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LETTER TO THE EDITOR

Comment and Reply on: *Relative efficacy/effectiveness and relative costs of treatment with insulin glargine and insulin detemir*

Dear Sir,

The recent articles examining the benefits (Currie *et al.*[1]) and relative costs (Poole *et al.*[2]) of insulin glargine and insulin detemir published in this journal (Vol. 23, Suppl. 1, 2007) make questionable claims which do not reflect the quality of the data which were examined. The authors assert that glargine showed marginal benefits over detemir in diabetes-related outcomes, and a marked benefit in terms of reduced hypoglycaemia. They also claim that it is appropriate to examine benefits of treatment in clinical practice in order to ascertain the superiority of one treatment strategy over another.

When we examine the reported data we find quite a different story to the claims made by the authors. We find, first, that there is no statistically significant difference in the glycaemic control achieved. When correctly reanalysed using a conditional maximum likelihood approach comparing rates of hypoglycaemia, there is in fact no significant difference ($p = 0.31$). In addition there is no difference in reported discontinuation rates and the authors' claims that 'sensitivity analysis on the assumptions favoured glargine' are also not supported by the evidence presented.

When considering the relative costs of insulin glargine and insulin detemir, there are several crucial errors. First, the authors' have not addressed the systematic differences between cohorts which will confound their treatment costs, as like is not being compared with like. Glargine was more frequently used in combination with oral antidiabetic drugs in a regimen called *basal only therapy* (BOT), while detemir was prescribed significantly more often as part of an intensive basal-bolus therapy in patients with type 2 diabetes. In fact, at the time that this study was conducted, detemir was not licensed for use in BOT, unlike glargine. Comparing the total cost for all patients is not a fair comparison as undoubtedly intensive insulin therapy has higher costs associated with it than more conservative types of insulin regimens[3]. At the very least results should be presented which account for observed cohort differences, although this approach is still inferior to analysis based upon a properly randomised trial. Second, median costs rather than appropriately constructed and analysed mean costs are presented, which may misrepresent the differences in costs of therapy as higher-cost subjects are not considered. Given that the appropriate analysis of cost data is well known[4], it is surprising to see data misrepresented here. Thirdly, data on the cost of therapies are of little use without an understanding of their outcomes. The analysis of the prescription costs by Poole *et al.* does not include the HbA1c reduction associated with each treatment. Instead it refers to the 'sister publication' by Currie *et al.*[1], which reports the analysis of a *different* cohort of patients.

As the relative benefits of different treatments tend to be small compared with patient variation in response, randomised trials have become the standard research tool for evaluating the effects of treatments. Randomisation has dual purposes, it allocates both known and unknown biases between the treatment groups on the basis of the play of chance, providing a good basis for comparison between the groups. In addition, randomisation ensures that differences in the results of treatments allocated in that way may be attributable either to the treatment or the play of chance. If it is implausible that the play of chance may have led to the observed treatment differences, the only alternative explanation is that differences are

attributable to the treatment characteristics. There has been only one direct comparison between insulins glargine and determir[5]. This trial in type 1 diabetes indicated a similar degree of glycaemic control (HbA1c –0.03%; 95% CI –0.25 to 0.19). The authors incorrectly suggest that the non-inferiority design of trials for regulatory purposes prevents appropriate interpretation of randomised trial evidence. In fact this trial indicates that the best available estimate of the difference in efficacy between the agents is –0.03% (almost identical in effect although marginally favouring detemir), with the plausible range of the true treatment effect ranging from –0.3% to 0.2%). In other words, when confounding is appropriately addressed, we see no evidence of important differences in efficacy between the treatments. In addition, the trial indicated that the risk of major and nocturnal hypoglycaemia was greater with insulin glargine than detemir, while the overall risk profiles were similar between the treatments.

The authors of these two linked articles are correct in their assertion that it is important to base health technology assessment on data derived from a real world setting. However, they are incorrect in asserting that observational data may provide robust estimates of differences in effects and costs between different treatment strategies. Instead, a hybrid design is required, which utilises the protection against bias offered by randomisation while ensuring patients are representative of, and managed similarly to, actual practice. Examples of such designs exist, including in diabetes[6].

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Authors' reply

Dear Sir,

Freemantle *et al.* make a number of observations regarding our studies comparing insulin glargine and insulin detemir[1,2]. The first study described the relative efficacy/effectiveness of the two products[1], the other the relative costs of treatment[2]. Where possible, we address their criticisms in the same order as they appeared in their Letter above.

Firstly, we believe that our conclusion in the outcome article[1] was unbiased and accurate in finding that: 'On balance, glargine showed marginal improvement over detemir in diabetes-related outcomes'. We believe that an independent reviewer would agree with this assertion. Regarding the statement that we made about reduced risk of hypoglycaemia when using glargine; the crude rates evident in our data revealed likely differences in this outcome. The crude rate of reported hypoglycaemia in people treated with glargine post-switching was 4.8 reports per 100 patient years versus 6.9 reports per 100 patient years. However, we accept that these data could have been better standardised when reviewing the risk of this adverse event. We did not agree with Freemantle *et al.* about the actual method we used to compare the rate of hypoglycaemia. They argued that we should have used a conditional maximum likelihood method. Unreliability in these methods is characterised by inflated estimates of relative risk (≥ 5) from a model with as many, or more, covariates than there are events in one of the exposure groups[3]; examples of this have been published previously[4]. This was not an issue in this instance. We were also a little surprised that they remarked upon our conclusion that there was no evidence of any difference in discontinuation patterns between the two products. As they correctly asserted, we could have published sensitivity analysis that favoured glargine but we were trying to give a balanced account.

Glargine was used more frequently than determir as a basal oral therapy ('BOT', as they have termed it) – as they state, an off-label use of determir. This is understandable since the pharmacokinetics of the two

products means that glargine can be used in this way, giving people with type 2 diabetes this therapy option. Regarding type 2 diabetes – those who can use BOT – the total mean insulin volume requirement was significantly higher for patients treated with detemir in the following insulin regimens: basal-bolus; basal-bolus-OHA; and basal-OHA. The only group not to reach statistical significance in this regard was the basal-only (BOT) group, which was limited by small numbers; although even in this group, the magnitude of the difference remained the same as other insulin regimens (23%). It is important to note that the improved pharmacokinetic profile of insulin glargine allows it to be used effectively in combination with oral agents; thus allowing for less expensive treatment regimens in type 2 diabetes when using glargine. Table 4 of the cost-related article[2] illustrated how we controlled for diabetes type, regimen type, weight, and exposure to basal analogue insulin. This was supported by data listed in Table 3 in Reference 2 calculating the mean insulin dose by insulin regimen and type of diabetes. Irrespective of how these data were cut, all analyses resulted in a far higher insulin requirement when using detemir than with glargine. This observation was also true in the Novo Nordisk trial that they referred to in their correspondence[5]. Here, people treated with insulin detemir required 34% more basal insulin than those treated with insulin glargine. This represented a substantial increase in the costs of basal insulin in type 1 diabetes when using detemir rather than glargine. Although we did not report these data, we did compare some outcome measures in the cohort used to evaluate treatment costs only; for example, HbA1c where there was no discernable difference in the cost study cohort[2].

Regarding the value of randomised controlled trials (RCTs). We agree entirely that RCT data is often fundamental to the evaluation of any new product or intervention, and for the reasons that the authors described. However, we differ in that it is our belief that a range of intelligence sources are collectively crucial in determining the impact of any given therapy, including observational data. RCTs have their own limitations: even the RCT dogmatists would think twice about using such a study design to characterise the relative effectiveness of parachutes for the prevention of severe trauma or mortality! When comparing costs too; most people do not require an RCT when they make decisions about similar goods at the supermarket. Furthermore, although individual RCT reporting is more often than not of high quality, overall reporting of product-related trials can be generally biased[5]. Interestingly, we also believe that the RCT that they refer to is so openly biased in favour of detemir that is has virtually no scientific value[6]. This is currently the subject of separate correspondence.

Finally, the findings of our studies were also entirely consistent with many of the Novo Nordisk phase III registration trials of detemir in both type 1 and type 2 diabetes, where there was a consistent increase in the mean bolus insulin requirement necessary to maintain normoglycaemia[7]. Regarding type 1 diabetes: of the seven studies submitted by Novo Nordisk to the FDA in support of registration of detemir, only one trial (1448) was accepted as a convincing demonstration of non-inferiority over relevant comparators. In the remaining five studies, an increase in bolus insulin was necessary in the detemir arm to achieve glycaemic targets (trials 1181, 1243, 1205, 1316 and 1335). In trial 1447, the overall daily dose was higher in the detemir arm. In the phase III registration trials in type 2 diabetes, only in one of the four studies was non-inferiority clearly demonstrated (trial 1530). Of the remainder, detemir was inferior to NPH in one trial (1166), and insulin requirements were higher in the detemir arm in both trials 1336 and 1337[7].

Although we value constructive criticism of our work, in this instance we defend unequivocally our conclusion that patients treated with glargine had lower antidiabetic prescribing costs than did similar patients treated with detemir, and this finding is supported by findings from Novo Nordisk's own clinical trial program. Furthermore, we also defend our conclusion that glargine had marginally improved diabetes-related outcome than did detemir using real-life THIN data. The corollary of this is that glargine was more cost-effective than was detemir for the treatment of both types 1 and 2 diabetes in the United Kingdom.

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