Dear Alana,

Re: Inhaled insulin for the treatment of type 1 and type 2 diabetes – comments on the Assessment Report for the above appraisal

Thank you for allowing the Association of British Clinical Diabetologists (ABCD) the opportunity to respond to the Assessment Report. I have been nominated by them to comment on this as the time frame allowed was much too short for wide dissemination within ABCD. I have read this with interest and have a number of major concerns. I agree with Dr Black and colleagues that many people with diabetes are not achieving adequate diabetes control increasing their risks of long term complications; that poor adherence to treatment is associated with poor control; that many people with type 2 diabetes with inadequate control on oral agents are reluctant to start insulin and once started are also reluctant to further intensify the treatment. I also agree that inhaled insulin is at least as effective in controlling blood glucose as standard subcutaneous (soluble) insulin with similar (perhaps even reduced) risks of hypoglycaemia and that the product appears to be safe.

There are, though, a number of major problems with the Aberdeen Report:

1. In Summary, Page VII - the issue is not just improved compliance with prescribed insulin, but also that inhaled insulin may allow easier intensification of treatment and thereby improved diabetes control. In addition, the authors conclude in their Summary (Page VIII) that inhaled insulin appears to be effective and safe, but will probably cost so much more that it is unlikely to be cost effective. We do not believe that this conclusion is correct (see later)
2. Page 3, bullet point 3, the authors make the point that patients on intensive regimens have to take multiple daily injections, but they fail to add that this leads to major issues of compliance and acceptability. They go on to point out (see Page 6) that various national and international bodies recommend very tight HbA1c targets, down to 6.5% - the only way to achieve these in patients requiring insulin is intensive treatment, which I believe in some patients will be helped by the availability of inhaled insulin!

3. On Page 16, Section 2.4, the authors state that “Currently, inhaled insulin is restricted to a short acting profile but for almost all patients would not, therefore, completely remove the need for injection”. This is not true for certain type 2 diabetic patients where one would expect a significant enhancement of control by adding pre-meal inhaled insulin to type 2 diabetic patients failing oral treatment without necessarily requiring a basal insulin injection.

4. On Page 17, section 2.6, Conclusions. The authors remind us that NICE guidance for management of type 1 diabetes mellitus suggests that a basal bolus approach is “best practice” or, where appropriate, continuous insulin infusion (pump therapy). Throughout their document the authors continually refer to pumps without any real recognition of the costs of such an approach. They even make the point that inhaled insulin would be as costly as pump therapy
which is ludicrous when considering the amount of support required for these patients over time.

Indeed, my own personal experience is that whilst PCTs are willing to cover the cost of pumps and related equipment this nowhere near compensates for the time and effort required by health professionals in supporting these patients! The authors in their “Key questions”, Section 2.7, Page 19, ask whether in people wishing to minimise the number of injections a day, would inhaled insulin be clinically effective compared to continuous subcutaneous insulin infusion. For the above reasons, this is not an appropriate comparison. Indeed, they even focus on pumps for type 2 diabetes and suggest a comparison with inhaled insulin be made in this group – against NICE recommendations!

5. Despite any limitations alluded to, the authors accept that the data strongly supports improved patient preference for inhaled over injected insulin. I do have a problem with the authors suggestion that injections per se are not really an issue for many patients. This is at variance with clinical experience in type 2 diabetes where many patients flatly refuse to go onto insulin despite very poor diabetes control (see enclosed letter from a patient). In addition, many patients with both type 1 and type 2 diabetes refuse to intensify insulin to improve control because they do not want to take multiple injections.
I accept that pain at injection sites is not the whole answer. There are a whole range of reasons why people will not accept injections including cultural issues surrounding injections. This is particularly relevant in certain ethnic minority groups including South Asians.

6. On Page 41, “Additional studies”, the authors again refer to insulin pumps even in type 2 diabetes. This is not a method recommended by NICE and indeed is rarely used in the management of type 2 diabetes. In addition, on Page 47, “Conclusions from clinical effectiveness review” – do the authors really think that pump therapy is a suitable alternative to inhaled insulin? The expense involved would be far in excess of the costs of provision of inhaled insulin.

7. The authors accept the Fremantle Study (Page 41) but then denigrate it as being “hypothetical” because inhaled insulin was not actually available to the patients studied. Given that inhaled insulin was at this time only in development we are not sure exactly what the authors of this report expected!

8. On Page 51, the authors conclude no difference in diabetic control or hypoglycaemic events between inhaled and subcutaneous insulin. They seem to have missed the point – inhaled insulin is insulin. It is the method of delivery which
differs so that patient preference, quality of life, adherence to medication are of paramount importance. They then ask the rhetorical question – given that there is no difference in diabetic control or hypoglycaemic events and given that inhaled insulin requires greater doses by injection (and hence higher costs) how can inhaled insulin be justified? I can only suppose that the authors have never dealt with diabetic patients. Would the authors like to inject insulin between 4 and 7 times per day – the best practice certainly for type 1 diabetes recommended by NICE? Of course, inhaled insulin is not the panacea for all things but it does offer patient choice and a means of avoidance of injections. In addition, the authors seem to think that avoidance of injections because of pain is the whole basis for the Industry case for inhaled insulin. This is not true. Many patients are reluctant to self-inject – not just because of pain but because of the method used. In addition, try telling the needle phobic patient that they are “overestimating the pain” (see Page 53) and that modern needles for injecting insulin are very fine and sharp. There are many patients who, even after detailed explanation, still refuse to start or intensify insulin because they do not want to inject (see enclosed letter from a patient).

9. It is interesting that the authors of the Report continuously refer not
only to pump therapy but also education support packages such as DAFNE which are themselves quite costly. **Education is a vital part of any management regime – it is not an “instead of”!**

10. **On Page 60, Sub-group D, the authors have no evidence that people on tablets/single basal regimen will regard intensification of insulin as less troublesome than the subjects in the Fremantle Study. In my experience, people with type 2 diabetes on a single basal injection are still reluctant to intensify with more injections.**

11. **In Sub-group E (Page 61) – patients with type 2 diabetes. Again, why do the authors refer to insulin pumps when this is not recommended by NICE in the management of this patient group.**

12. **On Page 63 the authors say “Our impression is that most clinicians would not hurry to start insulin for those with HbA1c just over 7.5%” – the new GMS Contract means that many patients are being referred with HbA1c just above this level for insulin treatment, so their comment is incorrect in the present climate.**

13. **On Page 66, Section 5.1, the authors state that use of Exubera may**
also affect patient quality of life through patient management of blood glucose levels and suggest two possibilities. Unfortunately, they once again fail to address the issue of potential ease of intensification by use of Exubera, rather than multiple injections. I believe that failure to appreciate some of the issues is apparent throughout the document causing a significant underestimate of the cost-effectiveness of this new technology.

14. I take particular issue with the estimates on Page 78 concerning the impact on health-related quality of life of transferring from Exubera plus an injection to extra injections alone. They suggest that this would not result in a significant impact on quality of life. It might seem entirely logical that the disutility from blindness in one eye or diabetic foot syndrome would be much greater than transferring to injected insulin. Logic does not always apply in these situations! For example, if one looks at hypoglycaemia data what seems logical to scientists is not always so when considering individual patients. It is well reported, for example, that a significant hypoglycaemic event, requiring third party intervention, has as serious effect on quality of life as a patient being told that they have a malignancy or are suffering from heart disease! One would not intuitively expect this but it is the case! We believe
their argument, although seemingly logical to those of us without diabetes, is actually fallacious.

15. On Page 87 the authors assume that since the clinical trials show no advantage from the point of view of control or hypoglycaemia over insulin injections that no note should be taken of the possibility long term of improved diabetes control by improved patient preference and adherence. All the evidence is that earlier and more aggressive treatment is associated with improved long term outcomes. At the very least the authors might have considered that use of inhaled insulin would be likely to encourage people with type 2 diabetes to start insulin earlier and also encourage both patients with type 1 and type 2 diabetes to intensify their insulin treatment. This would then be expected to improve long term HbA1c and also reduce the risk of long term complications.

16. On Page 89 “Scenario B” the authors assume that just because the patient is already injecting (once per day) that this group would be more likely to intensify their insulin therapy with the adoption of a bolus insulin injection. I know of no evidence for this. For this reason, I challenge the Conclusions, Section 5.7, Page 103, that modelling has assumed no downstream clinical benefit from adoption of Exubera as against the adoption of subcutaneous insulin. I believe this is unlikely to be the case and that long
term outcomes will indeed be improved by availability of inhaled insulin.

The authors also go on to point out that should all patients adopt insulin therapy within a reasonable period of 2-4 years it would be unlikely that downstream clinical benefits that arise with Exubera would result in Exubera being cost effective. This is against published data! There is now a wealth of data, both from Europe and worldwide, which shows that the delay to insulin treatment is much greater than the 2 years suggested by the Aberdeen group (and even the 4 years suggested by Industry). The 2 year figure is a gross underestimate. The average time to insulin initiation in different countries varies widely and many patients with type 2 diabetes have many years of poor diabetes control before insulin is even considered. This is in part because of the reluctance of the health professionals and patients to commence or intensify insulin treatment by injection.

17. I strongly disagree with the conclusion on Page 104 that the utility gain is far below 0.04 using the Industry submission – the authors suggest a figure of between 0.00 and 0.02. I believe that for reasons already discussed this is way too low and that the Industry figure of 0.04 is much closer to the truth.
18. In Chapter 6 (Page 105), Discussion, 6.1 – the authors discuss position statements from other bodies, including Diabetes UK. Interestingly, Diabetes UK identify two groups as being the highest priority for inhaled insulin – both coming from patients with type 1 diabetes. Although inhaled insulin could potentially be of great benefit to patients with type 1 diabetes wishing to intensify control without taking more injections, the other patient groups from those with type 2 diabetes must also be seriously considered. These include patients failing oral agents who will not, or are reluctant to, start insulin injections but also those patients who are already taking a single basal insulin with tablets who need to intensify but are reluctant to increase the number of injections.

19. I have significant concerns regarding the statement in the last sentence on Page 107 at the end of Section 6.3 (Issues in cost effectiveness). It is not for the authors to make such a provocative statement as “Whatever the costs, it would have to be taken away from other forms of care”. This could be claimed for virtually all NICE guidance and should not in itself be a factor in considering this technology. NICE is looking at cost effectiveness not political statements.

20. Page 110, Section 6.5, “Implications for practice” – again I would
argue with the statement that inhaled insulin will not completely 
eliminate the need for injections given that a proportion of patients 
failure oral agents with type 2 diabetes may well have 
significantly improved control with addition of inhaled insulin 
without injections. Similarly, on Page 111, the authors dismiss 
the clear preference data amongst patients for inhaled insulin 
over injected. Once again they go on about the benefits of 
conversion 2 years earlier as not being cost-effectiveness. This 
2 year figure is totally erroneous for reasons already 
discussed.

In addition, I cannot understand why the Aberdeen group failed to model 
various scenarios presented by Industry. How can the authors support their 
Conclusion that in Patient Group A (patients with type 1 diabetes 
uncontrolled on pre-mix regimens) that there would be no benefit when 
moving to a basal bolus regimen? See NICE guidance which suggests 
that twice daily biphasic insulin is not “best practice” and indeed basal 
bolus is!

In Patient Group B (patients with type 1 diabetes uncontrolled on basal bolus 
regimens) inhaled insulin offers an alternative to mealtime related injections. 
Many patients on basal bolus regimes, even when on these for many years, 
miss injections and/or have major problems with multiple injection therapies.
Patient Group E (patients with type 2 diabetes uncontrolled on pre-mixed insulin injections) - the Aberdeen group suggests an educational package as an alternative to intensification of insulin therapy as their reason for not modelling this group. Education though is not a replacement for best therapy and should be part of the package, rather than instead of it!

The argument for using inhaled insulin in type 2 diabetes patients inadequately controlled on injectable basal bolus regimen is less strong but many patients do miss injections and have problems with multiple injections so it would not have been unreasonable to model this group also.

I would also argue with the down-grading of the importance of patients having psychological issues with injecting insulin which seems to be a common theme throughout the Aberdeen Report. It is certainly not my experience! **There is considerable anxiety amongst patients about injecting which does not just relate to pain.**

My biggest concern, though, refers to the assumptions made by the Aberdeen group in their modelling. These include underestimates of uptake and intensification, an overestimate of the actual levels of HbA$_{1c}$ in the population (many patients refusing injected insulins have much higher HbA$_{1c}$ values and have had these for many years) – the same applies to those refusing intensification; and their estimates of disutility resulting from injections versus inhalation of insulin.
In conclusion, there are major problems with the Report of the Assessment Group. Assumptions have been made which are underestimates or indeed, in some cases, totally unfounded. The technology involves a new way of giving insulin rather than any fundamental differences in the insulin itself. The important question, therefore, is not whether inhaled insulin is superior to injectable insulin, but whether similar outcomes can be achieved effectively and safely with improved patient acceptability and quality of life. This should then result long term in better diabetes control and improved long term outcomes.

The benefits of early addition of insulin therapy in patients with type 2 diabetes, in particular, are well recognised. The fear of needles and/or the prospect of taking several injections per day, however, dissuades patients from accepting insulin therapy or (in both type 1 and type 2 diabetes) intensifying insulin treatments. The consequences are that patients may have years of inadequate diabetes control, with the increased likelihood of devastating long term complications. We believe that availability of non-invasive insulin may encourage more patients to accept insulin therapy and improve compliance. This may in turn improve diabetes control and reduce the burden of long term complications.

As the Aberdeen group agree, success of any treatment critically depends on patient satisfaction and adherence to the treatment. Several studies have now
demonstrated day-to-day patient satisfaction with inhaled insulin and better quality of life scores compared with other treatments. Patients also express greater preference for inhaled insulin and are more likely to accept insulin therapy when this option is available. Any extra costs of this treatment must be balanced against potential benefits of improved diabetes control and wellbeing with the potential to reduce the burden of long term complications. This technology will also enhance patient choice and will improve empowerment.

Yours sincerely

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This report is provided with the agreement of ABCD but is not sent on their behalf as unfortunately NICE did not allow sufficient time for full consultation with the membership of ABCD.