MEMORANDUM

From: Director, NVI
To: Director, EMP
Date: 01 March 2019

Our ref: 
Attention: Nicola Magrini

Your ref: WHOHQ-E19-81-17 
Through:

Originator: Coordinator, MND 
Subject: MEETING OF THE 22nd EXPERT COMMITTEE ON SELECTION AND USE OF ESSENTIAL MEDICINES. GENEVA, 1-5 APRIL 2019 - NVI-MND RESPONSE.

Thank you for sharing the applications received for updating the Model List of Essential Medicines and the Model List of Essential Medicines for Children relevant for the work of NVI technical units.

Please find the submissions on the proposed applications. Multiple micronutrient powders for anemia is not within our work and we have informed the department of Nutrition.

Thank you for the excellent work on the essential medicines list which is critical for advancing the management of NCDs.

Dr Etienne Krug

ENCL: (1)
Section 18: Addition of insulin analogues, including biosimilars for type 1 diabetes

The technical unit does not support the application to add long-acting insulin analogues nor their biosimilars to the 21st WHO Model List of Essential Medicines (EML). The application was not developed in consultation with this WHO department.

The terminology in the application is confusing: long-acting insulin is labeled as “human” when the review presumably does not include long-acting human insulin (discontinued), but intermediate-acting human insulin and long- and ultra-long-acting insulin analogues (and their biosimilars).

The selection of studies and data extraction raise concerns over the quality of the review. Despite the authors’ claim to have searched “grey” literature, the review does not include all eligible trials that could have been identified through searching trial registers and FDA reports. It is doubtful that fixed-effects meta-analysis is appropriate given the substantial heterogeneity between studies and the network meta-analysis should have been described in more detail in terms of evaluating its assumptions.

Many of the presented comparisons are confounding clutter and are not relevant because:
  a) some do not compare like with like (i.e. they simultaneously compare not only different insulins, but different injection regimens as well)
  b) some compare injection regimens not used in routine clinical practice, and
  c) some are not relevant to the review question because they compare different regimens of the same insulin.

In the comparisons that are relevant, the statistically significant benefit for HbA1c is small and is not considered to be of clinical significance by current criteria. Fasting blood glucose and weight change, although measured in clinical trials along with many other variables, have insufficient clinical relevance to be selected as primary outcomes. The only primary outcome where there indeed might be meaningful benefit with insulin analogues is serious hypoglycaemia. However, very few studies measured this outcome with hard data. Although the review authors considered all the selected outcomes to be objective and assigned them a low risk of certain types of bias, hypoglycaemia that is not documented by clinical data is a subjective outcome and thus prone to performance and detection bias. Presentation of the absolute as well as the relative risk of hypoglycaemia (as in GRADE tables) would add useful information on the magnitude of the problem and the benefit conferred by analogues. There is no assessment of the quality of the evidence, except for the assessment that the majority of studies had an unclear/high risk of bias. A similar application review used for WHO guidelines on insulin in 2017 graded the quality of evidence as being low or very low.

Cost-effectiveness is very much context-specific and depends on the particular country’s cost-effectiveness threshold per QALY gained, typically higher in higher income countries where the cited cost-effectiveness studies were conducted. A study from Thailand, not included in the review, did not find analogues to be more cost-effective. The results of cost-effectiveness
studies for pharmacological interventions have also been shown to depend on the source of funding.

The application does not address the very large differences in price between insulin analogues and human insulin. Although biosimilars are likely to cost less than proprietary insulin analogues, there is no evidence to support the claim that the emergence of biosimilar analogues will reduce the price of any analogue to that of human insulin. In many settings even human insulin is currently unaffordable, despite being on the EML for many years. It takes a substantial leap of faith to expect that inclusion of analogues, albeit biosimilars, in EML will improve insulin affordability.