Author’s response to reviews

Title: Makes FLASH the difference between intervention group and treatment-as-usual group in an evaluation study of a structured education and treatment programme for flash glucose monitoring devices in people with diabetes on an intensive insulin therapy: study protocol for a randomized controlled trial

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Author’s response to reviews:

Dear Ms Mader,

Thank you very much for giving us the opportunity to submit this revised version of our manuscript titled “Makes FLASH the difference? Protocol for a randomized controlled trial between intervention group and treatment-as-usual group to evaluate a structured education and treatment programme for flash glucose monitoring devices in people with diabetes on an intensive insulin therapy”, and to address the comments of the reviewers. We thank the reviewers for their comments, which have helped us improve the manuscript considerably. Please see below our specific responses to the comments.

We hope that you now find this manuscript suitable for publication in your Journal.

Best regards
Melanie Schipfer
Dear Mr Melmer, thank you for your valuable comments to improve our manuscript. Below you will find our answers to each of the issues. We hope that these responses will clarify all doubts.

1. The manuscript offers incomplete information about how FLASH was performed. The authors state that "FLASH uses different modern educational techniques". Please describe these techniques and also explain whether all of those techniques were used or if techniques were adapted to the patient individual capacities.

The education techniques are derived from the guiding principle of self-management, especially self-monitoring, self-assessment, and enhancing self-treatment. Participants are provided written material and worksheets and are encouraged to test the contents of each lesson on their own and to then discuss their experiences in the group setting. They are introduced to computer-based data analysis software and learn how to use it for optimising their own therapy. Additionally, patients define what they personally hope to achieve by attending the FLASH programme. Course instructors are provided core content about the interpretation of flash glucose monitoring results and also optional content in slides on a secondary level if more detailed information needed on a certain topic e.g. exercising or hypoglycemia. (See page 12).

2. The manuscript offers incomplete information about how "professional employees" were educated in using the program. Who was responsible for quality control, monitoring and/or queries?

The course instructors for FLASH will be certified diabetes educators (CDE). Prior to the study, the course instructors will undergo intensive 8-hour training in the study protocol and the education and treatment programme. This programme will be conducted by the research team. Course instructors will be provided with a written curriculum and audiovisual teaching material, along with detailed descriptions of each slide. Additionally, trainers from the coordination research institute (FIDAM) will visit each participating medical centre, and course instructors can then clear any doubts about the conduct of the programme. In these visits FIDAM employees will confirm that the slides of the FLASH will operate and could be displayed in each medical praxis and that the course instructor knows how to conduct the programme, fully understands the content of the programme and can clarify any likely questions, and knows how to upload the
therapy data from the flash glucose monitoring reader to DIASEND®. During the course of study, all study centres will have a hotline to FIDAM for support. FIDAM will communicate with all participating study centres via newsletters where every news can be presented promptly and reliable. The other way around, the coordinating centre will be available for the responsible personnel in the study centres for the entire duration of the study. In addition to conducting the education and treatment programme, the physicians at the study centres will be responsible for the therapy of their patients during and after the study. (See page 6ff)

3. The authors mention that "Randomly chosen study center will be audited by the responsible FIDAM employees to proof the adherence to the study protocol". Why did the authors perform draw sampling? What was the estimated/predefined number and/or frequency of draw samplings?

All study centres are instructed by a personal visit and each study centre were offered a hotline and were audited per telephone. In addition, 50% of the study centres will be audited by FIDAM to check the quality of study conduct. Glycaemic data from the flash glucose monitoring system will be uploaded via Diasend®, thus FIDAM can identify online incomplete data and notify the study centres whenever necessary. (See page 16)

4. Data were obtained from multiple participating study centers in Germany. In which way were those data collected? Where data written in CRFs or eCRFs? Who was responsible for data management? In which way were the data/CRFs/eCRFs transmitted? Is there a data safety committee, a website available for public information (as is recommended for multicenter studies), or monitoring procedures on a regular basis?

All CRFs will be in paper-and-pencil form; no electronical case report forms (eCRF) will be used. FIDAM will be responsible for the management of all collected data. This study is registered at clinicaltrials.gov (identifier: NCT03175315), where all relevant information is available to the public. There will be no external safety committee since this is a non-pharmacological intervention. The incidence of serious adverse events and device related adverse events are will be collected via standardised reporting forms and reported to FIDAM. (See page 16ff)
5. The authors state that "Financial grants for every patient who will fulfill the complete protocol will be agreed in a contract with every study centre. This shall motivate the responsible personnel as well as the participating patients in both groups." I'm not fully aware of the legal requirements in Germany, but financial devotions should be noted as a potential study limitation.

Financial grants will be issued for patients who complete the study. These financial grants will not be given to the patients but to the study centres to compensate them for the additional effort (i.e., recruitment of patients, informing the patients about the study, obtaining informed consent, conduct of treatment, checking questionnaire data and electronic data for completeness, answering queries, and reporting serious or device-related adverse events). All educational materials will be supplied free to the study centres and patients. (See page 19 and page 23ff)

6. In the section "inclusion criteria", the authors mention "indication for using a flash glucose monitoring system". Please describe the indication for using FGMS.

Indication for FLASH will be decided by the treating physician. The decision will be based on the following: 1) frequent unexplainable glucose levels and need for multiple daily measurement of blood glucose; 2) severe hypoglycaemia events, especially during the night; hypoglycaemia unawareness; and 3) undue patient anxiety about use of the lance, but otherwise good compliance with. (See page 9ff)

7. There is little information about the planned statistical analysis. The authors plan to conduct a plethora of questionnaires. Are all of these outcome variables continuous? In case of categorical data determined over more than 2 time points, different approaches may be required (ordinal regression analysis, Kruskal wallis, etc…). Please comment.

We fully agree with the reviewer that sometimes the questionnaire data may be skewed and may not fulfill criteria for interval data. Assuming that at least rank order data are available from the questionnaires, we will use either nonparametric tests for evaluation of questionnaires and glucose data, or perform a transformation of the scores and glucose parameters into van der Waerden scores before applying parametric tests. Based on the data distribution and the scale of
measurement, appropriate statistical methods will be selected. In the case of categorical data determined over several time points, we will use logistic regression analysis with adjustment for baseline values. (See page 20)

Dear Ms Bravo,

Thank you for your compliment and your kind words. We thank you for your comments, which have helped us improve our manuscript. Please find below our answers and statements addressing each of your mentioned points. We hope we have answered all of them sufficiently and to your fullest satisfaction.

1. Specially, description of the study design and procedures is not very clear. Table 1 should include the time (week of the treatment) each session will be held, since descriptions in the text are a bit confusing.

Thank you for this point. We have added the weeks of treatment in table 1.

(See page 13ff)

2. The same applies to the time elapsed between each visit (1 to 4), that should be included in Figure 1.

We added these details in Figure 1 (please see appendix figure 1)
3. Who will be responsible for the educational program in each of the 40 clinics? Please state clearly in the text.

We have clarified this in the manuscript (to address the comment of reviewer 1) as follows:

The course instructors for FLASH will be certified diabetes educators (CDE). Prior to the study, the course instructors will undergo intensive 8-hour training in the study protocol and the education and treatment programme. This programme will be conducted by the research team.

See our response to comment 2 of the first reviewer page 6ff.

4. In page 3, line 12 it is said that "three to eight patients aged 16 to 75 years" will be the group setting as established in the protocol of the trial. Although reduced groups of 3-8 participants is positive, maybe the efficacy of the educational program would be higher if more homogeneous age groups are formed, since the form of explaining and motivating teenagers would be quite different to how to address elderly patients.

We appreciate your comment and we partially agree with your opinion.

This wide age range was selected so that study centres could include as many eligible patients as possible. Previous experience has shown that it is difficult to recruit homogeneous age-groups. Having patients of widely differing ages is not necessarily a disadvantage, since younger people with diabetes can learn from the experiences of older ones and vice versa. If important differences are observed between the different age-groups, adjustment for these factors will be made during analysis of data. (See page 11)

We have added this information in the statistical analysis section. (See page 20)

5. Since the FLASH system is already available, an exclusion criterion should be previous use of this monitoring system by patients.
The REPLACE and IMPACT studies [1, 2] were not able to show significant improvement in glycemic control with flash glucose monitoring vs. SMBG. Assuming education might be able to improve the efficacy of flash glucose monitoring, exclusion of patients with previous flash glucose monitoring system use is not necessary (since the device alone does not seem to be efficacious in improving the HbA1c). The main objective of this study is not to prove the efficacy of flash glucose monitoring systems, but rather to evaluate the efficacy of the FLASH education and treatment programme. However, if there are substantial differences between the control and intervention group in previous flash glucose monitoring system usage, adjustment will be made during the analysis for previous flash glucose monitoring systems experience. (See page 10ff)