PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	INfluenza VaccInation To mitigate typE 1 Diabetes (INVITED): a study protocol for a randomized, double-blind, placebo-controlled clinical trial in children and adolescents with recent-onset type 1 diabetes
AUTHORS	Pedersen, Ida; Kjolby, Mads; Hjelholt, Astrid; Madsen, Mette; Christensen, Ann-Margrethe; Adolfsen, Ditte; Hjelle, Jesper; Kremke, Britta; Støvring, Henrik; Jessen, Niels; Vestergaard, Esben Thyssen; Kristensen, Kurt; Frobert, Ole

VERSION 1 – REVIEW

REVIEWER	Wysocka-Mincewicz, Marta Children's Memorial Health Institute, Endocrinology and Diabetology
REVIEW RETURNED	09-Apr-2024

GENERAL COMMENTS	Dear Authors, This is interesting and promising idea for patients with newly recognized type 1 diabetes, and in the future maybe in strategy for patients with stage 2 of type 1 diabetes. My only concern is that we do not know patients current immunological status against other influenza viruses, and other viruses which could influence on patients metabolic status. The study group possibly is too small to prove the hypothesis if immunological status will be not perfectly established.

REVIEWER	Prodam, Flavia University of Piemonte Orientale, Department of Health Sciences
REVIEW RETURNED	10-Apr-2024

GENERAL COMMENTS	Pedersen I et al. investigated the role of influenza vaccination in the mitigation of type 1 diabetes in children older than 6 years. It is a protocol of an ongoing study started in November 2022. Children younger than 6 years have been excluded for ethical issues (placebo control study). The study will start within 14 days from T1D diagnosis. Information on the protocol is detailed and complete. A clear discussion clarifies the hypothesis of the study. The stdy will give important data dor the management of T1D.

REVIEWER	Vyas , Arpita Kalla California Northstate University
REVIEW RETURNED	10-Apr-2024

GENERAL COMMENTS	The Manuscript is overall well written, and the trial addresses an important field of research relating to beta cell preservation. The

	trial is novel and could provide some critical information relating to the pleotropic effects of influenza vaccination on type 1 diabetes mellitus. Minor comment: Since insulin can be delivered via insulin pump or injection and intensive management will impact the overall beta cell burden. Would be helpful to document mode of insulin delivery and how the authors plan on controlling for variation in glycemic control on the results of the MMP at 12 months.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 comments:

1. This is interesting and promising idea for patients with newly recognized type 1 diabetes, and in the future maybe in strategy for patients with stage 2 of type 1 diabetes.

Response: We thank the reviewer for the positive evaluation of our study.

2. My only concern is that we do not know patients current immunological status against other influenza viruses, and other viruses which could influence on patients metabolic status. The study group possibly is too small to prove the hypothesis if immunological status will be not perfectly established

Response: Thank you for sharing your concerns with us. We acknowledge that the participants current immunological status against other influenza viruses and potential influences on their metabolic status is important. We include measurements of influenza virus antibody titers at all study visits (table 1, exploratory endpoints). Additionally, we will explore the feasibility of assessing other subtypes of influenza virus. Throughout the follow-up period, all vaccines administrated will be recorded, including previous vaccination status obtained at the baseline visit.

We agree with the importance of understanding the immunological state, and we aim to address this through a sub-study, as this is beyond the capacity of the current trial. **We have added this as a limitation in the "Discussion" section (line 428-431).**

- *"An additional limitation pertains to the absence of participant immunological status documentation at the time of randomization. It is anticipated that the pleiotropic effects of the vaccine may not be severely influenced by the current immunological status, given that the primary mechanism involves the attenuation of the inflammatory response (3, 46)."*

Reviewer 2 comments:

Pedersen I et al. investigated the role of influenza vaccination in the mitigation of type 1 diabetes in children older than 6 years.

It is a protocol of an ongoing study started in November 2022. Children younger than 6 years have been excluded for ethical issues (placebo control study).

The study will start within 14 days from T1D diagnosis.

Information on the protocol is detailed and complete. A clear discussion clarifies the hypothesis of the study.

The stdy will give important data dor the management of T1D.

Response: We thank the reviewer for the encouraging evaluation of our study. It is rewarding that our research in the management of T1D is appreciated.

Reviewer 3 comments:

1. The Manuscript is overall well written, and the trial addresses an important field of research relating to beta cell preservation. The trial is novel and could provide some critical information relating to the pleotropic effects of influenza vaccination on type 1 diabetes mellitus.

Response: We thank the reviewer for the positive feedback of our manuscript. We are happy that our research area is considered interesting.

2. Since insulin can be delivered via insulin pump or injection and intensive management will impact the overall beta cell burden. Would be helpful to document mode of insulin delivery and how the authors plan on controlling for variation in glycemic control on the results of the MMP at 12 months.
Response: Thank you for drawing attention to this important consideration. We will collect continuous glucose monitoring data (TIR, TAR, TBR, CV and GMI), mode of insulin delivery (MDI or insulin pump), and total daily insulin dosage at all three study visits. **This is further elaborated in the methods section (line 256).**
We plan on controlling for variation in glycaemic control by testing for differences between the intervention and placebo group. If there is no significant difference between the groups, we anticipate that these variations will not unduly influence the results of the mixed-meal tolerance test at 12 months. We do not expect that the mode of insulin delivery will impact the beta-cell function, as clinical trials have shown no significant difference between insulin pump and multiple daily injections. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3836135/).
Furthermore, given our focus on beta-cell preservation, we expect the coefficient of variance (CV) and glycaemic control to be improved in the intervention-group.