## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | The rationale and design of a randomized controlled trial testing the effect of personalized diet in individuals with prediabetes or type 2 diabetes mellitus treated with metformin |
| **AUTHORS** | Htet, Thaw; Godneva, Anastasia; Liu, Zhixin; Chalmers, Eliza; Kolobkov, Dmitry; Snaith, Jennifer; Richens, Renee; Toth, Krisztina; Danta, Mark; Hng, Tien-Ming; Elinav, Eran; Segal, Eran; Greenfield, Jerry; Samocha-Bonet, Dorit |

## VERSION 1 – REVIEW

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| **REVIEWER** | Kei Nakajima<br>School of Nutrition and Dietetics, Faculty of Health and Social Services, Kanagawa University of Human Services, Yokosuka, Japan. |
| **REVIEW RETURNED** | 03-May-2020 |

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| **GENERAL COMMENTS** | This article describes the rationale and design of a trial testing the effect of metformin administered with adjuvant personalized diet in individuals with prediabetes and untreated diabetes.<br>This article is well written and of clinical interest.<br><br>Major comments<br>1 The grouping and division of participants are unclear. In the descriptions of Metformin (both arms) and Monitoring and adherence evaluation (both arms), it is unclear what “both” means.<br>A figure depicting the relationship between groups may be helpful.<br><br>2 At the time of writing, COVID-19 is pandemic worldwide probably including Sydney.<br>Are there any effects and confounding factors on your trial that will be held on going or the period several months from now?<br><br>3 It is unclear for the selection of the low-fat high dietary fiber diet corresponding to PNP algorithm-based diet. In addition, although the authors claim that LFHF diet is designed to provide approximately 30% of the total daily energy intake from fat, I wonder 30% from fat may be normal but not low. Please add explanations for these issues.<br><br>4 Eligibility of participants in the text seems to be somewhat different from the inclusion and exclusion criteria described in the Table 1. How about the patients who have been treated with pharmacotherapy for hypertension or dyslipidemia, some of them can affect glycemic control?<br><br>5 Although the authors described “A target dose of 1000 mg/d is set for participants with mild to moderately decreased eGFR (45 – 59 |

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| | mL/min/1.73m2), or participants who cannot tolerate the higher dose", how to deal with the results from these participants at the final analysis?<br><br>Minor comments<br>There are a lot of abbreviations. Are all abbreviations required? |

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| **REVIEWER** | Prof Louise Maple-Brown<br>Menzies School of Health Research,<br>Australia |
| **REVIEW RETURNED** | 12-Jun-2020 |

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| **GENERAL COMMENTS** | Thank you for this excellent manuscript. This is a great study that is presented very well in this protocol manuscript. All details are adequately presented and I have no further requests nor questions for the authors. Wishing you all the best with this excellent study. |

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| **REVIEWER** | James Flory<br>Memorial Sloan Kettering Cancer Center<br>United States |
| **REVIEW RETURNED** | 18-Jun-2020 |

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| **GENERAL COMMENTS** | This clearly written and interesting protocol is suitable for publication as a protocol paper. I have a few minor comments:<br><br>1) My most substantive critique is that HbA1c is the primary outcome in a study that enrolls both patients with diabetes and pre-diabetes. HbA1c will probably fall much more in the diabetes group than in the pre-diabetes group, where it may not change at all. This raises a need for pre-specified stratified analysis and raises concerns about the power calculations, since the 0.4% fall in HbA1c assumed may not be realistic in patients with pre-diabetes.<br><br>2) The title is a little misleading. Since everybody gets metformin, this is really a comparison of two different diets in the setting of metformin use<br><br>3) page 8 lines 7-10 are a little unclear<br><br>4) For eligibility under page 9, renal disease is not included as an exclusion criterion (it is mentioned later in the paper). I would state this clearly and give the eGFR cutoff for eligibility (is it 45, or 30?). I'd also consider excluding patients with evidence of microvascular or macrovascular disease, who might require addition of other antidiabetic medications during the study period<br><br>5) I'd consider the possibility that metformin adherence will be affected by the diet, and add this to the list of potential mediators of study outcome. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name: Kei Nakajima
Institution and Country:
School of Nutrition and Dietetics, Faculty of Health and Social Services, Kanagawa University of Human Services, Yokosuka, Japan.
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
This article describes the rationale and design of a trial testing the effect of metformin administered with adjuvant personalized diet in individuals with prediabetes and untreated diabetes.
This article is well written and of clinical interest.

Major comments
1 The grouping and division of participants are unclear. In the descriptions of Metformin (both arms) and Monitoring and adherence evaluation (both arms), it is unclear what "both" means.
A figure depicting the relationship between groups may be helpful.

In "both" we mean that these sections are relevant to both study arms. We have clarified this in the headings in the revised version of the manuscript. We believe that the revisions made to the manuscript clarified the interventions, and that a Figure is not necessary. However, we will be happy to draw a Figure if the Reviewer still believes it is required.

2 At the time of writing, COVID-19 is pandemic worldwide probably including Sydney.
Are there any effects and confounding factors on your trial that will be held on going or the period several months from now?

We expect that the pandemic will have an effect on our study participants. For example, participants may be less adherent with metformin and their dietary intervention. We hope that we will be able to capture these effects with our adherence and monitoring tools.

To improve the engagement of participants and avoid potential increases in drop-out rate, we have increased the rate of contact we maintain with the study participants, for example by using remote video connection tools and phone calls on a regular basis.

In any case, we expect that the impact of the pandemic on this randomised controlled trial will be even across the intervention and control group in terms of both the intervention delivery and outcomes. However, we will be able to explore the impact of the pandemic on the study outcomes and adherence across groups of participants enrolled and followed up during the different study periods. We suggest sensitivity analysis using the timing of the enrolment (pre-pandemic / within pandemic / and post-pandemic, if relevant) as a covariate in the analysis. This has been added to the protocol manuscript (Analysis Plan).

3 It is unclear for the selection of the low-fat high dietary fiber diet corresponding to PNP algorithm-based diet. In addition, although the authors claim that LFHF diet is designed to provide approximately 30% of the total daily energy intake from fat, I wonder 30% from fat may be normal but not low. Please add explanations for these issues.

As alluded to in the introduction, there are many dietary approaches taken to treat individuals with dysglycaemia. However, a lower fat diet rich in wholegrain foods with high dietary fibre content is one of the most commonly prescribed. Aiming for a strong design powered to detect differences between groups, we decided to limit the study to 2 study arms, and selected the most common standard of care as our comparator.

The diet comparator chosen in the present study follows the Australian Healthy Eating Guide[1] principles, and is not merely restricting total fat content, as described in detail in the manuscript section '*Low-fat high fibre diet (LFHF) arm'*. Specifically, we aim for reducing saturated fat to less than 10% of the total fat consumed, the carbohydrates are from wholegrain low GI sources, generally rich in legumes and poor in refined (white) grains, added sugar, and food items typically perceived as "unhealthy", including pizza, cream and processed meat. Overall, this diet is considerably different from the diet of the average adult Australian[2]. These details have been added to the revised manuscript.

4 Eligibility of participants in the text seems to be somewhat different from the inclusion and exclusion criteria described in the Table 1.

How about the patients who have been treated with pharmacotherapy for hypertension or dyslipidemia, some of them can affect glycemic control?

Thank you for this comment, we have made the inclusion/exclusion criteria consistent throughout the protocol paper.

Indeed, the study target population is expected to be treated with other medications due to other co-morbidities. Other than excluding participants treated with diabetes medications, oral steroids and ongoing antibiotic medications, which may affect our endpoints, we chose to include participants on lipid lowering and anti-hypertension medications for the sake of completing the study in a timely manner. We will compare the distribution of background medications between the study arms and expect them to be similar between the groups.

In any case, as stated in the analysis plan, background medications will be accounted for in the model, together with other confounders (Analysis Plan section).

5 Although the authors described “A target dose of 1000 mg/d is set for participants with mild to moderately decreased eGFR (45 – 59 mL/min/1.73m2), or participants who cannot tolerate the higher dose”, how to deal with the results from these participants at the final analysis?

Thank you for raising this point. To account for lower metformin dose, an indicator for metformin dose status (full dose / reduced dose) will be created and adjusted as a covariate in the final analysis of the intervention efficacy. We will also conduct a sensitivity analysis including participants who are treated at the 1500 mg/d target dose only. This has been added to the manuscript’s Analysis Plan.

Minor comments
There are a lot of abbreviations. Are all abbreviations required?

We reduced the number of non-standard abbreviations in the revised manuscript.

Reviewer: 2

Reviewer Name: Prof Louise Maple-Brown

Institution and Country:
Menzies School of Health Research,
Australia
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
Thank you for this excellent manuscript. This is a great study that is presented very well in this protocol manuscript. All details are adequately presented and I have no further requests nor questions for the authors. Wishing you all the best with this excellent study.

Thank you!

Reviewer: 3
Reviewer Name: James Flory
Institution and Country:
Memorial Sloan Kettering Cancer Center
United States
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
This clearly written and interesting protocol is suitable for publication as a protocol paper. I have a few minor comments:

1) My most substantive critique is that HbA1c is the primary outcome in a study that enrolls both patients with diabetes and pre-diabetes. HbA1c will probably fall much more in the diabetes group than in the pre-diabetes group, where it may not change at all. This raises a need for pre-specified stratified analysis and raises concerns about the power calculations, since the 0.4% fall in HbA1c assumed may not be realistic in patients with pre-diabetes.

We understand the reviewer's concern and while we expect that we will be able to detect reductions in HbA1c in participants with prediabetes, the magnitude of the reduction is expected to depend on the baseline level measured. Since we utilise stratified randomization with baseline HbA1c level being one of the stratification factors, the number of participants with prediabetes and full-blown diabetes should be evenly distributed across the two groups.

Furthermore, we will explore the intervention effect in these sub-cohorts as described: "Subgroup analyses can be further performed to explore the intervention effect in specific sub-cohorts, for instance, the group of participants who have diabetes at baseline, the group of participants who achieve adherence standard and maintain the desired metformin dose; the group of participants with BMI >25 kg/m$^2$ at baseline, etc." (revised manuscript Analysis Plan section).

2) The title is a little misleading. Since everybody gets metformin, this is really a comparison of two different diets in the setting of metformin use

Thank you for drawing our attention to this. We have revised the title to read: "The rationale and design of a randomized controlled trial testing the effect of personalized diet in individuals with prediabetes or type 2 diabetes mellitus treated with metformin".

3) page 8 lines 7-10 are a little unclear

We have revised this sentence to read: "Adults with prediabetes or early-stage T2DM who are not treated with glucose-lowering medications are randomized, with equal allocation, to either the PNP or LFHF diet arms, in both arms participants are commenced on metformin Extended Release (XR) 1500 mg/d treatment for 6 months." We hope that the design is clearer now.

4) For eligibility under page 9, renal disease is not included as an exclusion criterion (it is mentioned later in the paper). I would state this clearly and give the eGFR cutoff for eligibility (is it 45, or 30?). I'd also consider excluding patients with evidence of microvascular or macrovascular disease, who might require addition of other antidiabetic medications during the study period

Thank you for noticing this. We have added the eGFR cut-off for exclusion (<45 mL/min/1.73m$^2$).

We already have current or recent (within the last 24 months) treatment with anti-diabetic medication in the previous 24 months as grounds for exclusion from entry to the study. Individuals who during the course of the study will require a glucose-lowering medication, other than the metformin prescribed in the study, will be excluded.

5) I'd consider the possibility that metformin adherence will be affected by the diet, and add this to the list of potential mediators of study outcome.

This is an interesting possibility which we will be able to explore and account for by comparing the metformin adherence between the study groups. We have added to the Analysis Plan of the revised manuscript: "The effect of the diet intervention mediated by metformin adherence on the study outcomes will also be tested."

## References


1. Australian Government National Health and Medical Research Council. Australian Guide to Healthy Eating 2015 [updated 01-05-2017. Available from: https://www.eatforhealth.gov.au/guidelines/australian-guide-healthy-eating2019.

2. Grech A, Rangan A, Allman-Farinelli M. Macronutrient Composition of the Australian Population's Diet; Trends from Three National Nutrition Surveys 1983, 1995 and 2012. *Nutrients* 2018;10(8):1045. doi: 10.3390/nu10081045

**VERSION 2 – REVIEW**

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| **REVIEWER** | Kei Nakajima<br>Kanagawa University of Human Services, 1-10-1 Heisei-cho, Yokosuka, Kanagawa 238-8522, Japan |
| **REVIEW RETURNED** | 20-Jul-2020 |

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| **GENERAL COMMENTS** | This protocol article aims to evaluate the efficacy of personalized diet as adjuvant to metformin in improving glycaemic control in individuals with dysglycemia.<br>The primary outcome measure is glycated haemoglobin (HbA1c).<br>The secondary outcomes are (1) time of interstitial glucose <7.8 mmol/L and (2) glycaemic variability (continuous glucose monitoring), (3) body weight, and so on.<br>This article is well designed and then of clinical interest.<br><br>Major comments<br>1 Although the authors mentioned as “a wide age range was selected to encompass different populations of individuals”, it is unclear how to interpret or analyze the outcomes. Are whole patients going to be divided into younger and older groups?<br>Probably, older people close to 70 years are unfamiliar with a smartphone application.<br><br>2 Do the authors consider alcohol consumption and smoking as confounding factors?, although these habits influence the diet and insulin sensitivity.<br><br>3 Is individual’s preference or taste considered in the arm of Personalized Nutrition Project?, which may influence the compliance for the diet.<br><br>4 Do the authors consider the balance between age generations or between men and women in advance?<br><br>5 Are there any criteria to terminate the trial, for instance, due to adverse effects such as frequent hypoglycemia?, because the combination of metformin, diet, and physical activity may exert a synergistic effect.<br><br>Minor comments<br>1 It may be better to express the HbA1c in National Glycohemoglobin Standardization Program (NGSP) and (IFCC) units (mmol/mol).<br>2 It may be better to provide the equation for eGFR or its reference because several equations are available in the world. |

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| **REVIEWER** | James Flory<br>Memorial Sloan Kettering<br>United States |
| **REVIEW RETURNED** | 29-Jul-2020 |

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| **GENERAL COMMENTS** | All comments were nicely addressed and this protocol is suitable for publication. |

**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 1

This protocol article aims to evaluate the efficacy of personalized diet as adjuvant to metformin in improving glycaemic control in individuals with dysglycemia.
The primary outcome measure is glycated haemoglobin (HbA1c). The secondary outcomes are (1) time of interstitial glucose <7.8 mmol/L and (2) glycaemic variability (continuous glucose monitoring), (3) body weight, and so on.
This article is well designed and then of clinical interest.

Major comments
1 Although the authors mentioned as “a wide age range was selected to encompass different populations of individuals”, it is unclear how to interpret or analyze the outcomes. Are whole patients going to be divided into younger and older groups?
Probably, older people close to 70 years are unfamiliar with a smartphone application.

Response: This type of analysis can be done. As stated in the Analysis Plan (page 17), subgroup analyses will be performed and age cut-off (20-49 and 50-70 years) could be applied. Furthermore, and as specified in the response to question 4, randomization is stratified by age group to achieve balance in age distribution across the 2 arms.
In regard to the concern raised that the app use by the older population may be sub-optimal, we are not concerned, and in fact, based on our experience so far is not the case. The participants are regularly supported by the study staff available to train and troubleshoot any issue with the app use. We recorded short (1-minute) videos demonstrating and covering the app use during baseline (the "profiling" stage) and treatment. We share the videos with the participants through emails, specific to the study stage and arm. This information has been added to the revised manuscript (page 9 and page 13). Furthermore, since refusal to use a smartphone application is ground for exclusion, individuals joining the study are familiar with smartphone applications, sometimes they are experienced with other nutritional/diet applications (e.g. my fitness pal), and are receptive for using the study app.

2 Do the authors consider alcohol consumption and smoking as confounding factors?, although these habits influence the diet and insulin sensitivity.

Response: Yes, alcohol consumption and smoking will be treated as confounding factors and will be adjusted as necessary in the model. Excessive alcohol consumption is grounds for exclusion (Table 1).

3 Is individual’s preference or taste considered in the arm of Personalized Nutrition Project?, which may influence the compliance for the diet.

Response: Yes, the individual food preferences and dislikes are easily addressed in the PREDICT study, in both arms. Participants choose from hundreds of recipes, and thousands of food items and are welcome to avoid foods and meals they dislike. Moreover, special sets of recipes are uploaded for individuals who practice vegetarianism, avoid dairy, eggs and fish/seafood. This has been clarified in the revised manuscript (page 12).

4 Do the authors consider the balance between age generations or between men and women in advance?

Response: Yes, age and gender, along with BMI and HbA1c are stratifying factors in the randomization, ensuring balanced arms (page 9).

5 Are there any criteria to terminate the trial, for instance, due to adverse effects such as frequent hypoglycemia?, because the combination of metformin, diet, and physical activity may exert a synergistic effect.

Response: We regularly lookout and monitor adverse events in the study. As metformin is generally safe, and does not cause hypoglycemia, we are not expecting that hypoglycemia (or other severe adverse events) will occur. All adverse events will be reviewed by the study investigators regularly. We use continuous glucose monitors twice during the treatment phase (at 3 and 6 months of treatment, Table 2) and will be in a position to identify abnormal glucose levels during the treatment.

Minor comments
1 It may be better to express the HbA1c in National Glycohemoglobin Standardization Program (NGSP) and (IFCC) units (mmol/mol).

Response: We have added the IFCC units next to the NGSP units throughout the revised manuscript.

2 It may be better to provide the equation for eGFR or its reference because several equations are available in the world.

Response: The reference used in the calculation of eGFR has been added to the manuscript (page 6 and footnote of Table 1, reference #17: Lamb EJ, Tomson CR, Roderick PJ. Estimating kidney function in adults using formulae. Ann Clin Biochem. 2005;42(Pt 5):321-45).

Reviewer: 3

All comments were nicely addressed and this protocol is suitable for publication.

Many thanks.

*Some minor additions and changes were made for accuracy and to improve readability (in red font).

**VERSION 3 – REVIEW**

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| **REVIEWER** | Kei Nakajima<br>School of Nutrition and Dietetics, Faculty of Health and Social Services, Kanagawa University of Human Services, 1-10-1 Heisei-cho, Yokosuka, Kanagawa 238-8522, Japan<br><br>Department of Endocrinology and Diabetes, Saitama Medical Center, Saitama Medical University, 1981 Kamoda, Kawagoe, Saitama 350-8550, Japan |
| **REVIEW RETURNED** | 28-Aug-2020 |

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| **GENERAL COMMENTS** | The manuscript has been improved according to the comments. Thank you for interesting protocol. |