4 Serious hypoglycaemia: three patients in the INH group reported four severe hypoglycaemia events vs two patients in s.c. insulin group reporting two events *Losses to follow-up*: one in INH group and four in s.c. insulin group (plus one in each group withdrew before treatment)	Sponsored by Pfizer Primary outcomes of trial were insulin antibodies and postprandial glucose disposal

continued

TABLE 39 *Data extraction (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Hollander, 2004[44,45]	*Trial design*: RCT *Randomisation procedure*: adequate *Blinding*: open *Setting*: multicentre *Country*: USA/Canada *ITT analysis*: no	*Inclusion criteria*: age 35–80 years; Stable SC insulin schedule: 2–3 injections day for ⩾2 months before study; not receiving OHA; HbA_{1c} 6–11% inclusive; BMI ⩽35 kg/m^2 *Exclusion criteria*: poorly controlled asthma; COPD; significant respiratory disease; smoking in last 6/12; abnormal screening CxR; abnormal screening PFT; predisposition to severe hypos (2+ events last 6/12); any hospitalisation or emergency treatment (for diabetes control) last 6/12; pump therapy; insulin requirement exceeding >150 U/day *Type of diabetes*: 2 *Numbers*: 299 (INH 149; SC 150) *Mean ages*: INH 58.7 (9.5); SC 56.2 (11.1) *Duration of diabetes (mean years)*: INH 13.8; SC 13.2 *Ethnic groups*: not stated	*Intervention*: preprandial INH plus single bedtime dose of ultralente *Control*: at least two daily injections of s.c. insulin (mixed regular/NPH insulin) *Duration of trial (weeks)*: 24	HbA_{1c}: INH: baseline 8.1%. 24 weeks 7.4% Change = 0.7% (no SDs given) SC: baseline 8.2%, 24 weeks 7.6%, change 0.6% (no SDs given) Difference between the adjusted means for INH vs SC: –0.07% (95% CI –0.32 to 0.17) *Proportion of patients achieving HbA_{1c} levels <7%*: INH 46.9%; SC 31.7% (OR 2.27, 95% CI 1.24 to 4.14) *Overall hypoglycaemia*: INH 1.40 events per subject-month; SC 1.57 events per subject-month Risk ratio (INH/SC) for any hypo event of 0.89 (95% CI 0.82 to 0.97) Severe hypoglycaemic events: INH = crude event rate of 0.5/100 subject-months; SC = 0.1/100 subject-months *Weight gain*: INH body weight remained stable at 90.5 kg. SC group increased (89.2 to 90.6 kg). Adjusted mean group difference –1.29 kg (95% CI –1.98 to –0.59) *Pulmonary function tests*: no significant change in FVC, FEV_1, TLC and DLCO for either SC or INH *Adverse effects*: frequency and nature comparable, apart from cough. Cough (mild to moderate with no discontinuation) was reported by more patients in the INH group than SC (21.5% vs 2.0%) *Treatment satisfaction*: mean overall satisfaction score improved significantly for INH group and worsened slightly for SC group ($p < 0.0001$) *Losses to follow-up*: 26	Trial designed to test 'non-inferiority' of INH to SC Support: Pfizer

continued

TABLE 39 *Data extraction (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Quattrin, 2004[46–48]	*Trial design*: RCT *Randomisation procedure*: unclear *Blinding*: open *Setting*: multicentre *Country*: USA/Canada *ITT analysis*: no	*Inclusion criteria*: diabetes >1 year; aged 12–65 years; 2+ injections insulin (or analogue) a day, for previous 2/12; HbA_{1c} 6–11%; BMI 30 kg/m^2 *Exclusion criteria*: poorly controlled asthma; COPD (or other respiratory disease); smoking in last 6/12; screening CxR abnormalities; abnormal PFTs; 2+ severe hypos in last 6/12; hospitalisation for poor diabetes in last 6/12; insulin requirement >150 U/day *Type of diabetes*: 1 *Numbers*: 335 (NH 169; SC 165) *Mean ages*: INH 33.5; SC 34.0 *Duration of diabetes* (mean years): INH 16.2; SC 16.5 *Ethnic groups*: not stated	*Intervention*: INH before meals + bedtime ultralente *Control*: NPH + regular insulin before breakfast, regular insulin before dinner, second NPH insulin before dinner or bedtime *Duration of trial (weeks)*: 24	**Primary** *HbA_{1c}*: INH: baseline 8.1 ± 1.0%, week 24 7.9 ± 1.1%; SC: baseline 8.1 ± 1.0%, week 24 7.7 ± 0.9%; adjusted group difference 0.16% (95% CI –0.01 to 0.32) *Percentage of patients achieving HbA_{1c} <7%*: INH 15.9%; SC 15.5%; adjusted OR 0.92 (95% CI 0.40 to 2.10) *Overall hypos*: INH 8.6 events/subject-month; SC 9.0 events/subject-month; RR 0.96 (95% CI 0.93 to 0.99) Serious hypoglycaemic events: INH 5.5; SC 4.7 events/100 subject-months; RR 1.16 (95% CI 0.76 to 1.76) *Weight gain*: both groups gained: INH 0.9 kg; SC 1.5 kg *Adverse effects*: with the exception of cough, adverse events comparable between treatment groups. Patients experiencing cough: INH 27%; SC 5% *Pulmonary function tests*: mean changes in FVC, FEV_1 and TLC were comparable between the two groups; greater mean decrease in DLCO in INH group OSSS improved significantly for INH ($p < 0.001$) and decreased significantly for SC ($p < 0.05$) *Losses to follow-up*: 32	Trial designed to test 'non-inferiority' of INH to SC Support: Pfizer

continued

TABLE 39 *Data extraction (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Skyler, 2001[49,50]	*Trial design*: RCT *Randomisation procedure*: unclear *Blinding*: open *Setting*: ten academic centres *Country*: USA *ITT analysis*: HbA_{1c} reported as ITT, but no ITT for patient satisfaction	*Inclusion criteria*: type 1 diabetes, age 18–55; 80–130% ideal weight; stable insulin schedule for >2 months involving 2–3 injections/day; HbA_{1c} 7–11.9%; fasting C peptide ≤0.2 pmol/ml; normal on CxR and pulmonary function tests; normal ECG; willing to monitor blood glucose at home four times/day *Exclusion criteria*: asthma/other suspected or actual respiratory disease; cardiac, cerebrovascular, liver disease or renal insufficiency; history of allergies, epilepsy, drug or alcohol abuse, systemic steroid use; pregnancy either actual or planned within 6 months; diabetic autonomic neuropathy; ≥2 serious hypoglycaemic episodes in previous year; hospital or emergency room admission with poor diabetic control in previous 6 months; use of insulin pump or regimen with ≥4 daily doses or total daily insulin > 150 U *Type of diabetes*: 1 *Numbers*: 72 (INH 35; SC 37) *Mean ages*: INH 35.4; SC 39.7 *Duration of diabetes (mean years)*: INH 14.6; SC 14.4 *Ethnic groups*: white 80%; black 3%; other 16%	*Intervention*: rapid-onset INH t.d.s. Dry powder aerosol (Inhale Therapeutics) plus single dose s.c. ultralente at bedtime *Control*: s.c. injections 2–3 times/day (no rapid acting analogues) and human NPH before breakfast and bedtime *Both groups*: had insulin adjusted weekly to achieve preprandial target of 5.6–8.9 mmol/l. 4-week lead-in phase before randomisation: all received advice from dietitian and 2-day admission to hospital for instruction on dosing and experience with preprandial INH *Duration of trial (weeks)*: 12	**Primary** *HbA_{1c}*: adjusted mean difference between groups: INH = –0.64 (0.98); SC = –0.83 (0.92) (both $n = 35$) (95% CI –0.2 to 0.5%) **Secondary** *Overall patient satisfaction*: increase in satisfaction from baseline significantly greater in INH vs SC. Difference in improvement 24.5% (95% CI 6.6 to 42.5%, $p < 0.01$) *Convenience/ease of use*: increase from baseline significantly greater in INH vs SC; difference in improvement 30.1% (95% CI 10.7 to 49.5%, $p < 0.01$) *Social comfort*: no statistically significant difference between treatment groups (95% CI –14.6 to 34.6%, $p = 0.42$) *Hypos*: total INH 35; SC 37. Severe: INH 5, SC 5. No significant difference between groups *Body weight*: no significant difference between groups *Insulin used*: INH: mean daily dose 12.2 mg (4.9) inhaled insulin [equivalent to about 36.6 (14.7) U s.c. insulin, assuming 10% bioavailability] and 24.8 U (9.3) of long-acting s.c. insulin at end of 12 weeks SC: mean daily dose 15.9 units (9.8) of short-acting regular insulin and 31.0 U (13.2) of long-acting insulin at end of 12 weeks *Adverse effects*: no serious or major adverse effects on pulmonary function reported *Losses to follow-up*: for HbA_{1c}: 1 on s.c. insulin; for patient satisfaction: INH 2 (8%); SC 4 (11%)	Support: Pfizer

continued

TABLE 39 *Data extraction (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Skyler, 2005[51,52]	*Trial design*: RCT *Randomisation procedure*: unclear *Blinding*: open *Setting*: 40 centres *Country*: USA and Canada *ITT analysis*: no	*Inclusion criteria*: type 1 diabetes; HbA_{1c} levels 6–11%; BMI ⩽30; stable insulin regimen (two or more injections daily for >2 months) *Exclusion criteria*: asthma; respiratory, renal, hepatic or cardiac disease; smoking within 6 months; drug or alcohol dependence; insulin allergy; recurrent severe hypoglycaemia; treatment with OHAs, systemic glucocorticoid use, or insulin pump therapy 2 months before screening; use of an inhaled insulin therapy in a previous clinical trial; insulin requirement >150 U/day; hospitalisation or emergency room visit due to poor glycaemic control within 6 months; pregnancy, lactation *Type of diabetes*: 1 *Numbers*: 328 (INH 163; SC 165) *Mean ages*: 29.5 (14.6); range 12–65 years *Duration of diabetes*: 13.8 years *Ethnic groups*: 90% white	*Intervention*: INH 10 minutes before meals, plus a morning and bedtime dose of NPH insulin (INH inhalations delivered as 1–2 inhalations of 1 or 3 mg) *Control*: premeal regular s.c. insulin ~30 minutes before meals, plus a morning and bedtime dose of NPH insulin *Duration of trial (weeks)*: 24	*HbA_{1c}*: mean HbA_{1c} decreased from baseline comparably between groups. INH: baseline 8.0 ± 1.0, 24 weeks 7.7 ± 1.0% (adjusted change from baseline –0.3%) SC: baseline 7.9 ± 1.0, 24 weeks 7.8 ± 1.2% (difference of 0.1%, but adjusted treatment group difference –0.16%, 95% CI –0.34 to 0.01) *Patient satisfaction and quality of life*: OSSS: subjects had greater improvement with INH vs SC ($p < 0.0001$). OQLS and subscales of behavioural and emotional control, general and hyperglycaemic symptom distress, overall cognition, mental acuity and awareness also improved more favourably for INH vs SC (all $p < 0.01$ to 0.05) *Hypoglycaemia*: overall hypoglycaemia rate (episodes per patient-month): lower in INH than SC group (9.3 vs 9.9; RR 0.94, 95% CI 0.91 to 0.97) Severe hypoglycaemic episodes (episodes per 100 patient-months): higher in the INH group (6.5 vs 3.3; RR 2.00, 95% CI 1.28 to 3.12), the four subjects receiving inhaled insulin accounting for 27 (46.6%) of the episodes, 22 of which occurred within the first 12 weeks of treatment *Adverse effects*: frequency and nature of adverse events were comparable between the groups. Cough was reported more often in the inhaled group (25 vs 7%), generally mild, decreased over the study period [incidence from 17 (10.5%, weeks 0–4) to 4 (2.6%, weeks 20–24); prevalence from 18 (11.1%) to 15 (9.7%) at study end] *Pulmonary function*: FEV_1: no difference between groups. DLCO: differed in treatment groups; difference –0.791 ml/minute/mmHg (95% CI –1.466 to –0.117) *Losses to follow-up*: 22	Support: Pfizer and Sanofi-Aventis

CxR, chest X-ray; ns, not significant; PFT, pulmonary function test.

Appendix 5

Cost-effectiveness results

Base case: simulation A

Simulation of moving from being poorly controlled on metformin and gliclazide to:

- metformin and Exubera; or
- metformin, gliclazide and basal subcutaneous glargine; or
- metformin and premix basal bolus in the form of mixtard 30.

TABLE 40 *Base case: simulation A*

	Exubera	Basal	Difference	Premix	Difference
Age 40, 5-year diabetes duration, 2-year treatment delay, no HbA_{1c} drift					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,819,498	£667,936	£1,151,562	£601,238	£1,218,260
Cost of complications	£1,216,854	£1,223,042	–£6,188	£1,223,042	–£6,188
Total cost	**£3,036,352**	**£1,890,978**	**£1,145,374**	**£1,824,280**	**£1,212,072**
QALYs					
Exubera utility increment = 0.00	1080.0	1078.9	1.1	1078.9	1.1
Exubera utility increment = 0.02	1104.5	1078.9	25.6	1078.9	25.6
Exubera utility increment = 0.04	1129.1	1078.9	50.2	1078.9	50.2
ICERs					
Exubera utility increment = 0.00			£1,076,854		£1,139,562
Exubera utility increment = 0.02			£44,661		£47,262
Exubera utility increment = 0.04			£22,803		£24,131
Age 50, 8-year diabetes duration, 2-year treatment delay, no HbA_{1c} drift					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,635,339	£600,770	£1,034,569	£541,127	£1,094,212
Cost of complications	£1,269,241	£1,281,452	–£12,211	£1,281,452	–£12,211
Total cost	**£2,904,580**	**£1,882,222**	**£1,022,358**	**£1,822,579**	**£1,082,001**
QALYs					
Exubera utility increment = 0.00	976.7	975.5	1.2	975.5	1.2
Exubera utility increment = 0.02	998.7	975.5	23.2	975.5	23.2
Exubera utility increment = 0.04	1020.8	975.5	45.3	975.5	45.3
ICERs					
Exubera utility increment = 0.00			£907,859		£960,823
Exubera utility increment = 0.02			£44,095		£46,668
Exubera utility increment = 0.04			£22,596		£23,914
Age 60, 12-year diabetes duration, 2-year treatment delay, no HbA_{1c} drift					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,232,858	£453,437	£779,421	£409,247	£823,611
Cost of complications	£1,103,531	£1,111,038	–£7,507	£1,111,038	–£7,507
Total cost	**£2,336,389**	**£1,564,475**	**£771,914**	**£1,520,285**	**£816,104**
QALYs			0		
Exubera utility increment = 0.00	769.8	768.0	1.8	768.0	1.8
Exubera utility increment = 0.02	786.3	768.0	18.3	768.0	18.3
Exubera utility increment = 0.04	802.9	768.0	34.9	768.0	34.9
ICERs					
Exubera utility increment = 0.00			£440,353		£465,561
Exubera utility increment = 0.02			£42,180		£44,595
Exubera utility increment = 0.04			£22,151		£23,419

Base case: simulation B

Simulation of moving from being poorly controlled on metformin and glargine to:

- metformin, glargine and Exubera; or
- metformin, glargine and lispro humalog; or
- metformin and premix.

TABLE 41 *Base case: simulation B*

	Exubera	Basal–bolus	Difference	Premix	Difference
Age 40, 5-year diabetes duration, 2-year treatment delay, no HbA_{1c} drift					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,524,947	£974,284	£550,663	£641,984	£882,963
Cost of complications	£1,216,854	£1,223,042	–£6,188	£1,223,042	–£6,188
Total cost	**£2,741,801**	**£2,197,326**	**£544,475**	**£1,865,026**	**£876,775**
QALYs					
Exubera utility increment = 0.00	1079.9	1079.0	0.9	1079.0	0.9
Exubera utility increment = 0.02	1104.5	1079.0	25.5	1079.0	25.5
Exubera utility increment = 0.04	1129.1	1079.0	50.1	1079.0	50.1
ICERs					
Exubera utility increment = 0.00			£560,954		£903,312
Exubera utility increment = 0.02			£21,307		£34,312
Exubera utility increment = 0.04			£10,860		£17,488
Age 50, 8-year diabetes duration, 2-year treatment delay, no HbA_{1c} drift					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,374,106	£878,854	£495,252	£581,704	£792,402
Cost of complications	£1,269,241	£1,281,452	–£12,211	£1,281,452	–£12,211
Total cost	**£2,643,347**	**£2,160,306**	**£483,041**	**£1,863,156**	**£780,191**
QALYs					
Exubera utility increment = 0.00	976.7	975.5	1.2	975.5	1.2
Exubera utility increment = 0.02	998.7	975.5	23.2	975.5	23.2
Exubera utility increment = 0.04	1020.8	975.5	45.3	975.5	45.3
ICERs					
Exubera utility increment = 0.00			£428,942		£692,814
Exubera utility increment = 0.02			£20,834		£33,650
Exubera utility increment = 0.04			£10,676		£17,244
Age 60, 12-year diabetes duration, 2-year treatment delay, no HbA_{1c} drift					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,044,169	£669,361	£374,808	£449,204	£594,965
Cost of complications	£1,103,531	£1,111,038	–£7,507	£1,111,038	–£7,507
Total cost	**£2,147,700**	**£1,780,399**	**£367,301**	**£1,560,242**	**£587,458**
QALYs			0		
Exubera utility increment = 0.00	769.8	768.0	1.8	768.0	1.8
Exubera utility increment = 0.02	786.3	768.0	18.3	768.0	18.3
Exubera utility increment = 0.04	802.9	768.0	34.9	768.0	34.9
ICERs					
Exubera utility increment = 0.00			£209,533		£335,126
Exubera utility increment = 0.02			£20,070		£32,101
Exubera utility increment = 0.04			£10,540		£16,857

Sensitivity analyses

TABLE 42 *Effect of a 60-year-old transferring at only 5 years' duration of diabetes, as opposed to the 12 years' duration assumed in the base case*

(a) Simulation A					
	Exubera	**Basal**	**Difference**	**Premix**	**Difference**
Age 60, 5-year diabetes duration, 2-year treatment delay, no HbA_{1c} drift					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,232,858	£453,437	£779,421	£409,247	£823,611
Cost of complications	£834,835	£838,835	–£4,000	£838,835	–£4,000
Total cost	**£2,067,693**	**£1,292,272**	**£775,421**	**£1,248,082**	**£819,611**
QALYs					
Exubera utility increment = 0.00	788.9	787.5	1.4	787.5	1.4
Exubera utility increment = 0.02	805.5	787.5	18.0	787.5	18.0
Exubera utility increment = 0.04	822.0	787.5	34.5	787.5	34.5
ICERs					
Exubera utility increment = 0.00			£545,138		£576,207
Exubera utility increment = 0.02			£43,146		£45,605
Exubera utility increment = 0.04			£22,462		£23,742
(b) Simulation B					
	Exubera	**Basal–bolus**	**Difference**	**Premix**	**Difference**
Age 60, 5-year diabetes duration, 2-year treatment delay, no HbA_{1c} drift					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,044,169	£669,361	£374,808	£449,204	£594,965
Cost of complications	£834,835	£838,926	–£4,091	£838,926	–£4,091
Total cost	**£1,879,004**	**£1,508,287**	**£370,717**	**£1,288,130**	**£590,874**
QALYs					
Exubera utility increment = 0.00	788.9	787.5	1.4	787.5	1.4
Exubera utility increment = 0.02	805.5	787.5	18.0	787.5	18.0
Exubera utility increment = 0.04	822.0	787.5	34.5	787.5	34.5
ICERs					
Exubera utility increment = 0.00			£260,652		£415,446
Exubera utility increment = 0.02			£20,630		£32,881
Exubera utility increment = 0.04			£10,740		£17,118

TABLE 43 *Simulation A: 4-year relative treatment delay*

	Exubera	Basal	Difference	Premix	Difference
Age 40, 5-year diabetes duration, 4-year treatment delay, no HbA_{1c} drift					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,676,386	£619,887	£1,056,499	£561,595	£1,114,791
Cost of complications	£1,242,013	£1,253,443	–£11,430	£1,253,443	–£11,430
Total cost	**£2,918,399**	**£1,873,330**	**£1,045,069**	**£1,815,038**	**£1,103,361**
QALYs					
Exubera utility increment = 0.00	1077.0	1075.2	1.8	1075.2	1.8
Exubera utility increment = 0.02	1099.3	1075.2	24.1	1075.2	24.1
Exubera utility increment = 0.04	1121.6	1075.2	46.4	1075.2	46.4
ICERs					
Exubera utility increment = 0.00			£568,810		£600,537
Exubera utility increment = 0.02			£43,320		£45,737
Exubera utility increment = 0.04			£22,517		£23,773
Age 50, 8-year diabetes duration, 4-year treatment delay, no HbA_{1c} drift					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,491,708	£552,318	£939,390	£501,072	£990,636
Cost of complications	£1,291,276	£1,309,256	–£17,980	£1,309,256	–£17,980
Total cost	**£2,782,984**	**£1,861,574**	**£921,410**	**£1,810,328**	**£972,656**
QALYs					
Exubera utility increment = 0.00	972.4	970.1	2.3	970.1	2.3
Exubera utility increment = 0.02	992.2	970.1	22.1	970.1	22.1
Exubera utility increment = 0.04	1011.9	970.1	41.8	970.1	41.8
ICERs					
Exubera utility increment = 0.00			£402,424		£424,805
Exubera utility increment = 0.02			£41,785		£44,109
Exubera utility increment = 0.04			£22,036		£23,262
Age 60, 12-year diabetes duration, 4-year treatment delay, no HbA_{1c} drift					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,092,679	£405,675	£687,004	£369,635	£723,044
Cost of complications	£1,124,046	£1,138,747	–£14,701	£1,138,747	–£14,701
Total cost	**£2,216,725**	**£1,544,422**	**£672,303**	**£1,508,382**	**£708,343**
QALYs					
Exubera utility increment = 0.00	763.5	760.3	3.2	760.3	3.2
Exubera utility increment = 0.02	777.8	760.3	17.5	760.3	17.5
Exubera utility increment = 0.04	792.1	760.3	31.8	760.3	31.8
ICERs					
Exubera utility increment = 0.00			£212,019		£223,385
Exubera utility increment = 0.02			£38,447		£40,508
Exubera utility increment = 0.04			£21,140		£22,273

TABLE 44 *Simulation A: 10-year time-horizon*

	Exubera	Basal	Difference	Premix	Difference
Age 40, 5-year diabetes duration, 2-year treatment delay, 10-year time-horizon					
Per 100 patients over 10 years					
Costs					
Cost of treatment	£1,036,833	£383,592	£653,241	£345,929	£690,904
Cost of complications	£431,155	£434,856	–£3,701	£434,856	–£3,701
Total cost	**£1,467,988**	**£818,448**	**£649,540**	**£780,785**	**£687,203**
QALYs					
Exubera utility increment = 0.00	708.4	707.7	0.7	707.7	0.7
Exubera utility increment = 0.02	722.2	707.7	14.5	707.7	14.5
Exubera utility increment = 0.04	736.1	707.7	28.4	707.7	28.4
ICERs					
Exubera utility increment = 0.00			£1,049,698		£1,108,857
Exubera utility increment = 0.02			£44,948		£47,481
Exubera utility increment = 0.04			£22,965		£24,260
Age 50, 8-year diabetes duration, 2-year treatment delay, 10-year time-horizon					
Per 100 patients over 10 years					
Costs					
Cost of treatment	£997,086	£367,909	£629,177	£332,778	£664,308
Cost of complications	£500,170	£501,600	–£1,430	£501,600	–£1,430
Total cost	**£1,497,256**	**£869,509**	**£627,747**	**£834,378**	**£662,878**
QALYs					
Exubera utility increment = 0.00	681.7	680.8	0.9	680.8	0.9
Exubera utility increment = 0.02	695.1	680.8	14.3	680.8	14.3
Exubera utility increment = 0.04	708.4	680.8	27.6	680.8	27.6
ICERs					
Exubera utility increment = 0.00			£641,060		£676,936
Exubera utility increment = 0.02			£43,932		£46,390
Exubera utility increment = 0.04			£22,745		£24,018
Age 60, 12-year diabetes duration, 2-year treatment delay, 10-year time-horizon					
Per 100 patients over 10 years					
Costs					
Cost of treatment	£877,256	£324,065	£553,191	£293,497	£583,759
Cost of complications	£573,076	£580,043	–£6,967	£580,043	–£6,967
Total cost	**£1,450,332**	**£904,108**	**£546,224**	**£873,540**	**£576,792**
QALYs					
Exubera utility increment = 0.00	611.4	610.2	1.2	610.2	1.2
Exubera utility increment = 0.02	623.1	610.2	12.9	610.2	12.9
Exubera utility increment = 0.04	634.8	610.2	24.6	610.2	24.6
ICERs					
Exubera utility increment = 0.00			£461,406		£487,228
Exubera utility increment = 0.02			£42,487		£44,865
Exubera utility increment = 0.04			£22,268		£23,515

TABLE 45 *Simulation A: low Exubera use or cost*

	Exubera	Basal	Difference	Premix	Difference
Age 40, 5-year diabetes duration, 2-year treatment delay, low Exubera use/cost					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,469,203	£667,936	£801,267	£601,238	£867,965
Cost of complications	£1,216,854	£1,223,042	–£6,188	£1,223,042	–£6,188
Total cost	**£2,686,057**	**£1,890,978**	**£795,079**	**£1,824,280**	**£861,777**
QALYs					
Exubera utility increment = 0.00	1080.0	1078.9	1.1	1078.9	1.1
Exubera utility increment = 0.02	1104.5	1078.9	25.6	1078.9	25.6
Exubera utility increment = 0.04	1129.1	1078.9	50.2	1078.9	50.2
ICERs					
Exubera utility increment = 0.00			£747,515		£810,223
Exubera utility increment = 0.02			£31,002		£33,603
Exubera utility increment = 0.04			£15,829		£17,157
Age 50, 8-year diabetes duration, 2-year treatment delay, low Exubera use/cost					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,399,308	£600,770	£798,538	£541,127	£858,181
Cost of complications	£1,269,241	£1,281,452	–£12,211	£1,281,452	–£12,211
Total cost	**£2,668,549**	**£1,882,222**	**£786,327**	**£1,822,579**	**£845,970**
QALYs					
Exubera utility increment = 0.00	976.7	975.5	1.2	975.5	1.2
Exubera utility increment = 0.02	998.7	975.5	23.2	975.5	23.2
Exubera utility increment = 0.04	1020.8	975.5	45.3	975.5	45.3
ICERs					
Exubera utility increment = 0.00			£698,263		£751,226
Exubera utility increment = 0.02			£33,915		£36,487
Exubera utility increment = 0.04			£17,379		£18,697
Age 60, 12-year diabetes duration, 2-year treatment delay, low Exubera use/cost					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,055,802	£453,437	£602,365	£409,247	£646,555
Cost of complications	£1,103,531	£1,111,038	–£7,507	£1,111,038	–£7,507
Total cost	**£2,159,333**	**£1,564,475**	**£594,858**	**£1,520,285**	**£639,048**
QALYs					
Exubera utility increment = 0.00	769.8	768.0	1.8	768.0	1.8
Exubera utility increment = 0.02	786.3	768.0	18.3	768.0	18.3
Exubera utility increment = 0.04	802.9	768.0	34.9	768.0	34.9
ICERs					
Exubera utility increment = 0.00			£339,347		£364,556
Exubera utility increment = 0.02			£32,505		£34,920
Exubera utility increment = 0.04			£17,070		£18,338

TABLE 46 *Simulation A: high Exubera use or cost*

	Exubera	Basal	Difference	Premix	Difference
Age 40, 5-year diabetes duration, 2-year treatment delay, high Exubera use/cost					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£2,344,325	£667,936	£1,676,389	£601,238	£1,743,087
Cost of complications	£1,216,854	£1,223,042	–£6,188	£1,223,042	–£6,188
Total cost	**£3,561,179**	**£1,890,978**	**£1,670,201**	**£1,824,280**	**£1,736,899**
QALYs					
Exubera utility increment = 0.00	1079.9	1079.0	0.9	1079.0	0.9
Exubera utility increment = 0.02	1104.5	1079.0	25.5	1079.0	25.5
Exubera utility increment = 0.04	1129.1	1079.0	50.1	1079.0	50.1
ICERs					
Exubera utility increment = 0.00			£1,720,752		£1,789,469
Exubera utility increment = 0.02			£65,362		£67,973
Exubera utility increment = 0.04			£33,314		£34,644
Age 50, 8-year diabetes duration, 2-year treatment delay, high Exubera use/cost					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£2,106,297	£600,770	£1,505,527	£541,127	£1,565,170
Cost of complications	£1,269,241	£1,281,452	–£12,211	£1,281,452	–£12,211
Total cost	**£3,375,538**	**£1,882,222**	**£1,493,316**	**£1,822,579**	**£1,552,959**
QALYs					
Exubera utility increment = 0.00	976.7	975.5	1.2	975.5	1.2
Exubera utility increment = 0.02	998.7	975.5	23.2	975.5	23.2
Exubera utility increment = 0.04	1020.8	975.5	45.3	975.5	45.3
ICERs					
Exubera utility increment = 0.00			£1,326,073		£1,379,037
Exubera utility increment = 0.02			£64,408		£66,981
Exubera utility increment = 0.04			£33,005		£34,324
Age 60, 12-year diabetes duration, 2-year treatment delay, high Exubera use/cost					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,586,143	£453,437	£1,132,706	£409,247	£1,176,896
Cost of complications	£1,103,531	£1,111,038	–£7,507	£1,111,038	–£7,507
Total cost	**£2,689,674**	**£1,564,475**	**£1,125,199**	**£1,520,285**	**£1,169,389**
QALYs					
Exubera utility increment = 0.00	769.8	768.0	1.8	768.0	1.8
Exubera utility increment = 0.02	786.3	768.0	18.3	768.0	18.3
Exubera utility increment = 0.04	802.9	768.0	34.9	768.0	34.9
ICERs					
Exubera utility increment = 0.00			£641,891		£667,100
Exubera utility increment = 0.02			£61,485		£63,900
Exubera utility increment = 0.04			£32,289		£33,557

TABLE 47 *Simulation B: 4-year relative treatment delay*

	Exubera	Basal–bolus	Difference	Premix	Difference
Age 40, 5-year diabetes duration, 4-year treatment delay, no HbA_{1c} drift					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,441,159	£930,543	£510,616	£640,124	£801,035
Cost of complications	£1,242,013	£1,253,443	–£11,430	£1,253,443	–£11,430
Total cost	**£2,683,172**	**£2,183,986**	**£499,186**	**£1,893,567**	**£789,605**
QALYs					
Exubera utility increment = 0.00	1077.0	1075.2	1.8	1075.2	1.8
Exubera utility increment = 0.02	1099.3	1075.2	24.1	1075.2	24.1
Exubera utility increment = 0.04	1121.6	1075.2	46.4	1075.2	46.4
ICERs					
Exubera utility increment = 0.00			£271,696		£429,766
Exubera utility increment = 0.02			£20,692		£32,731
Exubera utility increment = 0.04			£10,755		£17,013
Age 50, 8-year diabetes duration, 4-year treatment delay, no HbA_{1c} drift					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,289,386	£834,165	£455,221	£578,849	£710,537
Cost of complications	£1,291,276	£1,309,256	–£17,980	£1,309,256	–£17,980
Total cost	**£2,580,662**	**£2,143,421**	**£437,241**	**£1,888,105**	**£692,557**
QALYs					
Exubera utility increment = 0.00	972.4	970.1	2.3	970.1	2.3
Exubera utility increment = 0.02	992.2	970.1	22.1	970.1	22.1
Exubera utility increment = 0.04	1011.9	970.1	41.8	970.1	41.8
ICERs					
Exubera utility increment = 0.00			£190,964		£302,473
Exubera utility increment = 0.02			£19,828		£31,406
Exubera utility increment = 0.04			£10,457		£16,563
Age 60, 12-year diabetes duration, 4-year treatment delay, no HbA_{1c} drift					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£960,468	£624,369	£336,099	£444,810	£515,658
Cost of complications	£1,124,046	£1,138,747	–£14,701	£1,138,747	–£14,701
Total cost	**£2,084,514**	**£1,763,116**	**£321,398**	**£1,583,557**	**£500,957**
QALYs					
Exubera utility increment = 0.00	763.5	760.3	3.2	760.3	3.2
Exubera utility increment = 0.02	777.8	760.3	17.5	760.3	17.5
Exubera utility increment = 0.04	792.1	760.3	31.8	760.3	31.8
ICERs					
Exubera utility increment = 0.00			£101,356		£157,983
Exubera utility increment = 0.02			£18,379		£28,648
Exubera utility increment = 0.04			£10,106		£15,752

TABLE 48 *Simulation B: 50% initial adoption of Exubera, 40% of other therapy alternatives*

	Exubera	Basal–bolus	Difference	Premix	Difference
Age 40, 5-year diabetes duration, 2-year treatment delay, 50–40% initial adopters					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,545,858	£988,172	£557,686	£642,583	£903,275
Cost of complications	£1,213,265	£1,211,626	£1,639	£1,211,626	£1,639
Total cost	**£2,759,123**	**£2,199,798**	**£559,325**	**£1,854,209**	**£904,914**
QALYs					
Exubera utility increment = 0.00	1080.6	1080.3	0.3	1080.3	0.3
Exubera utility increment = 0.02	1105.8	1080.3	25.5	1080.3	25.5
Exubera utility increment = 0.04	1131.0	1080.3	50.7	1080.3	50.7
ICERs					
Exubera utility increment = 0.00			£1,585,801		£2,565,615
Exubera utility increment = 0.02			£21,928		£35,476
Exubera utility increment = 0.04			£11,040		£17,861
Age 50, 8-year diabetes duration, 2-year treatment delay, 50–40% initial adopters					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,395,184	£892,810	£502,374	£582,376	£812,808
Cost of complications	£1,265,874	£1,264,396	£1,478	£1,264,396	£1,478
Total cost	**£2,661,058**	**£2,157,206**	**£503,852**	**£1,846,772**	**£814,286**
QALYs					
Exubera utility increment = 0.00	977.4	977.0	0.4	977.0	0.4
Exubera utility increment = 0.02	1000.1	977.0	23.1	977.0	23.1
Exubera utility increment = 0.04	1022.7	977.0	45.7	977.0	45.7
ICERs					
Exubera utility increment = 0.00			£1,095,718		£1,770,815
Exubera utility increment = 0.02			£21,817		£35,259
Exubera utility increment = 0.04			£11,018		£17,807
Age 60, 12-year diabetes duration, 2-year treatment delay, 50–40% initial adopters					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,065,917	£683,498	£382,419	£450,119	£615,798
Cost of complications	£1,096,274	£1,100,180	–£3,906	£1,100,180	–£3,906
Total cost	**£2,162,191**	**£1,783,678**	**£378,513**	**£1,550,299**	**£611,892**
QALYs					
Exubera utility increment = 0.00	771.2	769.8	1.4	769.8	1.4
Exubera utility increment = 0.02	788.3	769.8	18.5	769.8	18.5
Exubera utility increment = 0.04	805.4	769.8	35.6	769.8	35.6
ICERs					
Exubera utility increment = 0.00			£266,035		£430,064
Exubera utility increment = 0.02			£20,402		£32,981
Exubera utility increment = 0.04			£10,607		£17,148

TABLE 49 *Simulation B: low Exubera use or cost*

	Exubera	Basal–bolus	Difference	Premix	Difference
Age 40, 5-year diabetes duration, 2-year treatment delay, low Exubera use/cost					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,393,433	£974,284	£419,149	£641,984	£751,449
Cost of complications	£1,216,854	£1,223,042	–£6,188	£1,223,042	–£6,188
Total cost	**£2,610,287**	**£2,197,326**	**£412,961**	**£1,865,026**	**£745,261**
QALYs					
Exubera utility increment = 0.00	1079.9	1079.0	0.9	1079.0	0.9
Exubera utility increment = 0.02	1104.5	1079.0	25.5	1079.0	25.5
Exubera utility increment = 0.04	1129.1	1079.0	50.1	1079.0	50.1
ICERs					
Exubera utility increment = 0.00			£425,460		£767,818
Exubera utility increment = 0.02			£16,161		£29,165
Exubera utility increment = 0.04			£8,237		£14,865
Age 50, 8-year diabetes duration, 2-year treatment delay, low Exubera use/cost					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,256,090	£878,854	£377,236	£581,704	£674,386
Cost of complications	£1,269,241	£1,281,452	–£12,211	£1,281,452	–£12,211
Total cost	**£2,525,331**	**£2,160,306**	**£365,025**	**£1,863,156**	**£662,175**
QALYs					
Exubera utility increment = 0.00	976.7	975.5	1.2	975.5	1.2
Exubera utility increment = 0.02	998.7	975.5	23.2	975.5	23.2
Exubera utility increment = 0.04	1020.8	975.5	45.3	975.5	45.3
ICERs					
Exubera utility increment = 0.00			£324,144		£588,015
Exubera utility increment = 0.02			£15,743		£28,560
Exubera utility increment = 0.04			£8,067		£14,635
Age 60, 12-year diabetes duration, 2-year treatment delay, low Exubera use/cost					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,044,169	£669,361	£374,808	£449,204	£594,965
Cost of complications	£1,103,531	£1,111,038	–£7,507	£1,111,038	–£7,507
Total cost	**£2,147,700**	**£1,780,399**	**£367,301**	**£1,560,242**	**£587,458**
QALYs					
Exubera utility increment = 0.00	769.8	768.0	1.8	768.0	1.8
Exubera utility increment = 0.02	786.3	768.0	18.3	768.0	18.3
Exubera utility increment = 0.04	802.9	768.0	34.9	768.0	34.9
ICERs					
Exubera utility increment = 0.00			£209,533		£335,126
Exubera utility increment = 0.02			£20,070		£32,101
Exubera utility increment = 0.04			£10,540		£16,857

TABLE 50 *Simulation B: high Exubera use or cost*

	Exubera	Basal–bolus	Difference	Premix	Difference
Age 40, 5-year diabetes duration, 2-year treatment delay, high Exubera use/cost					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,587,532	£974,284	£613,248	£641,984	£945,548
Cost of complications	£1,216,854	£1,223,042	–£6,188	£1,223,042	–£6,188
Total cost	**£2,804,386**	**£2,197,326**	**£607,060**	**£1,865,026**	**£939,360**
QALYs					
Exubera utility increment = 0.00	1079.9	1079.0	0.9	1079.0	0.9
Exubera utility increment = 0.02	1104.5	1079.0	25.5	1079.0	25.5
Exubera utility increment = 0.04	1129.1	1079.0	50.1	1079.0	50.1
ICERs					
Exubera utility increment = 0.00			£625,536		£967,894
Exubera utility increment = 0.02			£23,761		£36,765
Exubera utility increment = 0.04			£12,110		£18,738
Age 50, 8-year diabetes duration, 2-year treatment delay, high Exubera use/cost					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,430,356	£878,854	£551,502	£581,704	£848,652
Cost of complications	£1,269,241	£1,281,452	–£12,211	£1,281,452	–£12,211
Total cost	**£2,699,597**	**£2,160,306**	**£539,291**	**£1,863,156**	**£836,441**
QALYs					
Exubera utility increment = 0.00	976.7	975.5	1.2	975.5	1.2
Exubera utility increment = 0.02	998.7	975.5	23.2	975.5	23.2
Exubera utility increment = 0.04	1020.8	975.5	45.3	975.5	45.3
ICERs					
Exubera utility increment = 0.00			£478,893		£742,764
Exubera utility increment = 0.02			£23,260		£36,076
Exubera utility increment = 0.04			£11,919		£18,487
Age 60, 12-year diabetes duration, 2-year treatment delay, high Exubera use/cost					
Per 100 patients over 20 years					
Costs					
Cost of treatment	£1,086,365	£669,361	£417,004	£449,204	£637,161
Cost of complications	£1,103,531	£1,111,038	–£7,507	£1,111,038	–£7,507
Total cost	**£2,189,896**	**£1,780,399**	**£409,497**	**£1,560,242**	**£629,654**
QALYs					
Exubera utility increment = 0.00	769.8	768.0	1.8	768.0	1.8
Exubera utility increment = 0.02	786.3	768.0	18.3	768.0	18.3
Exubera utility increment = 0.04	802.9	768.0	34.9	768.0	34.9
ICERs					
Exubera utility increment = 0.00			£233,605		£359,197
Exubera utility increment = 0.02			£22,376		£34,406
Exubera utility increment = 0.04			£11,751		£18,068

Model parameters

The characteristics of the cohorts modelled are as outlined within the main body of the report. As noted within this, the modelling of the report does not attempt to identify the distribution of the age and duration of diabetes within the cohort that is switching to insulin therapy. In contrast to the industry submission, three plausible cohorts are modelled:

- age 40 with 5 years' duration of diabetes
- age 50 with 8 years' duration of diabetes
- age 60 with 12 years' duration of diabetes.

A cross-check of a cohort is also performed as a sensitivity analysis. It is not immediately clear what the distribution of activity levels and smoking status is assumed within the industry submission. Within the modelling of the report 60% are assumed to be of low physical activity, 40% medium activity and 0% high activity. As smoking excludes the use of Exubera, the distribution of smoking status has been assumed to be 35% being former smokers and 65% non-smokers. The other patient characteristics are the same within the report and the industry submission (*Table 51*).

The utility detriments arising from the complications of diabetes differ in some instances between the report and the industry submission. Utility detriments within the modelling are informed by the detriments reported across the studies of Bagust and Beale,[98] Clarke and colleagues[100] and Coffey and colleagues.[97]

The principal differences occur in end-stage renal disease, minor transplantation and blindness in one eye (*Table 52*). For end-stage renal disease and blindness in one eye it was felt that the value

TABLE 51

Population parameter	Value (SD)	Source
Mean SBP	140.13 (20.49)	HSE 2003 data set
Hypertension prevalence	0.12	HSE 2003 data set
Mean SBP of the hypertensive population	170.96 (13.37)	HSE 2003 data set
Mean SBP of the normotensive population	132.86 (14.12)	HSE 2003 data set
Mean triglyceride level	2.19 (1.78)	HSE 2003 data set
Mean LDL level	3.12 (0.71)	HSE 2003 data set
Mean HDL level	1.30 (0.36)	HSE 2003 data set
Mean total cholesterol level	5.17 (1.10)	HSE 2003 data set
Mean BMI	30.50 (5.70)	HSE 2003 data set

HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

TABLE 52

	Industry submission	Report model	Chronic
Diabetes	–0.186	–0.186	Yes
Complications			
Myocardial infarction	–0.055	–0.055	No
Coronary heart disease	–0.090	–0.090	Yes
Heart failure	–0.108	–0.100	Yes
Stroke	–0.164	–0.100	Yes
Dialysis	–0.078	–0.078	Yes
End-stage renal disease	–0.110	–0.140	Yes
Transplantation	–0.078	–0.078	No
Lower extremity disease			
Neuropathy	–0.065	–0.065	Yes
PVD	–0.065	–0.050	Yes
Foot ulcers	–0.099	–0.100	Yes
Amputation (minor)	–0.280	–0.100	Yes
Amputation (major)	–0.280	–0.280	Yes
Retinopathy			
Blindness in one eye	–0.074	–0.094	Yes
Obesity BMI > 30	–0.021	–0.021	Yes

TABLE 53

(a) Scenario A		(b) Scenario B	
All initially		**All initially**	
Metformin 2 g/day	£37.54	Metformin 2 g/day	£37.54
Gliclazide 160 mg/day	£66.31	Glargine 0.4 U/kg/day	£318.86
Monitoring strips 1	£109.50	Monitoring strips 1	£109.50
	£213.35		**£465.91**
switching to		switching to	
Option A 1		**Option B 1**	
Metformin 2 g/day	£37.54	Metformin 2 g/day	£37.54
Gliclazide 160 mg/day	£66.31	Glargine 0.2 U/kg/day	£159.43
Glargine 0.4 U/kg/day	£318.86	Lispro humalog 0.2 U/kg/day	£120.43
Monitoring strips 1	£109.50	Monitoring strips 4	£438.00
	£532.22		**£755.41**
or		or	
Option A 2		**Option B 2**	
Metformin 2 g/day	£37.54	Metformin 2 g/day	£37.54
Premix mixtard	£219.44	Premix mixtard	£219.44
Monitoring strips 2	£219.00	Monitoring strips 2	£219.00
	£475.99		**£475.99**
or		or	
Option A 3		**Option B 3**	
Metformin 2 g/day	£37.54	Metformin 2 g/day	£37.54
Exubera 0.15 mg/kg/day	£1,067.98	Glargine 0.2 U/kg/day	£159.43
Spirometer test	£25.00	Exubera 0.075 mg/kg/day	£533.99
Monitoring strips 3	£328.50	Spirometer test	£25.00
	£1,459.02	Monitoring strips 4	£438.00
			£1,193.96

TABLE 54

Complication	Cost year 1	Cost year 1+	Source
Severe hypoglycaemic event	£580	–	NHS reference costs 2004, Appendix 4[174]
Hypoglycaemic event with seizure or coma	£580	–	NHS reference costs 2004, Appendix 4[174]
Non-proliferative retinopathy	£89	£55	NHS reference costs 2004, Appendix 4[174]
Photocoagulation	£556	–	NHS reference costs 2004, Appendix 4[174]
Proliferative retinopathy	£89	£55	NHS reference costs 2004, Appendix 4[174]
Macular oedema	£89	£55	NHS reference costs 2004, Appendix 4[174]
Vitreous haemorrhage	£89	£55	NHS reference costs 2004, Appendix 4[174]
Blind in one eye	£936	£302	Clarke *et al.*, 2003[175]
Cataract	£793	–	NHS reference costs 2004, Appendix 4[174]
Cataract extraction	£717	–	NHS reference costs 2004, Appendix 4[174]
Myocardial infarction	£4,367	£498	Clarke *et al.*, 2003[175]
Angina	£2,102	£799	Clarke *et al.*, 2003;[175] BNF 49[176]
Heart failure	£2,383	£831	Clarke *et al.*, 2003;[175] BNF 49[176]
Stroke	£2,540	£267	Clarke *et al.*, 2003[175]
Microalbuminuria	£108	£108	Gordois *et al.*, 2004[177]
Macroalbuminuria	£6,321	£6,321	Gordois *et al.*, 2004[177]
End-stage renal disease	£29,013	£29,013	Gordois *et al.*, 2004[177]
Transplantation	£19,787	£240	Gordois *et al.*, 2004;[177] NHS reference costs 2004, Appendix 4[174]
Clinically confirmed neuropathy	£162	–	Gordois *et al.*, 2003[178]
Clinical neuropathy	£162	–	Gordois *et al.*, 2003[178]
Peripheral arterial disease and/or neuropathy	£162	–	Gordois *et al.*, 2003[178]
Amputation, minor	£9,077	£322	Clarke *et al.*, 2003[175]
Amputation, major	£9,077	£322	Clarke *et al.*, 2003[175]
Diabetic foot syndrome	£3,188		Gordois *et al.*, 2003[178]

within the industry submission was unduly conservative for Exubera and not entirely reflective of the values within the three main studies identified. While the quality of life detriment for a major amputation within the industry submission of –0.280 was felt to be appropriate, it seemed unreasonably large for a minor amputation and was consequently reduced to –0.100.

Drug costs are drawn from the British National Formulary (BNF), with Exubera costs being drawn from the industry submission (*Table 53*).

The costs of complications are the same across the industry submission and report modelling (*Table 54*).

In common with the industry submission, the baseline probability of complications was assumed to be zero. This will be an underestimate to some extent, given that many patients are diagnosed with diabetes due to presenting with complications. There is no ready data set for the prevalence of complications within the group of patients likely to be newly prescribed Exubera, but this assumption is likely to overestimate the benefits of Exubera to a small extent. Given the results of the modelling and the small impact on the reduction in the overall rate of complications from Exubera use, this was felt to be a justifiable assumption.

Appendix 6

Costs of inhaled and comparator regimens

TABLE 55 *Base case (Exubera 2.75 IU/mg)*

Patient weight (kg)	84		
Monitoring per 50 strip	£15.00		
Annual monitoring per strip	£109.50		
Metformin non-prop 84*500 mg	£2.16		
Gliclazide non-prop 60*80 mg	£5.45		
Glargine (Optiset) 1500 U	£39.00		
Lispro humalog pen 1500 U	£29.46		
Mixtard 30 1500 IU	£26.84		
Exubera annual per mg	£84.76		
Spirometer test	£25.00		
Scenario B		**Scenario A**	
All initially		*All initially*	
Metformin 2 g/day	£37.54	Metformin 2 g/day	£37.54
Glargine 0.4 U/kg/day	£318.86	Gliclazide 160 mg/day	£66.31
Monitoring strips 1	£109.50	Monitoring strips 1	£109.50
	£465.91		**£213.35**
switching to		switching to	
Option A 1		*Option A 1*	
Metformin 2 g/day	£37.54	Metformin 2 g/day	£37.54
Glargine 0.2 U/kg/day	£159.43	Gliclazide 160 mg/day	£66.31
Lispro humalog 0.2 U/kg/day	£120.43	Glargine 0.4 U/kg/day	£318.86
Monitoring strips 4	£438.00	Monitoring strips 1	£109.50
	£755.41		**£532.22**
Option A 2		*Option A 2*	
Metformin 2 g/day	£37.54	Metformin 2 g/day	£37.54
Premix mixtard	£219.44	Premix mixtard	£219.44
Monitoring strips 2	£219.00	Monitoring strips 2	£219.00
	£475.99		**£475.99**
or		or	
Option B		*Option B*	
Metformin 2 g/day	£37.54	Metformin 2 g/day	£37.54
Glargine 0.2 U/kg/day	£159.43		
Exubera 0.075 mg/kg/day	£533.99	Exubera 0.15 mg/kg/day	£1,067.98
Spirometer test	£25.00	Spirometer test	£25.00
Monitoring strips 4	£438.00	Monitoring strips 3	£328.50
	£1,193.96		**£1,459.02**
Net costs	**Net B**		**Net A**
Initial to A 1	£289.50		£318.86
Initial to A 2	£10.08		£262.64
Initial to B	£728.06		£1,245.67
A 1 relative to B	£438.56		£926.81
A 2 relative to B	£717.98		£983.04

TABLE 56 *Type 1 patient: cost comparison of standard and Exubera (BNF 51[179])*

Patient weight (kg)	84									
Exubera blister reusable	No									
Exubera annual per mg	£84.76									
Spirometer test	£25.00									
Daily insulin requirement (IU/kg)	0.40	0.50	0.60	0.70	0.80	0.90	1.00	1.10	1.20	1.30
of which basal	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
of which bolus	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Basal daily requirement (IU)	17	21	25	29	34	38	42	46	50	55
Bolus daily requirement (IU)	17	21	25	29	34	38	42	46	50	55
Total IU per day	34	42	50	59	67	76	84	92	101	109
Bolus per meal requirement (IU)	5.6	7	8.4	9.8	11.2	12.6	14	15.4	16.8	18.2
Exubera conversion rate (IU/mg)	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75
Exubera 1-mg blisters per meal	3	3	4	4	5	5	6	6	7	7
Exubera 1-mg blisters per day	9.0	9.0	12.0	12.0	15.0	15.0	18.0	18.0	21.0	21.0
Subcutaneous cost										
Glargine										
Insulin	£159.43	£199.29	£239.15	£279.01	£318.86	£358.72	£398.58	£438.44	£478.30	£518.15
Pen	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33
Needles	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28
Lispro humalog										
Insulin	£120.43	£150.54	£180.65	£210.76	£240.86	£270.97	£301.08	£331.19	£361.30	£391.41
Pen	£4.90	£4.90	£4.90	£4.90	£4.90	£4.90	£4.90	£4.90	£4.90	£4.90
Needles	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28
Monitoring strips	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00
Total	**£792.66**	**£862.62**	**£932.59**	**£1,002.56**	**£1,072.52**	**£1,142.49**	**£1,212.46**	**£1,282.42**	**£1,352.39**	**£1,422.35**
Subcutaneous/Exubera cost										
Glargine										
Insulin	£159.43	£199.29	£239.15	£279.01	£318.86	£358.72	£398.58	£438.44	£478.30	£518.15
Pen	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33
Needles	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28
Exubera cost	£762.84	£762.84	£1,017.12	£1,017.12	£1,271.40	£1,271.40	£1,525.69	£1,525.69	£1,779.97	£1,779.97
Monitoring strips	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00
Spirometer testing	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00
Total	**£1,423.89**	**£1,463.75**	**£1,757.89**	**£1,797.74**	**£2,091.88**	**£2,131.74**	**£2,425.88**	**£2,465.74**	**£2,759.88**	**£2,799.73**
Exubera additional cost	**£631.23**	**£601.12**	**£825.29**	**£795.19**	**£1,019.36**	**£989.25**	**£1,213.42**	**£1,183.32**	**£1,407.49**	**£1,377.38**
Required QoL increment at £20,000	0.032	0.030	0.041	0.040	0.051	0.049	0.061	0.059	0.070	0.069
Required QoL increment at £30,000	0.021	0.020	0.028	0.027	0.034	0.033	0.040	0.039	0.047	0.046

TABLE 57 *Type 2 patient: cost comparison of standard and Exubera (BNF 51[179]) – scenario A: gliclazide plus glargine*

Patient weight (kg)	84									
Exubera blisters reusable	No									
Daily insulin requirement (IU/kg)	0.40	0.50	0.60	0.70	0.80	0.90	1.00	1.10	1.20	1.30
Total IU per day	34	42	50	59	67	76	84	92	101	109
Bolus per meal requirement (IU)	11.2	14	16.8	19.6	22.4	25.2	28	30.8	33.6	36.4
Exubera conversion rate (IU/mg)	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75
Exubera 1-mg blisters per meal	5	6	7	8	9	10	11	12	13	14
Exubera 1-mg blisters per day	15.0	18.0	21.0	24.0	27.0	30.0	33.0	36.0	39.0	42.0
Subcutaneous cost										
Glargine										
Insulin	£318.86	£398.58	£478.30	£558.01	£637.73	£717.44	£797.16	£876.88	£956.59	£1,036.31
Pen	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33
Needles	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28
Gliclazide	£66.31	£66.31	£66.31	£66.31	£66.31	£66.31	£66.31	£66.31	£66.31	£66.31
Monitoring strips	£109.50	£109.50	£109.50	£109.50	£109.50	£109.50	£109.50	£109.50	£109.50	£109.50
Total	**£533.29**	**£613.00**	**£692.72**	**£772.43**	**£852.15**	**£931.87**	**£1,011.58**	**£1,091.30**	**£1,171.01**	**£1,250.73**
Subcutaneous/Exubera cost										
Exubera cost	£1,271.40	£1,525.69	£1,779.97	£2,034.25	£2,288.53	£2,542.81	£2,797.09	£3,051.37	£3,305.65	£3,559.93
Monitoring strips	£328.50	£328.50	£328.50	£328.50	£328.50	£328.50	£328.50	£328.50	£328.50	£328.50
Spirometer testing	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00
Total	**£1,624.90**	**£1,879.19**	**£2,133.47**	**£2,387.75**	**£2,642.03**	**£2,896.31**	**£3,150.59**	**£3,404.87**	**£3,659.15**	**£3,913.43**
Exubera additional cost	**£1,091.62**	**£1,266.18**	**£1,440.75**	**£1,615.31**	**£1,789.88**	**£1,964.44**	**£2,139.01**	**£2,313.57**	**£2,488.14**	**£2,662.70**
Required QoL increment at £20,000	0.055	0.063	0.072	0.081	0.089	0.098	0.107	0.116	0.124	0.133
Required QoL increment at £30,000	0.036	0.042	0.048	0.054	0.060	0.065	0.071	0.077	0.083	0.089

TABLE 58 *Type 2 patient: cost comparison of standard and Exubera (BNF 51[179]) – scenario A: premix*

Patient weight (kg)	84									
Exubera blisters reusable	No									
Daily insulin requirement (IU/kg)	0.40	0.50	0.60	0.70	0.80	0.90	1.00	1.10	1.20	1.30
of which basal	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
of which bolus	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Basal daily requirement (IU)	17	21	25	29	34	38	42	46	50	55
Bolus daily requirement (IU)	17	21	25	29	34	38	42	46	50	55
Total IU per day	34	42	50	59	67	76	84	92	101	109
Bolus per meal requirement (IU)	11.2	14	16.8	19.6	22.4	25.2	28	30.8	33.6	36.4
Exubera conversion rate (IU/mg)	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75
Exubera 1-mg blisters per meal	5	6	7	8	9	10	11	12	13	14
Exubera 1-mg blisters per day	15.0	18.0	21.0	24.0	27.0	30.0	33.0	36.0	39.0	42.0
Subcutaneous cost										
Lispro humalog										
Insulin	£219.44	£274.30	£329.17	£384.03	£438.89	£493.75	£548.61	£603.47	£658.33	£713.19
Pen	£9.82	£9.82	£9.82	£9.82	£9.82	£9.82	£9.82	£9.82	£9.82	£9.82
Needles	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28
Monitoring strips	£219.00	£219.00	£219.00	£219.00	£219.00	£219.00	£219.00	£219.00	£219.00	£219.00
Total	**£479.54**	**£534.41**	**£589.27**	**£644.13**	**£698.99**	**£753.85**	**£808.71**	**£863.57**	**£918.43**	**£973.29**
Subcutaneous/Exubera cost										
Exubera cost	£1,271.40	£1,525.69	£1,779.97	£2,034.25	£2,288.53	£2,542.81	£2,797.09	£3,051.37	£3,305.65	£3,559.93
Monitoring strips	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00
Spirometer testing	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00
Total	**£1,734.40**	**£1,988.69**	**£2,242.97**	**£2,497.25**	**£2,751.53**	**£3,005.81**	**£3,260.09**	**£3,514.37**	**£3,768.65**	**£4,022.93**
Exubera additional cost	**£1,254.86**	**£1,454.28**	**£1,653.70**	**£1,853.12**	**£2,052.54**	**£2,251.96**	**£2,451.38**	**£2,650.80**	**£2,850.22**	**£3,049.64**
Required QoL increment at £20,000	0.063	0.073	0.083	0.093	0.103	0.113	0.123	0.133	0.143	0.152
Required QoL increment at £30,000	0.042	0.048	0.055	0.062	0.068	0.075	0.082	0.088	0.095	0.102

TABLE 59 *Type 2 patient: cost comparison of standard and Exubera (BNF 51[179]) – scenario B: glargine plus lispro*

Patient weight (kg)	84									
Exubera blister reusable	No									
Exubera annual per mg	£84.76									
Spirometer test	£25.00									
Daily insulin requirement (IU/kg)	0.40	0.50	0.60	0.70	0.80	0.90	1.00	1.10	1.20	1.30
of which basal	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
of which bolus	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Basal daily requirement (IU)	17	21	25	29	34	38	42	46	50	55
Bolus daily requirement (IU)	17	21	25	29	34	38	42	46	50	55
Total IU per day	34	42	50	59	67	76	84	92	101	109
Bolus per meal requirement (IU)	5.6	7	8.4	9.8	11.2	12.6	14	15.4	16.8	18.2
Exubera conversion rate (IU/mg)	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75
Exubera 1-mg blisters per meal	3	3	4	4	5	5	6	6	7	7
Exubera 1-mg blisters per day	9.0	9.0	12.0	12.0	15.0	15.0	18.0	18.0	21.0	21.0
Subcutaneous cost										
Glargine										
Insulin	£159.43	£199.29	£239.15	£279.01	£318.86	£358.72	£398.58	£438.44	£478.30	£518.15
Pen	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33
Needles	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28
Lispro humalog										
Insulin	£120.43	£150.54	£180.65	£210.76	£240.86	£270.97	£301.08	£331.19	£361.30	£391.41
Pen	£4.90	£4.90	£4.90	£4.90	£4.90	£4.90	£4.90	£4.90	£4.90	£4.90
Needles	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28
Monitoring strips	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00
Total	**£792.66**	**£862.62**	**£932.59**	**£1,002.56**	**£1,072.52**	**£1,142.49**	**£1,212.46**	**£1,282.42**	**£1,352.39**	**£1,422.35**
Subcutaneous/Exubera cost										
Glargine										
Insulin	£159.43	£199.29	£239.15	£279.01	£318.86	£358.72	£398.58	£438.44	£478.30	£518.15
Pen	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33
Needles	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28
Exubera cost	£762.84	£762.84	£1,017.12	£1,017.12	£1,271.40	£1,271.40	£1,525.69	£1,525.69	£1,779.97	£1,779.97
Monitoring strips	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00
Spirometer testing	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00
Total	**£1,423.89**	**£1,463.75**	**£1,757.89**	**£1,797.74**	**£2,091.88**	**£2,131.74**	**£2,425.88**	**£2,465.74**	**£2,759.88**	**£2,799.73**
Exubera additional cost	**£631.23**	**£601.12**	**£825.29**	**£795.19**	**£1,019.36**	**£989.25**	**£1,213.42**	**£1,183.32**	**£1,407.49**	**£1,377.38**
Required QoL increment at £20,000	0.032	0.030	0.041	0.040	0.051	0.049	0.061	0.059	0.070	0.069
Required QoL increment at £30,000	0.021	0.020	0.028	0.027	0.034	0.033	0.040	0.039	0.047	0.046

TABLE 60 *Type 2 patient: cost comparison of standard and Exubera (BNF 51[179]) – scenario B: premix*

Patient weight (kg)	84									
Exubera blister reusable	No									
Daily insulin requirement (IU/kg)	0.40	0.50	0.60	0.70	0.80	0.90	1.00	1.10	1.20	1.30
of which basal	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
of which bolus	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Basal daily requirement (IU)	17	21	25	29	34	38	42	46	50	55
Bolus daily requirement (IU)	17	21	25	29	34	38	42	46	50	55
Total IU per day	34	42	50	59	67	76	84	92	101	109
Bolus per meal requirement (IU)	5.6	7	8.4	9.8	11.2	12.6	14	15.4	16.8	18.2
Exubera conversion rate (IU/mg)	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75
Exubera 1-mg blisters per meal	3	3	4	4	5	5	6	6	7	7
Exubera 1-mg blisters per day	9.0	9.0	12.0	12.0	15.0	15.0	18.0	18.0	21.0	21.0
Subcutaneous cost										
Mixtard										
Insulin	£219.44	£274.30	£329.17	£384.03	£438.89	£493.75	£548.61	£603.47	£658.33	£713.19
Pen	£9.82	£9.82	£9.82	£9.82	£9.82	£9.82	£9.82	£9.82	£9.82	£9.82
Needles	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28
Monitoring strips	£219.00	£219.00	£219.00	£219.00	£219.00	£219.00	£219.00	£219.00	£219.00	£219.00
Total	**£479.54**	**£534.41**	**£589.27**	**£644.13**	**£698.99**	**£753.85**	**£808.71**	**£863.57**	**£918.43**	**£973.29**
Subcutaneous/Exubera cost										
Glargine										
Insulin	£159.43	£199.29	£239.15	£279.01	£318.86	£358.72	£398.58	£438.44	£478.30	£518.15
Pen	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33	£7.33
Needles	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28	£31.28
Exubera cost	£762.84	£762.84	£1,017.12	£1,017.12	£1,271.40	£1,271.40	£1,525.69	£1,525.69	£1,779.97	£1,779.97
Monitoring strips	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00	£438.00
Spirometer testing	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00
Total	**£1,423.89**	**£1,463.75**	**£1,757.89**	**£1,797.74**	**£2,091.88**	**£2,131.74**	**£2,425.88**	**£2,465.74**	**£2,759.88**	**£2,799.73**
Exubera additional cost	**£944.34**	**£929.34**	**£1,168.62**	**£1,153.62**	**£1,392.89**	**£1,377.89**	**£1,617.17**	**£1,602.17**	**£1,841.44**	**£1,826.44**
Required QoL increment at £20,000	0.047	0.046	0.058	0.058	0.070	0.069	0.081	0.080	0.092	0.091
Required QoL increment at £30,000	0.031	0.031	0.039	0.038	0.046	0.046	0.054	0.053	0.061	0.061

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We look forward to hearing from you.

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