1 Guidance

1.1 Inhaled insulin is not recommended for the routine treatment of people with type 1 or type 2 diabetes mellitus.

1.2 Inhaled insulin may be used as a treatment option for people with type 1 or type 2 diabetes mellitus who show evidence of poor glycaemic control despite other therapeutic interventions (including, where appropriate, diet, oral hypoglycaemic agents [OHAs] and subcutaneous insulin) and adequate educational support, and who are unable to initiate or intensify pre-prandial subcutaneous insulin therapy because of either:

- a marked and persistent fear of injections that meet DSM-IV criteria for specific phobia ‘blood injection injury type’ diagnosed by a diabetes specialist or mental health professional

- severe and persistent problems with injection sites (for example, as a consequence of lipohypertrophy) despite support with injection site rotation.

1.3 In patients receiving inhaled insulin under the circumstances set out in section 1.2, treatment should only be continued beyond 6 months, and in the longer term, if there is evidence of a sustained improvement in glycated haemoglobin
(HbA1c) that is judged to be clinically relevant to the individual patient’s overall risk of developing long-term complications of diabetes.

1.4 Initiation of inhaled insulin treatment and monitoring of response should be carried out at a specialist diabetes centre. The responsible clinician should discuss the risks and benefits of inhaled insulin with the patient so that an informed choice can be made regarding appropriate options for diabetes management, including psychological support and therapy for needle phobia if necessary.

1.5 Data on the use of inhaled insulin according to this guidance should be collected as part of a coordinated prospective observational study. The data collected should include individual patient outcomes, adverse events and measurements of lung function.

2 Clinical need and practice

2.1 Diabetes mellitus is a chronic metabolic disorder caused by defects in insulin secretion and action. It is associated with acute metabolic disturbances such as hyperglycaemia (high blood glucose) and ketoacidosis (severe insulin deficiency which can result in coma). If prolonged, hyperglycaemia can cause microvascular and macrovascular damage. Microvascular complications result from damage to small blood vessels and include diabetic retinopathy (visual impairment), nephropathy (kidney damage), neuropathy (nerve damage) and foot ulceration. Macrovascular complications result from damage to large blood vessels and include heart disease, cerebrovascular disease and peripheral vascular disease.

2.2 It is estimated that there are over 2 million people with diabetes in the UK, of whom approximately 80% have type 2 diabetes. Around 90,000 people are newly diagnosed with diabetes each year. Type 1 diabetes usually affects younger people. Type 2 diabetes usually appears in people over the age of 40 years, but it often appears earlier in South Asian and African-Caribbean people.
2.3 The key goal in the management of diabetes is to achieve blood glucose levels as near normal as possible. Current guidelines recommend that treatment should aim to achieve a blood level of glycated haemoglobin (HbA1c) of between 6.5% and 7.5%, although it is acknowledged that such targets may not be achieved in all patients.

2.4 In type 1 diabetes, the pancreas makes little or no insulin, and individuals usually depend on daily insulin injections to survive. There are three main types of insulin preparations: (1) short-acting, which have a relatively rapid onset of action and are injected just before meals ('pre-prandial' injections); (2) intermediate acting; and (3) long-acting, which have a slower onset of action and act for long periods, meeting an individual's background (round-the-clock) needs. The duration of action of a particular type of insulin varies considerably from one patient to another, and needs to be assessed individually. Insulin is given by subcutaneous injection into the layer of tissue immediately beneath the skin. Short-acting insulins can also be given by continuous subcutaneous infusion using a portable infusion pump. This device delivers a continuous basal insulin infusion and patient-activated bolus doses at meal times.

2.5 NICE guidelines state that the insulin regimen for people with type 1 diabetes should be tailored to meet the needs of the individual, including taking into account preference for number of injections. People with type 1 diabetes often need to adjust their dosage on a day-to-day basis in order to achieve optimal control. A common management strategy for type 1 diabetes is the basal–bolus regimen, which involves the use of a short-acting insulin before each meal (the ‘bolus’ or mealtime dose), and a long-acting insulin at bedtime (the ‘basal’ dose). Typically, doses of insulin at mealtimes change to reflect a given meal's carbohydrate content. Alternatively, pre-mixed insulin regimens can be used, which contain a fixed mixture of short- and intermediate-acting insulin; this may be more convenient but cannot be adjusted easily. Under certain circumstances, continuous subcutaneous insulin infusion via an insulin
pump may be used. This provides the opportunity to vary both mealtime doses and basal infusion rates.

2.6 Type 2 diabetes results from reduced insulin production and/or reduced tissue sensitivity to insulin (insulin resistance). Type 2 diabetes is managed initially through diet and exercise. Most individuals require oral hypoglycaemic agents (OHAs) to maintain satisfactory blood glucose levels. When the disease progresses further, insulin therapy may be necessary, and most patients with type 2 diabetes ultimately require insulin therapy. The 2002 NICE guideline on the management of blood glucose in people with type 2 diabetes concluded that there was little research evidence available about optimal insulin regimens and recommended that local experience, patient preference and relative costs should determine the choice of insulin type and regimen.

2.7 Some people with diabetes experience problems with insulin injections. A recent study identified problems related to the frequency of injections, locating suitable injection sites, pain, fear of needles and a dislike of injecting in public.

3 The technology

3.1 Inhaled insulin (Exubera, Pfizer Ltd) is an inhaled, rapid-acting, dry-powder, human insulin produced by recombinant DNA technology. It may be administered before meals as part of a daily treatment regimen that also includes injected long-acting insulin or OHAs. It has a UK marketing authorisation for the treatment of adults with type 1 diabetes, in addition to long- or intermediate-acting subcutaneous insulin, for whom the potential benefits of inhaled insulin outweigh the safety concerns. It also has a UK marketing authorisation for the treatment of adults with type 2 diabetes not adequately controlled with OHAs and requiring insulin therapy.

3.2 Inhaled insulin is administered into the lung using a specifically designed hand-held inhaler device. This allows the insulin to be delivered to the alveoli in the lungs, from where it is absorbed into the bloodstream.
3.3 The most commonly observed side effects of inhaled insulin are hypoglycaemia and mild cough, the latter of which appears to decrease over time. There is also concern about whether lung damage might occur with long-term use. It is stated in the ‘Summary of product characteristics’ (SPC) that people with diabetes must have stopped smoking at least 6 months before starting treatment and must not smoke during therapy. Exubera is contraindicated in people with poorly controlled, unstable or severe asthma, or severe chronic obstructive pulmonary disease. The SPC also states that Exubera should not be used during pregnancy. For full details of side effects and contraindications, see the SPC.

3.4 For this appraisal, the estimated cost of the inhaled insulin regimens were taken from the manufacturer’s submission, which assumed that people with diabetes would need to receive 0.15 mg of insulin per kilogram of body weight per day. Using average weights of 76.5 kg and 83.7 kg for people with type 1 and type 2 diabetes respectively, a dosage of 13 mg/day and a unit cost of £0.23/mg, the annual cost per person was estimated to be £1102. This cost was provided in the manufacturer’s submission and includes the device. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

4.1.1 The Assessment Group identified five randomised controlled trials (RCTs) in type 1 diabetes and two in type 2 diabetes. The manufacturer identified the same studies in type 1 and type 2 diabetes. In addition, the manufacturer added one Phase II trial and one unpublished study in type 1 diabetes. The duration of the seven studies ranged from 12 to 52 weeks, and a total of 2204 people were enrolled. All studies included people who were stable on their
current insulin regimen (entry HbA1c level was in the range 5–11%) and who used at least two injections of insulin per day. None of the studies compared inhaled insulin with continuous subcutaneous infusion or with regimens using rapid-acting insulin analogues. Only two studies compared regimens, which varied only in terms of bolus insulin, with basal insulin being kept standard between the inhaled and control groups. Most studies gave little or no detail about the patients recruited and had a large number of exclusion criteria.

**Diabetes control**

4.1.2 The primary outcome measure was change in HbA1c. This reflected the average blood glucose level over the preceding 3 months, as a measure of how well the diabetes was controlled.

4.1.3 In six RCTs in type 1 diabetes, the relative risk (RR) of a HbA1c level of less than 7.0% with inhaled insulin compared with short-acting subcutaneous insulin was: 0.80 (95% CI, 0.33 to 1.91), 0.99 (95% CI, 0.59 to 1.66); 1.06 (95% CI, 0.70 to 1.59); 0.73 (95% CI, 0.60 to 0.88); 1.53 (95% CI, 0.90 to 2.60); and 0.77 (95% C.I, 0.57 to 1.03). In the remaining study, the mean change from baseline HbA1c was +0.1% for short-acting subcutaneous insulin and −0.3% for inhaled insulin.

4.1.4 The manufacturer undertook a meta-analysis of six of the identified RCTs in type 1 diabetes. The pooled RR associated with attaining a HbA1c level of less than 7.0% with inhaled insulin compared with short-acting subcutaneous insulin was 0.89 (95% CI, 0.72 to 1.10). The Assessment Group undertook a meta-analysis of two of these trials that used the same basal insulin regimen and found that the weighted mean difference in change in HbA1c level from baseline between the two groups was 0.09% (95% CI, −0.20 to 0.37).

4.1.5 In the two RCTs described in the manufacturer’s submission that involved people with poorly controlled type 2 diabetes (HbA1c levels of 8–11%) despite diet and exercise or OHAs, inhaled insulin alone led to a statistically significant decrease in HbA1c levels compared with OHAs alone. One study
showed a decrease in HbA1c levels of 2.3% with inhaled insulin and 1.4% with OHAs, the other showed a decrease in HbA1c levels of 1.53% with inhaled insulin and 0.3% with OHAs.

4.1.6 In the first of two RCTs in type 2 diabetes, the RR of a HbA1c level of less than 7.0% with inhaled insulin compared with short-acting subcutaneous insulin was 1.49 (95% CI, 1.10 to 2.00). In the second study, the mean change from baseline HbA1c was –0.7% for both short-acting subcutaneous insulin and inhaled insulin.

4.1.7 Overall, there was consistent evidence for both type 1 and type 2 diabetes that inhaled insulin was as effective in lowering blood glucose as conventional short-acting subcutaneous insulin.

**Adverse events**

4.1.8 In the RCTs in type 1 diabetes, compared with short-acting subcutaneous insulin, inhaled insulin was found to be associated with a slightly lower RR of overall hypoglycaemic episodes in two studies: RR = 0.96 (95% CI, 0.93 to 0.99) and RR = 0.94 (95% CI, 0.91 to 0.97), respectively. However, there was little difference in the rate of adverse events in four further studies, in which the RRs were: 1.17 (95% CI, 0.98 to 1.40); 1.01 (95% CI, 0.99 to 1.04); 1.05 (95% CI, 0.96 to 1.15); and 1.00 (95% CI, 0.97 to 1.03). A higher rate of adverse events was found in one study: RR = 1.24 (95% CI, 1.17 to 1.31).

4.1.9 Of the two RCTs in type 2 diabetes, which compared inhaled insulin with short-acting subcutaneous insulin, one reported no difference in the incidence of hypoglycaemic episodes and the other reported a slightly lower risk of overall hypoglycaemic episodes in favour of inhaled insulin (RR = 0.89; 95% CI, 0.82 to 0.97).

4.1.10 All seven studies in type 1 diabetes reported on severe hypoglycaemic events. Of these, two studies identified a higher risk of a severe hypoglycaemic event with inhaled insulin than with short-acting subcutaneous
insulin: RR = 2.00 (95% CI, 1.28 to 3.12) and RR = 2.87 (95% CI, 0.32 to 25.55). Four studies found similar rates of severe hypoglycaemic events in the two treatment groups, with RRs of 1.29 (95% CI, 0.38 to 4.40), 1.18 (95% CI, 0.78 to 2.00), 1.16 (95% CI, 0.76 to 1.76), and 0.77 (95% CI, 0.56 to 1.06). One trial reported fewer severe hypoglycaemic episodes with inhaled insulin than with short-acting subcutaneous insulin: RR = 0.52 (95% CI, 0.30 to 0.86).

4.1.11 The manufacturer undertook a meta-analysis of six of the trials in type 1 diabetes. The pooled RR (inhaled insulin compared with short-acting subcutaneous insulin) was 1.01 (95% CI, 0.99 to 1.03) for hypoglycaemic events and 0.93 (95% CI, 0.74 to 1.16) for severe hypoglycaemic events.

4.1.12 Both trials in type 2 diabetes reported similar rates of severe hypoglycaemic events between treatment groups. No events were reported in any treatment group in one study, and in the other study the rate of severe hypoglycaemic events was 0.5 per patient month for inhaled insulin and 0.1 per patient month for subcutaneous insulin.

4.1.13 Data on pulmonary outcomes were reported in the trial, including pulmonary function, carbon monoxide diffusing capacity and cough. No significant differences between intervention groups in terms of any pulmonary outcome were identified. Four studies reported a greater incidence of cough with inhaled insulin, but the cough appeared to be mild and decreased during the study period. Some RCTs reported a significantly greater mean decrease in carbon monoxide diffusing capacity for inhaled insulin compared with subcutaneous insulin. The assessment report stated that the higher insulin antibody levels observed in the trial groups receiving inhaled insulin, compared with the trial groups receiving subcutaneous insulin, did not result in any apparent clinical change.

4.1.14 Of the six RCTs in type 1 diabetes that reported on weight change, none identified any statistically significant differences between inhaled insulin and short-acting subcutaneous insulin. Of the two studies in type 2 diabetes, one
found a statistically significantly greater weight gain with short-acting subcutaneous insulin (adjusted mean group difference –1.29 kg [95% CI, –1.98 to –0.59]). The second study found no difference between treatment groups. The manufacturer’s meta-analysis of studies involving people with type 1 diabetes or insulin-experienced people with type 2 diabetes reported a statistically significant greater gain in body weight with short-acting subcutaneous insulin, compared with inhaled insulin (adjusted mean group difference –0.74 kg [95% CI, –1.02 to –0.47 kg]).

Patient satisfaction

4.1.15 Five trials (three involving people with type 1 diabetes and two involving insulin-experienced people with type 2 diabetes) reported on patient satisfaction, measured using the Patient Satisfaction with Insulin Therapy Questionnaire. All five trials showed statistically significantly greater satisfaction with the inhaled insulin regimen compared with subcutaneous insulin (in overall satisfaction and most subscales). The manufacturer’s meta-analysis identified a pooled difference in overall satisfaction score of 24.3 (95% CI, 18.14 to 30.44) in favour of inhaled insulin.

Patient preference

4.1.16 Two trials reported on patient preferences (one in type 1 diabetes and one in type 2 diabetes). Both found that patients receiving inhaled insulin were statistically significantly more likely to prefer to continue with the insulin modality they received during the trial than patients who had received subcutaneous insulin.

4.1.17 In addition, a preference study was submitted by the manufacturer, which involved people with type 2 diabetes in whom dietary control and/or OHA therapy had failed to achieve glycaemic control. One group of patients was given written information about existing treatment options (OHAs and subcutaneous insulin). The second group received the same information plus information about inhaled insulin. Both groups were then asked to make hypothetical choices about future diabetes therapy. When the choices of
insulin therapy included inhaled insulin, 43% chose to start insulin, and 35% chose inhaled insulin. In the group for which inhaled insulin was not an option, 15.5% chose to start (subcutaneous) insulin.

**Quality of life**

4.1.18 Three RCTs reported on diabetes-related quality of life (two in type 1 diabetes and one in type 2 diabetes). All reported that overall quality of life and subscales showed more favourable improvement among people taking inhaled insulin compared to subcutaneous insulin (p < 0.05).

4.1.19 In its submission, the manufacturer described a utility elicitation study in 132 people with type 1 diabetes and 212 people with type 2 diabetes, using the time-trade-off method and the EQ5D questionnaire. The utility gain from using inhaled insulin compared with injected insulin derived by the time-trade-off method was between 0.043 and 0.088, depending on the type of diabetes and current treatment. The utility gain from using inhaled insulin compared with subcutaneous insulin derived by the EQ5D method was between 0.020 and 0.043, depending on the type of diabetes and current treatment.

**4.2 Cost effectiveness**

4.2.1 The Assessment Group and the manufacturer’s submission did not identify any published cost-effectiveness studies on inhaled insulin.

4.2.2 The manufacturer’s submission provided an economic analysis. This was based on a probabilistic Monte Carlo simulation model, using a modified Markov process with yearly intervals and a 20-year time horizon. The model was validated against the study data used in the development of the model itself (internal validation) and showed that all model results were within a deviation of ±10%. External validation was undertaken against studies not used in the model’s construction.

4.2.3 Only patients with uncontrolled diabetes with respect to glycaemia (HbA1c level greater than 7.4%) were considered in the model. It was assumed that
inhaled and subcutaneous basal–bolus insulin regimens achieve the same level of blood glucose control: once insulin or intensification therapy was started, it was assumed that patients’ HbA1c levels were below 7.5%. Compliance was assumed to be 100%. The patients were assumed to be white non-smokers with a medium level of physical activity. A cost of £25/year was added to the costs of inhaled insulin and glucose monitoring to take into account the annual spirometry tests that may be required.

4.2.4 In the original model submitted by the manufacturer, it was assumed that 35% of people with poorly controlled diabetes in the inhaled insulin arm of the model would move to inhaled insulin therapy immediately, and the remaining 65% would start inhaled insulin 4 years later, based on the hypothetical preference study carried out in insulin-naïve people with diabetes (see 4.1.17). For the modelling of the control arm (subcutaneous insulin), it was assumed that 15% of people with poorly controlled diabetes would move to subcutaneous insulin immediately, and the remaining 85% would start subcutaneous insulin 4 years later.

4.2.5 In the original modelling, utility gains from the use of inhaled insulin compared with subcutaneous insulin, which were used in the manufacturer’s model, were derived from the time-trade-off method used in the utility elicitation study submitted by the manufacturer (see 4.1.19).

4.2.6 During the consultation period of this appraisal, the manufacturer submitted remodelled cost-effectiveness estimates. In this remodelling, the following model parameters were changed: discount rate, utility decrements for complications, treatment costs, some patient characteristics, and baseline HbA1c levels. In addition, the utility gains from using inhaled insulin compared with injected insulin were changed from the values described in section 4.1.19 to 0.02 for all subgroups. Assumptions on the initial uptake and length of delay were changed from the values described in section 4.2.3 to a different scenario, based on a presently unpublished observational patient-record study on insulin use. This assumed a difference in uptake between inhaled
insulin and subcutaneous insulin of 10–12% (favouring inhaled insulin), with a gradual increase in uptake over 12 years, and led to a larger difference between the inhaled and injected arms of the model than in the original modelling carried out by the manufacturer.

4.2.7 In the manufacturer’s model, patient subgroups were analysed on the basis of their current treatment regimen as follows.

- **Type 1 diabetes currently uncontrolled on subcutaneous pre-mixed insulin regimens.** In the original modelling the utility gain used was 0.074; the incremental cost-effectiveness ratio (ICER) for inhaled insulin compared with moving to a basal–bolus subcutaneous insulin regimen was £7091 per quality-adjusted life year (QALY). In the remodelling, the corresponding ICER was £8510/QALY.

- **Type 1 diabetes currently uncontrolled on subcutaneous basal–bolus insulin regimens.** In the original modelling the utility gain used was 0.076; inhaled insulin was more effective and less costly than allowing the diabetes to stay uncontrolled on subcutaneous basal–bolus insulin regimens. This was also the case in the remodelling.

- **Type 2 diabetes currently uncontrolled on two or more oral anti-diabetic therapies.** In the original modelling the utility gain used was 0.053; the ICER for inhaled insulin was £4733/QALY when compared with adding a basal regimen, and £7275/QALY when compared with moving to pre-mixed subcutaneous regimens. In the remodelling, the corresponding ICERs were £28,260/QALY and £28,571/QALY, respectively.

- **Type 2 diabetes currently uncontrolled on a subcutaneous basal regimen.** In the original modelling the utility gain used was 0.043; the ICER for inhaled insulin was £16,496/QALY when compared with moving to a pre-mixed regimen, or £14,932/QALY when compared with moving to a subcutaneous basal–bolus insulin regimen. In the remodelling, the corresponding ICERs were £21,663/QALY and £10,657/QALY, respectively.
• **Type 2 diabetes currently uncontrolled on a subcutaneous pre-mixed regimen.** In the original modelling the utility gain used was 0.088; the ICER for inhaled insulin was £6499/QALY when compared with moving to a subcutaneous basal–bolus regimen. In the remodelling, the corresponding ICER was £10,153/QALY.

• **Type 2 diabetes currently uncontrolled on a subcutaneous basal–bolus regimen.** In the original modelling the utility gain used was 0.088; the ICER was £3979/QALY when compared to staying uncontrolled on a subcutaneous basal–bolus regimen. In the remodelling, the corresponding ICER was £2141/QALY.

4.2.8 The Assessment Group adapted the manufacturer’s model to model two different type 2 diabetes patient populations, using different assumptions on estimates of utility decrements associated with complications (such as heart failure, stroke, end-stage renal disease, peripheral vascular disease and minor amputation). The Assessment Group used a 2-year delay for the take up of insulin treatment in the base-case scenarios, rather than the 4-year delay used in the manufacturer’s original submission.

4.2.9 The Assessment Group presented the following scenarios.

- People with type 2 diabetes currently uncontrolled on two OHAs (metformin and gliclazide) moving to one of the following regimens: (1) metformin and inhaled insulin; (2) metformin, gliclazide and basal subcutaneous insulin glargine (a long-acting human insulin analogue); (3) metformin and pre-mixed basal–bolus in the form of Mixtard 30.

- People with type 2 diabetes currently uncontrolled on a basal regimen (metformin and insulin glargine) moving to one of the following regimens: (1) metformin, insulin glargine and inhaled insulin; (2) metformin, insulin glargine and insulin lispro (a short-acting human insulin analogue); (3) metformin and pre-mixed basal–bolus in the form of Mixtard 30.

Furthermore, the Assessment Group explored alternative scenarios with regard to patient age and duration of diabetes (patients aged 40, 50 and
60 years were assumed to have durations of diabetes of 5, 8 and 12 years, respectively).

4.2.10 The Assessment Group reviewed the utility gains derived from inhaled insulin compared with injected insulin derived from the manufacturer’s utility elicitation study. The Assessment Group thought that it was not credible that the use of inhaled insulin would be sufficient to result in utility gains similar to avoiding blindness in one eye or diabetic foot syndrome. Using the EQ5D profiles from the manufacturer’s utility elicitation study, the Assessment Group reanalysed the utility gains using different assumptions on the impact of inhaled insulin on EQ5D levels. As a consequence, the utility gain from taking insulin by the inhaled rather than the subcutaneous route was judged by the Assessment Group to more likely lie below 0.02.

4.2.11 The Assessment Group calculated the cost effectiveness for inhaled insulin in different ways: firstly assuming greater and earlier acceptance of insulin therapy alone (without any change in health-related quality of life; that is, utility gain 0.00), and secondly also assuming an increase in health-related quality of life from taking insulin by inhalation rather than injection (utility gains 0.02 and 0.04).

4.2.12 When only the greater and earlier acceptance of insulin therapy alone was considered with no utility gain, the ICERs were above £200,000 for both scenarios and all age groups analysed. When a utility gain of 0.02 was used, the ICERs for inhaled insulin were above £30,000 for all groups analysed, apart from patients with type 2 diabetes currently uncontrolled on a subcutaneous basal regimen when compared with moving to a basal–bolus regimen. For these patients, the ICERs were around £21,000 for all age groups considered. When a utility gain of 0.04 was used, the ICERs for inhaled insulin were between £22,000 and £24,000 for patients with type 2 diabetes currently uncontrolled on an oral regimen and between £10,000 and
£17,000 for patients with type 2 diabetes currently uncontrolled on a subcutaneous basal regimen.

4.2.13 Both the manufacturer’s analysis and the Assessment Group’s model contained various sensitivity analyses, which used different assumptions on discount rate, costs data, compliance data and uptake of insulin. These sensitivity analyses did not lead to substantially different ICERs.

4.2.14 In summary, the manufacturer’s analyses led to much lower ICERs than the Assessment Group’s analysis. This was because of different assumptions about the utility gain derived from taking insulin by the inhaled rather than the subcutaneous route, the delay in uptake or intensification of insulin treatment, and the degree of control and compliance with therapy.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of inhaled insulin for the treatment of diabetes (types 1 and 2), having considered evidence on the nature of the condition and the value placed on the benefits of inhaled insulin by people with diabetes mellitus, those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.

4.3.2 The Committee discussed the opinion of the clinical and patient experts about the likely level of need for inhaled insulin in clinical practice. The experts advised the Committee that using injected insulin is not usually a major concern for the majority of people with diabetes, given the availability of patient support and education, modern small needles and insulin pens. The experts also pointed out that the availability of inhaled insulin would not completely replace the need for injections of insulin for most people with diabetes because the inhaled formulation is intended only to replace the need for pre-prandial injected insulin. In addition, the Committee appreciated that inhaled insulin might not fully alleviate any problems relating to fear of
injections, because individuals would still need to use needles for glucose testing.

4.3.3 The Committee understood that there are reasons why some people with diabetes who need insulin to improve their glycaemic control are reluctant either to start insulin therapy or to intensify their injection regimen. For example, some people with type 2 diabetes are concerned about hypoglycaemic attacks, or believe that the move to insulin therapy represents a failure on their part with oral therapy. Some people with diabetes may also be concerned about the impact of using insulin on their driving licence status and employment. However the Committee understood that these concerns would be equally relevant with inhaled insulin.

4.3.4 The Committee also heard from the clinical and patient experts that a small group of people with diabetes are so averse to injections that they would rather face the prospect of diabetic complications than use subcutaneous insulin. Additionally, the Committee was aware that some patients, despite being willing to inject insulin, have great difficulty in finding suitable injection sites for various reasons, such as severe lipohypertrophy resulting from frequent insulin injections.

Clinical effectiveness

4.3.5 The Committee considered the evidence on clinical effectiveness and was persuaded that inhaled insulin can be regarded as being as effective in controlling HbA1c levels as short-acting subcutaneous insulin, as shown in the groups treated in the RCTs. The Committee also understood that there have been improvements in standards for diabetes care in the UK over the last few years, including the development of more formal approaches to education and the use of a range of alternative injection therapies including insulin pens and insulin analogues including insulin glargine, insulin detemir, insulin lispro, and insulin aspart. The Committee was concerned about the design of the reported RCTs, none of which compared inhaled insulin with this current standard of care in the UK, and concluded that this limited the
assessment of the generalisability of the results to routine clinical practice in the UK. In addition, the Committee noted that none of the RCTs examined the effectiveness of inhaled insulin exclusively in people with type 1 diabetes whose blood glucose levels are uncontrolled on their current insulin regimen, or specific subgroups of people with diabetes.

4.3.6 The Committee was aware of the studies in people with type 2 diabetes that was inadequately controlled by diet and exercise or OHAs, and the beneficial effect that inhaled insulin had shown in comparison with OHAs. It recognised that these results confirm that inhaled insulin improves glycaemic control in people with diabetes that is inadequately controlled by OHA therapy. However, the Committee concluded that the results did not show that inhaled insulin improves glycaemic control more effectively than pre-prandial injections of short-acting insulin in this patient group or that it might effectively replace other approaches such as single night-time injections of long-acting insulin.

4.3.7 The Committee discussed the use of inhaled insulin in people with type 1 diabetes, many of whom need to adjust their dosage on a day-to-day basis in order to achieve optimal control. The Committee heard concerns from the patient experts that the inhaled insulin device does not allow sufficiently fine adjustment of insulin dosage for this purpose and that this limitation may lead to difficulties in glucose control compared with injections.

4.3.8 The Committee also discussed the current uncertainties regarding the long-term use of inhaled insulin. It was mindful of the potential long-term pulmonary effects of inhaled insulin, and the reported higher levels of insulin antibodies in people with type 1 diabetes on inhaled insulin therapy.

Cost effectiveness

4.3.9 The Committee discussed the analyses of the cost effectiveness of inhaled insulin. The Committee concluded that because inhaled insulin is more expensive than injected short-acting insulin but not more clinically effective,
overall it was not an effective use of NHS resources in the routine setting. The Committee therefore explored other factors that could potentially improve the cost effectiveness of inhaled insulin. Additionally, the Committee explored if there were any subgroups of people with diabetes who could gain greater clinical benefit from inhaled insulin.

4.3.10 The Committee noted from the manufacturer’s submission that improved patient satisfaction and preference could lead to a more cost-effective use of inhaled insulin. The Committee agreed that these factors would only be relevant to the cost effectiveness if they translated into either: (1) proven changes in health-related quality of life and utility gain, or (2) proven earlier uptake of insulin or intensification of current injection regimen and therefore improved glycaemic control in people with poorly controlled diabetes, with consequent improvements in health outcomes associated with better diabetes control.

4.3.11 The Committee considered the effect of earlier uptake of insulin therapy on the cost effectiveness of inhaled insulin and, in particular, the evidence provided by the manufacturer on patient preference and their estimate of probable improvements in uptake of inhaled insulin. The Committee was concerned about the methods and generalisability of the manufacturer’s preference elicitation study and, in particular, the hypothetical scenarios used. People with type 2 diabetes in whom dietary control or OHA therapy failed to improve HbA1c levels, were asked to make theoretical choices about whether to use inhaled insulin, based on an information leaflet (see 4.1.17). The Committee was concerned that the leaflet contained unbalanced information about the size, portability and functionality of the inhaler and the potential for dose adjustment, and included statements about how the inhaled insulin was judged by other patients. The Committee considered that patients may well state an initial preference for inhaled insulin, but some may reconsider when they become aware of the possible difficulties in the day-to-day use of the device, the time taken to set it up, and that its use is less discreet and less flexible than the use of injected insulin for blood glucose control.
4.3.12 The Committee further explored the data provided by the manufacturer on the effects on health outcomes of possible delay in initiation or intensification of insulin therapy. It understood that delays in the initiation or intensification of insulin therapy could increase the risk of long-term complications of diabetes. The Committee accepted that many people with type 2 diabetes do not achieve satisfactory glucose control, and that this could persist over a period of years. However, it was not convinced that the data provided by the manufacturer reflected current diabetes care, including patient education and support as specified in the new General Medical Services contract. The Committee additionally considered the Assessment Group’s economic modelling of improved uptake of insulin or intensification in type 2 diabetes (in the absence of any utility gain) and were persuaded that this sensitivity analysis indicated that, even if earlier uptake were assumed, this effect alone was insufficient to provide support for a cost-effective use of this technology for most patients.

4.3.13 Therefore, the Committee concluded that the cost effectiveness of inhaled insulin was principally dependent on the magnitude of the utility gain for the individual derived from inhaled insulin compared with injected insulin. The Committee explored the utility elicitation study submitted by the manufacturer (section 4.1.19). The Committee was concerned about aspects of the methods used in this study, particularly that the participants were not randomly selected and were not a representative sample of people with diabetes, so that there was a possibility of selection bias. The Committee concluded that the utility values suggested in the manufacturer's submission were unlikely to be realistic in general clinical practice. The Committee took note of the indicative re-estimation of the utilities carried out by the Assessment Group and, most importantly, the comparisons with published utility values for other conditions. Based on this, the Committee concluded that, on balance, a utility gain from moving from injected to inhaled insulin of more than 0.02 across the entire population of people with diabetes was unproven. The Committee considered the likely utility gains that people with
type 1 diabetes would derive from inhaled insulin. The Committee was aware that fewer people with type 1 diabetes than with type 2 diabetes expressed a preference for inhaled insulin and therefore concluded that, for the majority of patients, the magnitude of the utility gain in type 1 diabetes would be lower than in type 2 diabetes.

4.3.14 The Committee discussed the ICERs derived from the original manufacturer’s analysis, the Assessment Groups analysis and the remodelling provided by the manufacturer. It considered that a utility gain of more than 0.02 was needed for inhaled insulin to be a cost-effective use of NHS resources. The Committee also noted that the remodelling provided by the manufacturer included a number of changes in parameter inputs and assumptions (for example costs and revised differential uptake rates) that it believed were based on hypothetical studies or were unrealistic in the light of current practice. Therefore, the Committee did not consider that this remodelling changed its initial judgement on the cost effectiveness of inhaled insulin for the general population of people with diabetes who require insulin treatment, and concluded that the case for cost effectiveness in the general population of people with diabetes was not supported.

4.3.15 The Committee was, however, persuaded that inhaled insulin could be cost effective in those people with diabetes who are unable to inject because they experience marked and persistent fear of injections or because they cannot find suitable injection sites (for example, due to severe lipohypertrophy) which cannot be overcome by patient support and education or by injection site rotation. The Committee appreciated that for such people, there is no readily available alternative, and they would remain at high risk of diabetes-associated complications without the use of inhaled insulin. Although the current evidence base does not allow an evaluation of the clinical effectiveness of inhaled insulin with any certainty in this context, the Committee agreed that it was reasonable to assume that inhaled insulin was likely to be clinically effective in this population. Furthermore, the Committee agreed that it was likely that the utility gain in this patient group would be
sufficiently high to make the use of inhaled insulin cost effective. This judgement was based on the modelling provided by the Assessment Group, which showed that the use of a utility gain of 0.04 for inhaled insulin led to ICERs of less than £25,000.

4.3.16 The Committee discussed how people with a marked and persistent fear of injections resulting in poor glycaemic control, could be reliably identified. The Committee heard that healthcare professionals with appropriate training could identify those people with marked and persistent fear of injections, using the DSM-IV criteria for specific phobia ‘blood injection injury type’. The Committee agreed that it was not essential for a psychiatrist or psychologist to make this diagnosis, but that such diagnosis should be carried out by a diabetes specialist or a mental health professional.

4.3.17 The Committee understood that individuals who, on the basis of the DSM-IV criteria, could be regarded as having marked and persistent fear of injections might reasonably be expected to benefit from desensitisation therapy and could therefore at some time reconsider the use of injected insulin. The Committee therefore concluded that while it would be inappropriate to delay the initiation of inhaled insulin in the short term, they should be offered the opportunity of desensitisation therapy for the longer term management of their fears if this was appropriate.

4.3.18 The Committee also appreciated that some patients have severe and persistent problems with injection sites, such as those associated with lipohypertrophy, despite support with injection site rotation. The Committee was persuaded that this situation would make it extremely difficult for such people to intensify their therapy and that they should also be considered for the use of inhaled insulin because without an alternative to short-acting subcutaneous injections of insulin there is a likelihood of their developing long-term adverse effects of hyperglycaemia.

4.3.19 In summary, the Committee concluded that inhaled insulin should not be recommended for the routine treatment of people with diabetes. However, the
Committee agreed that inhaled insulin should be a treatment option for people who have poor glycaemic control despite other appropriate therapeutic interventions and adequate educational support and who are unable to initiate or intensify pre-prandial subcutaneous insulin therapy because of (1) a marked and persistent fear of injections (diagnosed by a diabetes specialist or a mental health professional according to DSM-IV criteria), or (2) severe and persistent problems with injection sites, for example as a consequence of lipohypertrophy.

4.3.20 The Committee concurred with the advice from the professional organisations that in these patients, treatment with inhaled insulin should only be continued beyond 6 months and in the longer term, if there is evidence of a sustained improvement in HbA1c which is judged to be clinically relevant to the individual patient’s overall risk of developing long-term complications of diabetes. Further continuation should be dependent on regular monitoring to ensure that improved control is still being achieved. The Committee discussed whether to specify precise HbA1c targets, but agreed that it was more appropriate for clinicians to consider the appropriate HbA1c level in the context of the individual patient’s overall risk profile of developing long-term complications of diabetes. Furthermore, the Committee recommended that initiation of inhaled insulin treatment and monitoring of response should be carried out at a specialist centre, where the need for monitoring and evaluation could be fully explained and implemented.

4.3.21 The Committee was persuaded of the need for ongoing evaluation of the use of inhaled insulin in people who meet the criteria outlined in this guidance. The Committee concluded that data on the use of inhaled insulin according to this guidance should be collected as part of a prospective observational study (registry study). The data collected should include individual patient outcomes and adverse events. In particular the Committee was concerned about the potential for long-term effects of inhaled insulin on lung function.
5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in ‘Standards for better health’ issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX). [Note: tools will be available when the final guidance is issued]

6 Recommendations for further research

6.1 Ongoing clinical trials related to this guidance include the Exubera Real World Classic study, which aims to assess the impact of inhaled insulin on glycaemic control in people with poorly controlled type 2 diabetes receiving two or more oral anti-diabetic agents.
6.2 The Committee recommended that a coordinated prospective observational registry study should be developed in people with type 1 or type 2 diabetes receiving inhaled insulin under the conditions outlined in section 1 in order to evaluate the effectiveness of the use of inhaled insulin in this group. The data collected should include individual patient outcomes, adverse events and measurements of lung function.

7 Related guidance

7.1 NICE has issued the following related clinical guidelines.


7.2 NICE has issued the following related technology appraisals.


## 8 Review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be reviewed in September 2009.

David Barnett
Chair, Appraisal Committee
September 2006

**Appendix A. Appraisal Committee members**

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch
considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam
Radiologist, St George’s Hospital, London

Dr Amanda Adler
Consultant Physician, Addenbrooke’s Hospital, Cambridge

Professor A E Ades
MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Dr Tom Aslan
General Practitioner, Stockwell, London

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Mrs Elizabeth Brain
Lay Member

Dr Karl Claxton
Health Economist, University of York

Dr Richard Cookson
Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice, University of East Anglia
Mrs Fiona Duncan  
Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Professor Christopher Eccleston  
Director, Pain Management Unit, University of Bath

Dr Paul Ewings  
Statistician, Taunton & Somerset NHS Trust, Taunton

Professor John Geddes  
Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston  
Director of Finance, Barts and the London NHS Trust

Mr Adrian Griffin  
Health Outcomes Manager, Johnson & Johnson Medical Ltd

Ms Linda Hands  
Consultant Surgeon, John Radcliffe Hospital

Dr Elizabeth Haxby  
Lead Clinician in Clinical Risk Management, Royal Brompton Hospital

Dr Rowan Hillson  
Consultant Physician, Diabeticare, The Hillingdon Hospital

Dr Catherine Jackson  
Clinical Senior Lecturer in Primary Care Medicine, University of Dundee

Professor Richard Lilford  
Professor of Clinical Epidemiology, Department of Public Health and Epidemiology, University of Birmingham
Dr Simon Mitchell
Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Ms Judith Paget
Chief Executive, Caerphilly Local Health Board, Hengoed

Dr Katherine Payne
Health Economist, The North West Genetics Knowledge Park, The University of Manchester

Dr Ann Richardson
Independent Research Consultant

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Mr Mike Spencer
General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Professor Andrew Stevens (Vice Chair)
Professor of Public Health, University of Birmingham

Dr Cathryn Thomas
General Practitioner, and Associate Professor, Department of Primary Care & General Practice, University of Birmingham

Dr Norman Vetter
Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Professor Mary Watkins
Professor of Nursing, University of Plymouth

Dr Paul Watson
Medical Director, Essex Strategic Health Authority, Chelmsford
Appendix B. Sources of evidence considered by the Committee

A  The assessment report for this appraisal was prepared by the University of Aberdeen.


B  The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, Assessment Report and the Appraisal Consultation Documents (the first and second ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I  Manufacturer/sponsors:
   - Pfizer Limited

II  Professional/specialist and patient/carer groups:
   - Association of British Clinical Diabetologists
   - Association of Diabetes Specialist Nurses
   - British Dietetic Association
   - Department of Health
   - Diabetes UK
   - Insulin Dependent Diabetes Trust
   - Royal College of Nursing
   - Royal College of Physicians
   - South Warwickshire PCT
   - Welsh Assembly Government
III  Commentator organisations (without the right of appeal):

- Aberdeen HTA Group
- Eli Lilly & Co Ltd
- EUCOMED
- National Collaborating Centre for Chronic Conditions
- National Coordinating Centre for Health Technology Assessment
- NHS Quality Improvement Scotland
- Novo Nordisk Ltd

C  The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee’s deliberations. They gave their expert personal view on inhaled insulin in diabetes mellitus by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Stephanie Amiel, Professor of Diabetic Medicine, clinical expert nominated by the Association of British Clinical Diabetologists
- Professor Anthony Barnett, Professor of Medicine, clinical expert nominated by the Association of British Clinical Diabetologists
- Jenny Hirst, patient expert nominated by the Royal College of Physicians
- Ms Anne Hitchins, patient expert nominated by the Royal College of Physicians
- Mrs Maureen Elizabeth Wallymahmed, Nurse Consultant – Diabetes, clinical expert nominated by the UK Association of Diabetes Specialist Nurses