Comments on ACD, review of guidance 57
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Provisional recommendations
I believe that the recommendations made in section 1 are sound and form a suitable basis for NHS guidance.

I welcome the introduction of the new categories of those people suitable for a trial of CSII, viz. those with type 1 diabetes in whom it has been impossible to maintain an HbA1c <8.5% on best MDI, and those children where MDI is considered to be inappropriate.

The Committee's consideration of the evidence in section 4.3 is balanced and well judged, particularly assessing the totality of evidence favouring reduction in HbA1c and severe hypoglycaemia on CSII, the better expected results in those with poor control on MDI, the Committee's view on the difficulties and differences of opinion on performing meaningful cost effectiveness studies, and the conclusion that CSII is an appropriate use of resources.

The proposed review of guidance in February 2011 is appropriate in my view.

Has the relevant evidence been taken into account and are the summaries of evidence a reasonable interpretation of the evidence?

Section 4.1.8.
This section states that 'In summary, there is little evidence from RCTs of a significant difference between CSII and MDI therapy in terms of a decrease in HbA1c levels or in the rate of severe hypoglycaemic episodes in people with diabetes mellitus'. The Committee wisely later considers that 'the small number of RCTs cannot be relied upon to capture the benefits of CSII' (section 4.3.2). However, I believe that the conclusions of 4.1.8, and the discussion of the data in section 4.1.12 upon which the conclusions are based, need modification and rewording for the following reasons.

There are 5 RCTs comparing CSII with MDI based on long-acting insulin analogues (Doyle 2004, Maran 2005, Hirsch 2005, Bolli 2006 and Thomas 2007). The mean HbA1c was lower on CSII than MDI in 4 of the studies and equal in one. Meta-analysis shows that the mean HbA1c difference is significantly lower on CSII vs. MDI: 0.21 (95% CI 0.06 to 0.35)%.

In three RCTs of CSII vs. MDI based on isophane insulin (Cohen 2003, Weintrob 2003 and Hoogma 2006), the mean difference in HbA1c is also 0.21 (0.03 to 0.39)% when meta-analysis is performed.

Thus, the evidence from RCTs suggests a small but significant difference in mean HbA1c and that the results are similar for MDI based on either isophane or long-acting analogues. However, the subjects in these trials were relatively well controlled, with a

mean HbA1c of 7.5% on MDI. A pooled analysis of individual patient data from 3 RCTs comparing MDI vs CSII confirms what is known from observational studies - that the difference in HbA1c on switching to CSII is greatest in those worst controlled on MDI (Retnakaran R et al. Continuous subcutaneous insulin infusion versus multiple daily injections. The impact of baseline A1c. *Diabetes Care* 2004; 27: 2590-6). Thus, although the difference in HbA1c was 0.2% on average in RCTs, it was much larger in individual, poorly controlled subjects in RCTs.

No study using MDI based on long-acting analogues is suitable for analysis of severe hypoglycaemia (as the ACD notes), but there are 3 RCTs based on isophane that can be analysed (Cohen, Weintrob and Hoogma). The severe hypoglycaemia rate was reduced in all three studies (79, 66 and 60% reduction), with a mean rate ratio of 3.4. An HTA systematic review concludes that long-acting insulin analogues do not reduce severe hypoglycaemia compared with isophane MDI (Warren 2004).

Although, as the ACD correctly says, observational studies show an apparently greater improvement in HbA1c than RCTs, this is partly because the clinic-based subjects are more poorly controlled on MDI, and when statistical adjustment is made for HbA1c and age, the difference between RCTs and observational studies is very small (mean 0.2% HbA1c).

I therefore recommend that the Committee consider rewording the summary of the clinical evidence section as: ‘There is good evidence from both a relatively small number of RCTs and from a larger number of observational studies that HbA1c and the frequency of severe hypoglycaemia are significantly reduced by switching from MDI to CSII’.

<u>Minor point:</u>
Section 3.1. The Starlet pump is not yet available.