RESPONSE FROM THE INTERNATIONAL INSULIN FOUNDATION (IIF) TO THE PROPOSAL TO INCLUDE LONG-ACTING INSULIN ANALOGUES FOR TYPE 1 DIABETES ON THE WORLD HEALTH ORGANISATION (WHO) ESSENTIAL MEDICINES LIST (EML).

We wish to record our objection to the proposed inclusion of long-acting insulin analogues for type 1 diabetes in the WHO’s Model EML. The International Insulin Foundation (IIF) was formed in 2002, and is a United Kingdom-based charity (www.access2insulin.org). We are an international group of diabetes specialists, and our mission is to ensure the global provision of affordable insulin for those with type 1 diabetes, as well as persons with type 2 diabetes who require insulin for optimal control. We also launched the 100 Campaign (www.100campaign.org) which sets the target of 100% affordability and 100% availability of insulin worldwide by the year 2022 (100 years after the introduction of insulin for people with diabetes).

Our objections are based mainly on an inadequate evidence-base for benefit and excessive cost, as detailed below –

1. Evidence. The application is mainly supported by a systematic review and network meta-analysis by Tricco and colleagues. This examines 39 studies (including 27 randomised trials) comparing glargine or detemir insulins (long-acting analogues) with human isophane (NPH) insulin in patients with type 1 diabetes. The hypothesis is explored that long-acting analogues reduce the prevalence of nocturnal hypoglycaemia, improve glycaemic control, and are associated with less weight gain. Many of these studies were unblinded, and often sponsored by insulin-manufacturing companies. The risk of bias in most of these studies is described as “serious” or “very serious” in all but two studies (see Tables 1 to 3 of the application to WHO). The benefits of analogues over isophane insulin were statistically small - in the Tricco meta-analysis long-acting analogues were described as only “probably superior” to human intermediate-acting insulins. In the application to WHO the phrase “slightly superior” is used. With regards to glycated haemoglobin (HbA1c), Tricco et al say the “difference is small” and “no differences are likely to be clinically relevant”. With regard to cost-effectiveness, the authors say that “results were inconsistent across studies.”
2. **Cost.** Analogue insulins are significantly more expensive than human preparations. The price excess varies between countries, but recent (2016) data from the ACCISS (“Addressing the Challenge and Constraints of Insulin Sources and Supply”) Study shows that prices for glargine and detemir insulins were seven to nine times higher than human insulins\(^3\). Diabetes is already a major cause of what has been called “catastrophic health expenditure” in lower and middle-income countries (LMIC), a situation which may be exacerbated by the wider introduction of analogue insulins\(^4,5\). Also, though the current application is directed at type 1 diabetes only, it is likely that market forces will encourage spread of analogue use to those with insulin-requiring type 2 diabetes, leading to an even greater economic burden.

WHO criteria for the inclusion of drugs in the EML state that addition to the list “must always be based on valid scientific evidence”, and also that inclusion depends on “financial resources”\(^6\). We believe that the considerations above argue strongly against inclusion of long-acting insulin analogues for type 1 diabetes onto the WHO’s Model EML, under current criteria. It would also seem empirically wrong that these drugs be regarded as “essential” when cheaper and effective alternatives are widely available.

There is widespread concern over the cost and affordability of analogue insulins, including in high-income countries such as the USA\(^7\). A 2016 *British Medical Journal* article was entitled “The travesty of expensive insulin”\(^8\), and in 2015 the *New England Journal of Medicine* published a review article entitled “Why is there no generic insulin? Historical origins of a modern problem”\(^9\).

Finally, we note with interest that a very recent editorial in *Lancet Diabetes & Endocrinology*\(^10\) also argued strongly against the inclusion of long-acting insulin analogues in the EML. The editorial noted that “access to human insulin is still despairingly low for many populations worldwide” and that “adding more expensive analogues to the list is unlikely to improve the situation”\(^8\). We fully agree, and request WHO to reject the current proposal.

**Trustees of the International Insulin Foundation (IIF).**

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2. Tricco AC, Ashoor HM, Antony JM et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systemic review and network meta-analysis. *BMJ* 2014; 349:g5459 doi: 10.1136/bmj.g5459


7. Luo J, Kesselheim AS, Greene J, Lipska KJ. Strategies to improve the affordability of insulin in the USA. *Lancet Diabetes & Endocrinology* 2017, [http://dx.doi.org/10.1016/S2213-8587(17)30041-4](http://dx.doi.org/10.1016/S2213-8587(17)30041-4)

