

## Reviewers' answers

### A. Reviewer code 01424366

1. The review is thorough and is well written.

**Author:** Thank you.

2. The main shortcoming is that inhaled insulin is not commonly prescribed compared to injected forms, and technosphere-administered inhaled insulin even less so. As the major drive of technology at present is towards CGM and pump algorithms I think the review will reinforce opinion that inhaled insulins are not the way to go for the vast majority of patients. There is a place for such a report though.

**Author:** I agree. That is why I already mentioned in the paragraph entitled "Place of technosphere insulin in treatment of diabetes" that its use is "most appropriate in the following *selected* groups of patients ..."

3. It is mentioned that a major shortcoming of TI is coughing, and that 40% of insulin is wasted and never absorbed as it is lost to the gut. This seems to be an important economic argument for not using TI. Some mention of economic modelling of TI vs. injection of rapid insulins or pumps would be useful.

**Author:** To the best of my knowledge, no direct economic data exists to compare inhaled insulin with various types of insulins or insulin pump. I added in table 4, under the "limitations of technosphere insulin:" that its cost is high, and I mentioned the average cost followed by the supporting reference as follows: "**average price of ninety 4-unit cartridges and 2 inhalers is \$271 [21].**"

4. Another issue with inhaled insulin is that it is unreliable when patients are congested and dosage becomes guess work. Presumably there are

recommendations around this.

**Author:** I already addressed this issue by saying in table 4 under limitations item # 6:” “Safer to switch to subcutaneous insulin in case of upper or lower respiratory infections to avoid exacerbation of the disease and possible unreliable pulmonary absorption”

#### A. Reviewer’s code 00504962

1. This is minireview regarding the place of technosphere inhaled insulin in treatment of diabetes. The topic must be important in the future.

Please describe the possibility of inhaled insulin to adolescents.

Author: to the best of my knowledge, no studies are available in pediatric or adolescent population, and I already mentioned that point in table 4 under the limitation section by saying “ 6. No data available for pediatric and pregnant populations.”

2. High cost is one limitation. Please describe the point in greater detail.

Author: I totally agree, and this point is addressed under limitation in table 4 by saying: “9. High cost **e.g. average price of ninety 4-unit cartridges and 2 inhalers is \$271 [21].**”