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# BMJ Open

## Efficacy of time restricted feeding and behavioral economic interventions in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted feeding alone or usual care in patients with impaired fasting glucose: protocol for a randomized controlled trial

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Manuscripts

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3 **Efficacy of time restricted feeding and behavioral economic intervention in reducing**  
4 **fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time**  
5 **restricted feeding alone or usual care in patients with impaired fasting glucose: protocol**  
6 **for a randomized controlled trial**  
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## Abstract

**Introduction:** Impaired fasting glucose (IFG) is a significant risk factor of diabetes mellitus (DM) and also diabetic complications. Time restricted feeding (TRF) is one type of diet that showed positive effects on many metabolic signal pathways from animal studies. However, the effects of TRF toward cardiometabolic risk factors in human are still limited. In addition, compliance of TRF remains problematic for some people despite their intention to follow the diet control. Therefore, this study aims to investigate the efficacy of TRF with behavioral economic interventions, compared to TRF alone and usual care, in reducing fasting plasma glucose (FPG), hemoglobin A1c(HbA1c), and other cardiometabolic risk factors in patients with IFG.

**Methods and analysis:** This parallel randomized controlled trial will be conducted at the outpatient clinic of Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. Patients aged 18-65 years with IFG defined as FPG 100-125 mg/dl, and having body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup> will be recruited between October 2021 and October 2022. Patients will be randomly allocated to 3 groups (1:1:1 ratio) as 1) TRF with behavioral economic interventions, 2) TRF alone, or 3) usual care. The duration of intervention will be 12 weeks. Primary outcomes are FPG and HbA1c levels measured at 12 weeks after randomization. Secondary outcomes are body weight, systolic and diastolic blood pressure, fasting insulin, serum triglyceride, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and high sensitivity C-reactive protein.

**Ethics and dissemination:** The study protocol have been approved by the Ethics Committee of Faculty of Medicine, Ramathibodi Hospital, Mahidol University (MURA2021/389). All patients will be informed about the details of the study and sign written inform consents before enrollment to the study. Results from this study will be published in peer-reviewed journal.

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**Trial registration number: TCTR20210520002**

For peer review only

### Strengths and limitations of this study

- This is the first study that evaluate the effect of time restricted feeding on blood sugar levels and other cardiometabolic risk factors in patients with impaired fasting glucose.
- The impact of behavioural economic interventions on adherence to time restricted feeding intervention will be assessed.
- The study has longer term follow up than previous studies.
- The interventions cannot be blinded; hence, the results may be affected by observer and information bias.
- There may be contamination of intervention (time restricted feeding) in patients randomized to usual care group because time restricted feeding has been promoted in some social media in Thailand.

## Background and rationale

Diabetes mellitus (DM) is one of the important health problems in Thailand. The results from the National health examination survey reported that the prevalence of DM in Thai population has increased from 7.7% in 2004 to 9.9% in 2014<sup>1</sup>. Diabetes is a risk factor for cardiovascular diseases (CVD) and also the cause of microvascular complications such as chronic kidney disease (CKD) and diabetic retinopathy. Moreover, around 4% of mortality in Thai population is caused by DM<sup>2</sup>. Hence, prevention of DM in Thai population is critical to decrease further morbidity and mortality in the future.

Impaired fasting glucose (IFG) or intermediate hyperglycemia is the condition in which blood sugar level is higher than normal but not reach the DM threshold. A person with IFG has a higher risk for DM about 13 times than a person with normal blood glucose level<sup>3</sup>. Evidence from a previous umbrella review found that lifestyle modifications by diet control and exercise significantly decreased risk of DM in persons with IFG<sup>4</sup>. Most of diet interventions including low and very low-calorie diets are mainly focused on caloric restriction (CR) with the main objective of body weight reduction. Although the efficacy of these diet interventions in decreasing DM risk is well established, most patients could not sustain their healthy behaviors or maintain their healthy lifestyle permanently<sup>5</sup>. As a result, other methods of diet control such as time restricted feeding (TRF) have been introduced as an alternative, which may help patients permanently maintaining their behaviors.

TRF is one type of intermittent fasting (IF) that is characterized by prolonged fasting and limited feeding time<sup>6</sup>. Previous literatures found that increased fasting time has positive effects on many metabolic signal pathways, i.e., prolonged fasting stimulated autophagy and cell repair including mitochondria biogenesis resulting in better metabolic signal pathway in animal. In human study, the TRF could significantly lower body weight but could not decline fasting plasma glucose (FPG), fasting insulin, and hemoglobin A1c (HbA1c) when

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3 compared to normal feeding style in metabolic syndrome patients<sup>7</sup>. Likewise, a study in  
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5 obese patients also found that TRF could reduce body weight, blood pressure, low density  
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7 lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein (HDL) cholesterol but  
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9 could not reduce FPG, fasting insulin and HbA1c<sup>8</sup>. Contrastingly, meta-analyses found  
10  
11 beneficial of TRF in lowering not only a body weight but also FPG, blood pressure and  
12  
13 triglyceride levels<sup>9 10</sup>. Until now, there are few small randomized controlled trials (RCT) that  
14  
15 examined the effect of TRF in patients with prediabetes. A cross-over RCT assessing the  
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17 effects of early or delayed TRF in 15 men at risk for type 2 DM found that both early and  
18  
19 delayed TRF improved glycemic response, but only early TRF could lower mean FPG in men  
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21 with high risk of DM<sup>11</sup>. Another RCT assessed the effect of early TRF in 8 prediabetic men  
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23 and found that early TRF could reduce insulin level, blood pressure and food appetite,  
24  
25 increased insulin sensitivity and beta-cell responsiveness but not for FPG<sup>12</sup>. However, these  
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27 RCT focused on only men with very short follow-up times (i.e., 7 days and 5 weeks).  
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29 Therefore, further RCT investigating the long-term effect of TRF in both male and female  
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31 patients is still needed.  
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38 Although TRF may have positive effects on cardiometabolic risk factors but the  
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40 long-term adherence to the TRF is still questionable in the real life of some people. Such a  
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42 gap occurs because the benefits of reducing cardiometabolic risks are intangible and will  
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44 occur in the far future, whereas the cost of adherence to this diet control, namely being  
45  
46 disciplined on diet time instead of eating freely whenever desire, happens immediately. Thus,  
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48 some people who place much greater weight on the present than the future will be less likely  
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50 to adhere to the diet control. This is called present bias from behavioral economics  
51  
52 perspective<sup>13 14</sup>.  
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56 Behavioral economics is a field that integrates insights and methods from  
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58 psychology and economics to understand human decision-making<sup>15-17</sup>. It has gained increased  
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3 attention in promoting healthy behaviors, such as healthy food choice<sup>18-20</sup>, physical activity<sup>20</sup>  
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5 <sup>21</sup>, smoking cessation<sup>20 22 23</sup>, and reduced alcohol consumption<sup>20 24</sup>. While conventional  
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7 economics assumes rational/quantitative informed decision making, yet in reality, irrational  
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9 health behaviors including overeating are common<sup>14 16 25</sup>. In contrast, behavioral economics  
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11 accounts for irrational behaviors, perspective, or bias in explaining and predicting behavior<sup>13</sup>  
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17 A few behavioral economics tools have been used to deal with present bias to  
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19 promote adherence to diet control, i.e., financial incentives and text reminder<sup>26</sup>. Previous  
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21 studies show that financial incentive was an effective tool to promote healthy lifestyle such as  
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23 smoking cessation and physical activity by providing immediate benefits if clients could  
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25 achieve a pre-specified goal from adherence rather than letting them wait only for the  
26  
27 intangible future health benefits<sup>27</sup>. In addition, findings from RCT also suggest the efficacy of  
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29 financial incentive in decreasing body weight in obesity subjects<sup>28</sup>.

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33 Text reminder about individual's own commitment, performance, or goal (e.g., "Your  
34  
35 goal is to stick to the TRF plan for 5 days a week.") or desired behavior can immediately  
36  
37 remind them of the priority. Such reminders have been proven effective in many domains,  
38  
39 such as for the promotion of savings<sup>29</sup>, weight loss<sup>30 31</sup> and medication adherence<sup>32</sup>. An  
40  
41 evidence of a RCT showed that text reminder was effective in improving adherence to a  
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43 healthy diet and medication and could be a promising strategy for attaining permanent  
44  
45 adherence to healthy behavior in different chronic disease<sup>33</sup>. As a result, using behavioral  
46  
47 economics might be helpful in increasing compliance of lifestyle modification such as TRF  
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49 or even maintaining behavioral change and finally improve the efficacy of lifestyle  
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51 intervention in people with IFG who require a lifelong healthy lifestyle in prevention of DM  
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55 conversion.  
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3 Nevertheless, there has been no study that assesses the efficacy of combined TRF  
4 with behavioral economic interventions in patients with IFG. Therefore, this RCT protocol is  
5 developed which aims to compare the efficacy of additional behavioral economic  
6 interventions in TRF to TRF alone and usual care in IFG patients with following objectives:  
7  
8 First, to compare FPG and HbA1c levels between IFG patients who receive behavioral  
9 economic interventions plus TRF, TRF alone, and usual care. Second, to compare body  
10 weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting insulin, serum  
11 triglyceride, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density  
12 lipoprotein cholesterol (HDL-C), and high sensitivity C-reactive protein (hs-CRP) between  
13 these three interventions.  
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## 26 **Methods and analysis**

### 27 *Study design*

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30 This study is a parallel RCT, which will be conducted at the outpatient clinic of  
31 Family Medicine (OFM), Faculty of Medicine, Ramathibodi Hospital, during October 2021  
32 to October 2022. This research method is complied with the Consolidated Standards of  
33 Reporting Trials (CONSORT) statement. The trial protocol has been registered at the Thai  
34 Clinical Trials Registry (TCTR20210520002).  
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### 42 *Patient recruitment*

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44 Patients and staffs of Ramathibodi Hospital who are diagnosed as IFG will be  
45 recruited during October 2021 to October 2022, and they will be followed up until the 12<sup>th</sup>  
46 week after received interventions. Trained investigators and research assistants will approach  
47 and inform patients about study protocol, randomization process, and details of intervention  
48 and comparisons. Participants will sign informed consent before participating.  
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### 56 *Participants*

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3 Patients will be included in this study, if they meet all of the following criteria: 1) age  
4 18 to 65 years, 2) having FPG of 100-125 mg/dl with or without HbA1c of 5.7-6.49%, and 3)  
5  
6 body mass index  $\geq 25$  kg/m<sup>2</sup>. Patients will be ineligible if 1) they have been involved with  
7  
8 Ketogenic or vegetarian diets, 2) doing night shift work at least  $\geq 3$  hours during 10:00 PM-  
9  
10 5:00 AM more than 1 day/week, 3) having more than 5 kg body weight changes during the 3  
11  
12 months before enrolment to the study, 4) taking medicines that must be taken with food in the  
13  
14 early morning (i.e., before 8:00 AM) or late evening (i.e., after 5:00 PM), 5) pregnancy or  
15  
16 breastfeeding, 6) having psychiatric disorders such as eating disorder or mood disorder but  
17  
18 not including depression, 7) taking corticosteroid or anti-diabetic drugs, 8) having history of  
19  
20 bariatric surgery, and 9) having impaired nutrients absorption.  
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### 26 ***Randomizations***

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28 Patients will be randomly assigned to any of three interventions including behavioural  
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30 economic interventions plus TRF, TRF alone, usual care with a ratio 1:1:1. A block  
31  
32 randomization with varying block sizes of 6 and 9 will be generated by a Biostatistician who  
33  
34 does not involve in the trial using STATA program version 16. Randomization will be  
35  
36 stratified according to age groups (i.e., 18-59 years and 60-65 years). Random sequence list  
37  
38 will be then concealed using sequential opaque sealed envelopes, which will be kept at the  
39  
40 OFM. A research assistant will administer and open the sealed envelope once patients are  
41  
42 eligible.  
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### 47 ***Blinding***

48  
49 Participants and clinicians cannot be blinded due to the nature of interventions.  
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51 However, data collectors and biostatistician will be blinded about the intervention allocation.  
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53 In addition, outcomes of this study will be objectively measured that will not be affected by  
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55 unblinded intervention.  
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### 58 ***Study interventions***

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3 Interested interventions are TRF and behavioural economic interventions. TRF is a  
4 limitation of the daily time of food intakes to 9 hours with prolong fasting in the night-time of  
5 15 hours. Participants will be requested to limit their periods of food intakes from 8:00 AM to  
6 5:00 PM without restriction of types of food and beverages. Participants will be asked for  
7 complying with TRF as much as they can or at least five days per week.  
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11 Behavioural economic interventions will consist of financial incentives and text  
12 reminder. For financial incentive, participant will receive a monetary compensation of 1000  
13 Bath per month if they can adhere to TRF at least 5 days/week. TRF adherence will be  
14 evaluated every week by asking participants record their first and last mealtime every day via  
15 logbook and financial incentive will be provided at 4<sup>th</sup>, 8<sup>th</sup>, and 12<sup>th</sup> week after randomisation.  
16 In addition, text reminder will be sent to participants every 2 days to remind them about their  
17 own commitment, performance, and goal (e.g., “Your goal is to stick to the TRF plan for at  
18 least 5 days a week”, “Last week you have successfully stuck to the TRF plan for 5 days”)  
19 and also about the TRF interval (e.g., “It’s almost 5 pm. Let’s be patient until the morning for  
20 our good health”, “It’s 8 AM. Well done! You gave yourself good care.”).  
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38 Comparator of the study is a usual care according to the current practice guideline of  
39 diabetes prevention. Patients will be educated about their conditions and disease progression,  
40 dietary control, exercise to prevent disease progression. In addition, patients will be asked to  
41 record their first and last mealtime every day, which will be the same as patients in the other  
42 two interventions to evaluate protocol violation. All patients in 3 groups will received a  
43 leaflet that provides knowledge about healthy food and lifestyle modification to control their  
44 weight and reduce the risk of progression to DM.  
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### 54 **Outcomes**

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56 The primary outcomes of this study are FPG and HbA1c levels which will be  
57 measured at the end of the study, i.e., 3 months after randomisation. Fasting plasma glucose  
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3 and HbA1c will be measured by hexokinase glucose-6 phosphate dehydrogenase and turbid  
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6 metric inhibition immunoassay certified by the National Glycohemoglobin Standardization  
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8 Program (NGSP).

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10 Secondary outcomes are body weight, SBP, DBP, fasting insulin, serum triglyceride,  
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12 total cholesterol, LDL-C, HDL-C, and high sensitivity C-reactive protein (hs-CRP). Body  
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14 weight and blood pressure measurement will be taken by trained research assistants. Body  
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16 weight will be measured without shoes to the nearest 100 g. Blood pressure will be measured  
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18 after the resting for at least 15 minutes with an automatic blood pressure monitoring. Fasting  
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20 insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and hs-CRP will be measured  
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22 by chemiluminescent microparticle immunoassay, glycerol phosphate oxidase, enzymatic  
23  
24 method, liquid selective detergent, accelerator selective detergent, and immunonephelometry,  
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26 respectively.  
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30 All primary and secondary outcomes will be measured at the baseline, 1, 2, and 3  
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32 months after randomization.  
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### 35 *Adverse events*

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37 Adverse events such as syncope, dizziness, and light headiness will be measured  
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39 during all study periods.  
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### 42 *Co-variables*

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44 Other covariables will be collected as follows.  
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- 47 1. Demographic data including age, sex, educational level, and marital status
  - 48 2. Underlying diseases such as hypertension, dyslipidaemia, fatty liver  
49 disease, and history of gestational diabetes mellitus
  - 50 3. Health risk behaviours including smoking and alcohol intake
  - 51 4. Family history of DM in the first degree relatives
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5. Sleep factors including sleep duration, sleep quality measured by the Thai version of the Pittsburgh Sleep Quality Index<sup>34</sup>, and morningness and eveningness preference using the validated Thai version of the Composite Scale of Morningness (CSM)<sup>35</sup>
6. Physical activity level measured by Global Physical Activity Questionnaire (GPAQ)<sup>36</sup>
7. Details of food intakes assessed by 24-hour food recall
8. Time and risk preference assessed by multiple price list method<sup>37-42</sup>

### ***Study protocol and data collection***

Schedule matrix consisting of data collections and time at measurements are presented in Table 1. At the first visit, trained investigator and research assistants will explained about the study protocol, process of data collection, and detail of TRF, behavioural economic interventions, and comparator. At one week after enrolment (2<sup>nd</sup> visit), participants will be interviewed by research assistants about demographic data, underlying diseases, health risk behaviours, 24-hour food recall, sleep factors, physical activity level, and time and risk preference questionnaire. Physical examination including blood pressure, body weight, and height will be measured by trained research assistants. Laboratory measurement (i.e., FPG, HbA1c, serum triglyceride, total cholesterol, LDL-C, HDL-C, fasting insulin, and hs-CRP) will be performed after fasting at least 8 hours or longer. After that participant will be randomly assigned to any of 3 groups as behavioural economic intervention plus TRF, TRF alone, and usual care.

Physical activity level, sleep factors, 24-hour food recall, body weight, SBP, DBP, and laboratory measurement will be obtained at 3<sup>rd</sup> visit (4<sup>th</sup> weeks after randomization), 4<sup>th</sup> visit (8<sup>th</sup> weeks after randomization), and 5<sup>th</sup> visit (12<sup>th</sup> weeks after randomization or the end of the study).

### ***Data management***

All data will be collected and filled in hard case record forms (CRF). All CRFs will be checked by researchers for completeness and correction before data entry. Hard CRFs will be independently computerised by two research assistants using Epidata version 3.1 software. Data will be cleaned and checked every month by investigators (US and TA). Any unclear or missing information will be cross-checked against the source documents of CRFs and medical records if required. Hospital number will be encrypted and keep confidentiality, unique identification number (ID) will be assigned instead to each patient. All data will be backed up using Google drive to prevent data loss.

### ***Data monitoring***

A formal data and safety monitoring board (DSMB) is not required because of no expected major adverse event from study's interventions. If adverse events are occurred, these will be managed by the trial committee, including all authors of this protocol. Recruitment and retention rates, and any protocol violations will be monitored by the trial committee via regular meeting every month.

### ***Sample size calculation***

Sample size is calculated based on a superiority trial using one way analysis of variance method in STATA version 17.0. Baseline mean and standard deviation (SD) of FPG in patients of prediabetes cohort conducted in the OFM was 105 and 9 mg/dl. We expected that receiving behavioural economic interventions plus TRF and TRF alone should be able to decrease FPG around 7% and 5% relative to the control, i.e., the FBGs were about 98 and 100 mg/dl, respectively. Type I error, power, and follow up are set at 0.05, 0.8, and 20%; a total of 117 participants with 39 per group will be required to detect these differences.

### ***Statistical analysis***

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3 Baseline characteristics and outcomes among 3 groups will be described using mean  
4 (SD) or median (range) where appropriate for continuous data, and frequency (percentage)  
5 for categorical data. Means of primary and secondary outcomes will be compared among  
6 three groups using a mixed-effect linear regression model by regress outcome on intervention  
7 and time considering patients as a random effect (i.e., repeated measured at 4, 8, and 12  
8 weeks) and the intervention arms (TRF with behavioral economic interventions and TRF  
9 alone versus usual care) as a fixed-effect. Marginal means and differences between any pair  
10 of the three interventions will be then estimated accordingly.  
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21 Protocol violation will be dealt using an intention to treat analysis (ITT) and per-  
22 protocol analysis (PPA). For the PPA, patients in the TRF plus behavioral economic  
23 interventions and TRF alone who do not comply with TRF (i.e., comply < 5 days per week)  
24 throughout the study or patients in the usual care group who take TRF 5 days of more per  
25 week will be excluded from analysis.  
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33 All analyses will be performed using STATA 17.0. P value of less than 0.05 will be  
34 considered as a statistical significance.  
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### 37 **Ethics and dissemination**

38  
39 The study protocol is approved by the Ethics Committee of Ramathibodi Hospital,  
40 Mahidol University, (MURA 2021/389) and will be conducted in agreement with the Helsinki  
41 declaration. All participants will sign informed consent at the baseline of the study. Protocol  
42 amendments will be reported to the institutional ethics committee. Identification numbers will  
43 be used instead of hospital number to protect the confidentiality of study's participants. All  
44 data will be stored in database with password protection and can be accessed by only authorized  
45 staff.  
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3 Results of this study will be presented at national or international conferences and will  
4 be published in peer review journal. We plan to disseminate the results to participants,  
5 endocrinologists, and primary care physicians.  
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## 10 Discussion

11  
12 Patients with IFG have a significant increased risk of DM. Diet interventions focused  
13 mainly on caloric restriction has been proved to decrease DM risk in this population.  
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15 However, long term adherence to this diet control was very low. TRF is one type of diet  
16 intervention that has positive effects on many metabolic signal pathways from animal studies  
17 but evidence in human is limited especially in patients with IFG. Therefore, this RCT is the  
18 first study that evaluate the effect of TRF on blood sugar levels and other cardiometabolic  
19 risk factors in patients with IFG. In addition, this is the first study that assess the impact of  
20 behavioural economic interventions such as financial incentive and text reminder on  
21 adherence to TRF intervention.  
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33 Our study design has some critical issues. First, our interventions cannot be blinded;  
34 hence, the results may be affected by observer and information bias. However, most of our  
35 outcomes are objectively measured, thus measurement or ascertainment bias should be less  
36 likely. Second, although our study has longer term follow up than previous studies, 3-month  
37 assessment is still conserved as a short-term follow-up. Therefore, only surrogate outcomes  
38 as FBG, HbA1c, body weight, and other laboratory tests will be assessed; either a long-term  
39 effect of TRF on cardiometabolic risk factors or permanent change of participant's behaviour  
40 cannot be evaluated. Fourth, there may be contamination of TRF in patients randomized to  
41 usual care group because TRF has been promoted in some social media in Thailand.  
42  
43 Therefore, patients in usual care group can adopt TRF by themselves and this may dilute the  
44 effect of TRF in our study. We hope that this contamination should be minimized because we  
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3 will carefully assess patients who may have already performed TRF before the beginning of  
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5 this study; but once occur, this protocol violation will be dealt with ITT/PPA.  
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8 In conclusion, we will conduct an opened labeled randomized controlled trial to  
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10 evaluate the efficacy of behavioral economic interventions plus TRF, TRF alone, and usual  
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12 care in improving FPG, HbA1c, and other cardiometabolic risk factors in patients with  
13  
14 prediabetes. The findings from this study will be applied for the recommendation of lifestyle  
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16 modification used for diabetes prevention in patients with prediabetes. Findings about the  
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18 efficacy of behavioral economic intervention will inform policy makers about the novel method  
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20 to help people change and maintain their healthy behaviour.  
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23  
24 **Authors' contributions:** US and TA are the principal investigators. US, TA, SB, SP, AC, SR,  
25  
26 and AT designed the study. US and TA drafted the manuscript. US, TA, SB, SP, AC, SR, and  
27  
28 AT critically revised the study protocol and the manuscript. The entire project will be  
29  
30 supervised by TA, SR, and AT.  
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34  
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**Table 1.** Schedule matrix including activities and time at measurements/data collection

Activity	Time point				
	Screening visit	Visit 1 (baseline)	Visit 2 (4 week)	Visit 3 (8 week)	Visit 4 (12 week)
<b><i>Enrolment</i></b>					
- Eligibility screen	√				
- Informed consent		√			
- Allocation		√			
<b><i>Intervention</i></b>					
- TRF with economic behavioural intervention		√	√	√	√
- TRF		√	√	√	√
- Usual care		√	√	√	√
<b><i>Assessment</i></b>					
- Demographic data		√			
- Underlying diseases		√			
- Health risk behaviour		√			
- Family history of DM		√			
- Physical activity		√	√	√	√
- Sleep factors		√	√	√	√
- 24-hour food recall		√	√	√	√
- Time and risk preference		√			√
<b><i>Primary outcomes</i></b>					

- FPG		√	√	√	√
- HbA1c		√	√	√	√
<i>Secondary outcomes</i>					
- Body weight		√	√	√	√
- Blood pressure		√	√	√	√
- Fasting insulin		√	√	√	√
- Serum triglyceride		√	√	√	√
- Serum cholesterol		√	√	√	√
- LDL-cholesterol		√	√	√	√
- HDL-cholesterol		√	√	√	√
- hs-CRP		√	√	√	√

# BMJ Open

## Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

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<b>Primary Subject Heading</b>:	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, NUTRITION & DIETETICS

SCHOLARONE™  
Manuscripts

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3 **Efficacy of time restricted eating and behavioral economic intervention in reducing**  
4 **fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time**  
5 **restricted eating alone or usual care in patients with impaired fasting glucose: Protocol**  
6 **for a randomized controlled trial**  
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## Abstract

**Introduction:** Impaired fasting glucose (IFG) is a significant risk factor of diabetes mellitus (DM) and also diabetic complications. Time restricted eating (TRE) is one type of diet that showed positive effects on many metabolic signal pathways from animal studies. However, the effects of TRE on cardiometabolic risk factors in humans are still limited. In addition, compliance with TRE remains problematic for some people despite their intention to follow the diet control. Therefore, this study aims to investigate the efficacy of TRE with behavioral economic interventions, compared to TRE alone and usual care, in reducing fasting plasma glucose (FPG), hemoglobin A1c(HbA1c), and other cardiometabolic risk factors in patients with IFG.

**Methods and analysis:** This parallel randomized controlled trial will be conducted at the outpatient clinic of Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. Patients aged 18-65 years with IFG defined as FPG 100-125 mg/dl, and having body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup> will be recruited between October 2021 and October 2022. Patients will be randomly allocated to 3 groups (1:1:1 ratio) as 1) TRE with behavioral economic interventions which include financial incentives and text reminders, 2) TRE alone, or 3) usual care. The duration of intervention will be 12 weeks. Primary outcomes are FPG and HbA1c levels measured at 12 weeks after randomization. Secondary outcomes are body weight, systolic and diastolic blood pressure, fasting insulin, serum triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and high sensitivity C-reactive protein.

**Ethics and dissemination:** The study protocol has been approved by the Ethics Committee of Faculty of Medicine, Ramathibodi Hospital, Mahidol University (MURA2021/389). All patients will be informed about the details of the study and sign written informed consent before enrollment in the study. Results from this study will be published in peer-reviewed

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6 **Trial registration number:** TCTR20210520002 (18 January 2022, version 2)  
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For peer review only

### Strengths and limitations of this study

- First randomized controlled trial that assesses the efficacy of time restricted eating on blood sugar levels and other cardiometabolic risk factors in patients with impaired fasting glucose.
- The study has longer-term follow up than previous studies.
- The interventions cannot be blinded; hence, the results may be affected by observer and information bias.
- Contamination of time restricted eating in usual care group might be occurred due to the promoting of time restricted eating in some social media in Thailand.

## Background and rationale

Diabetes mellitus (DM) is one of the important health problems in Thailand. The results from the National health examination survey reported that the prevalence of DM in Thai population has increased from 7.7% in 2004 to 9.9% in 2014<sup>1</sup>. Diabetes is a risk factor for cardiovascular diseases (CVD) and also the cause of microvascular complications such as chronic kidney disease (CKD) and diabetic retinopathy. Moreover, around 4% of mortality in Thai population is caused by DM<sup>2</sup>. Hence, prevention of DM in Thai population is critical to decrease further morbidity and mortality in the future.

Impaired fasting glucose (IFG) or intermediate hyperglycemia is the condition in which blood sugar level is higher than normal but not reach the DM threshold. A person with IFG has a higher risk for DM about 13 times than a person with normal blood glucose level<sup>3</sup>. Evidence from a previous umbrella review found that lifestyle modifications by diet control and exercise significantly decreased risk of DM in persons with IFG<sup>4</sup>. Most of diet interventions including low and very low-calorie diets are mainly focused on caloric restriction (CR) with the main objective of body weight reduction. Although the efficacy of these diet interventions in decreasing DM risk is well established, most patients could not sustain their healthy behaviors or maintain their healthy lifestyle permanently<sup>5</sup>. As a result, other methods of diet control such as time restricted eating (TRE) have been introduced as an alternative, which may help patients permanently maintaining their behaviors.

TRE is one type of dietary approaches that limits daily eating window to commonly lower than 10 h/day and prolong fasting time<sup>6-8</sup>. Previous literatures found that increased fasting time has positive effects on many metabolic signal pathways, i.e., prolonged fasting stimulated autophagy and cell repair including mitochondria biogenesis resulting in better metabolic signal pathway in animal. In human study, the TRE could significantly lower body weight but could not decline fasting plasma glucose (FPG), fasting insulin, and hemoglobin



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3 A1c (HbA1c) when compared to normal eating style in metabolic syndrome patients<sup>9</sup>.

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5 Likewise, a study in obese patients also found that TRE could reduce body weight, blood  
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7 pressure, low density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein  
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9 (HDL) cholesterol but could not reduce FPG, fasting insulin and HbA1c<sup>10</sup>, while study of  
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11 Schroder et al found the significant reduction of body mass index, body fat percentage, and  
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13 waist circumference in obese middle-aged women receiving TRE but FPG, HbA1c, fasting  
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15 insulin, LDL-C, HDL-C, serum uric acid, and blood pressure were not significantly different  
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17 between TRE and control groups<sup>11</sup>. Contrastingly, meta-analyses found beneficial of TRE in  
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19 lowering not only a body weight but also FPG, blood pressure and triglyceride levels<sup>12 13</sup>.

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21 Until now, there are few small randomized controlled trials (RCT) that examined the effect of  
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23 TRE in patients with prediabetes. A cross-over RCT assessing the effects of early or delayed  
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25 TRE in 15 men at risk for type 2 DM found that both early and delayed TRE improved  
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27 glycemic response, but only early TRE could lower mean FPG in men with high risk of  
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29 DM<sup>14</sup>. Another RCT assessed the effect of early TRE in 8 prediabetic men and found that  
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31 early TRE could reduce insulin level, blood pressure and food appetite, increased insulin  
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33 sensitivity and beta-cell responsiveness but not for FPG<sup>15</sup>. However, these RCT focused on  
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35 only men with very short follow-up times (i.e., 7 days and 5 weeks). Therefore, further RCT  
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37 investigating the long-term effect of TRE in both male and female patients is still needed.  
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45 Although several studies found that TRE was well accepted by study's  
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47 participants<sup>16</sup> and well tolerated even in older adults<sup>17</sup> but the long-term adherence to the  
48  
49 TRE is still questionable in the real life of some people. Such a gap occurs because the  
50  
51 benefits of reducing cardiometabolic risks are intangible and will occur in the far future,  
52  
53 whereas the cost of adherence to this diet control, namely being disciplined on diet time  
54  
55 instead of eating freely whenever desire, happens immediately. Thus, some people who place  
56  
57 much greater weight on the present than the future will be less likely to adhere to the diet  
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3 control. This is called present bias from behavioral economics perspective<sup>18 19</sup>. Behavioral  
4  
5 economics is a field that integrates insights and methods from psychology and economics to  
6  
7 understand human decision-making<sup>20-22</sup>.  
8  
9

10 A few behavioral economics tools have been used to deal with present bias to promote  
11 adherence to diet control, i.e., financial incentives and text reminder<sup>23</sup>. Previous studies show  
12 that financial incentive was an effective tool to promote healthy lifestyle such as smoking  
13 cessation, physical activity<sup>24</sup> and weight loss<sup>25</sup>. Text reminders about individual's own  
14 commitment, performance, or goal can immediately remind them of the priority. Such  
15 reminders have been proven effective in many domains, such as for the promotion of  
16 savings<sup>26</sup>, weight loss<sup>27 28</sup> and medication adherence<sup>29</sup>. As a result, using behavioral  
17 economics might be helpful in increasing compliance of lifestyle modification such as TRF  
18 or even maintaining behavioral change and finally improve the efficacy of lifestyle  
19 intervention in people with IFG who require a lifelong healthy lifestyle in prevention of DM  
20 conversion.  
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35 Nevertheless, there has been no study that assesses the efficacy of combined TRE  
36 with behavioral economic interventions in patients with IFG. Therefore, this RCT protocol is  
37 developed which aims to compare the efficacy of additional behavioral economic  
38 interventions in TRE to TRE alone and usual care in IFG patients with following objectives:  
39  
40 First, to compare FPG and HbA1c levels between IFG patients who receive behavioral  
41 economic interventions plus TRE, TRE alone, and usual care. Second, to compare body  
42 weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting insulin, serum  
43 triglyceride, total cholesterol, LDL-C, HDL-C, and high sensitivity C-reactive protein (hs-  
44 CRP) between these three interventions.  
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## 55 **Methods and analysis**

### 56 ***Study design***

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3 This study is a parallel RCT, which will be conducted at the outpatient clinic of  
4 Family Medicine (OFM), Faculty of Medicine, Ramathibodi Hospital, during October 2021  
5 to October 2022. This research method is complied with the Consolidated Standards of  
6 Reporting Trials (CONSORT) statement. The trial protocol has been registered at the Thai  
7 Clinical Trials Registry (TCTR20210520002).  
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### 14 ***Patient recruitment***

15  
16 Patients and staffs of Ramathibodi Hospital who are diagnosed as IFG will be  
17 recruited during October 2021 to October 2022, and they will be followed up until the 12<sup>th</sup>  
18 week after received interventions. Trained investigators and research assistants will approach  
19 and inform patients about study protocol, randomization process, and details of intervention  
20 and comparisons. Participants will sign informed consent before participating.  
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### 28 ***Participants***

29  
30 Patients will be included in this study, if they meet all of the following criteria: 1) age  
31 18 to 65 years, 2) having FPG of 100-125 mg/dl with or without HbA1c of 5.7-6.49%, and 3)  
32 body mass index  $\geq 25$  kg/m<sup>2</sup>. Patients will be ineligible if 1) they have been involved with  
33 Ketogenic or vegetarian diets, 2) doing night shift work at least  $\geq 3$  hours during 10:00 PM-  
34 5:00 AM more than 1 day/week, 3) having more than 5 kg body weight changes during the 3  
35 months before enrolment to the study, 4) taking medicines that must be taken with food in the  
36 early morning (i.e., before 8:00 AM) or late evening (i.e., after 5:00 PM), 5) pregnancy or  
37 breastfeeding, 6) having psychiatric disorders such as eating disorder or mood disorder but  
38 not including depression, 7) taking corticosteroid or anti-diabetic drugs, 8) having history of  
39 bariatric surgery, and 9) having impaired nutrients absorption.  
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### 54 ***Randomizations***

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56 Patients will be randomly assigned to any of three interventions including behavioural  
57 economic interventions plus TRE, TRE alone, usual care with a ratio 1:1:1. A block  
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3 randomization with varying block sizes of 6 and 9 will be generated by a Biostatistician who  
4 does not involve in the trial using STATA program version 16. Randomization will be  
5 stratified according to age groups (i.e., 18-59 years and 60-65 years). Random sequence list  
6 will be then concealed using sequential opaque sealed envelopes, which will be kept at the  
7 OFM. A research assistant will administer and open the sealed envelope once patients are  
8 eligible.  
9

### 16 ***Blinding***

17  
18  
19 Participants and clinicians cannot be blinded due to the nature of interventions.  
20  
21 However, data collectors and biostatistician will be blinded about the intervention allocation.  
22  
23 In addition, outcomes of this study will be objectively measured that will not be affected by  
24 unblinded intervention.  
25  
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### 28 ***Study interventions***

29  
30 Interested interventions are TRE and behavioural economic interventions. TRE is a  
31 limitation of the daily time of food intakes to 9 hours with prolong fasting in the night-time of  
32 15 hours. Participants will be requested to limit their periods of food intakes from 8:00 AM to  
33 5:00 PM without restriction of types of food and beverages. Participants will be asked for  
34 complying with TRE as much as they can.  
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42 Behavioural economic interventions will consist of financial incentives and text  
43 reminder. For financial incentive, participant will receive a monetary compensation of 1000  
44 Bath per month if they self-report that they can adhere to TRE at least 5 days/week for 4  
45 weeks. TRE adherence will be evaluated every week by asking participants to record their  
46 first and last mealtime every day via logbook and financial incentive will be provided at 4<sup>th</sup>,  
47 8<sup>th</sup>, and 12<sup>th</sup> week after randomisation. In addition, text reminder will be sent to participants  
48 every 2 days to remind them about their own commitment (Your goal is to stick to the TRE  
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3 plan for at least 5 days a week.), performance (Last week you have successfully stuck to the  
4  
5 TRE plan for 5 days.), and also about the TRE interval.  
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7

8       Comparator of the study is a usual care according to the current practice guideline of  
9  
10 diabetes prevention. Patients will be educated about their conditions and disease progression,  
11  
12 dietary control, exercise to prevent disease progression. Participants in TRF and behavioural  
13  
14 economic interventions and TRE alone groups also will receive the education about dietary  
15  
16 control and exercise similar to patients in the usual care group. In addition, patients will be  
17  
18 asked to record their first and last mealtime every day, which will be the same as patients in  
19  
20 the other two interventions to evaluate protocol violation. All patients in 3 groups will  
21  
22 received a leaflet that provides knowledge about healthy food and lifestyle modification to  
23  
24 control their weight and reduce the risk of progression to DM.  
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### 28 ***Outcomes***

29  
30       The primary outcomes of this study are FPG and HbA1c levels which will be  
31  
32 measured at the end of the study, i.e., 3 months after randomisation. Fasting plasma glucose  
33  
34 and HbA1c will be measured by hexokinase glucose-6 phosphate dehydrogenase and turbid  
35  
36 metric inhibition immunoassay certified by the National Glycohemoglobin Standardization  
37  
38 Program (NGSP).  
39  
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41  
42       Secondary outcomes are body weight, SBP, DBP, fasting insulin, serum triglyceride,  
43  
44 total cholesterol, LDL-C, HDL-C, and hs-CRP. Body weight and blood pressure  
45  
46 measurement will be taken by trained research assistants. Body weight will be measured  
47  
48 without shoes to the nearest 100 g. Blood pressure will measured after the resting for at least  
49  
50 15 minutes with an automatic blood pressure monitoring. Fasting insulin, serum triglyceride,  
51  
52 total cholesterol, LDL-C, HDL-C, and hs-CRP will be measured by chemiluminescent  
53  
54 microparticle immunoassay, glycerol phosphate oxidase, enzymatic method, liquid selective  
55  
56 detergent, accelerator selective detergent, and immunonephelometry, respectively.  
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3 All primary and secondary outcomes will be measured at the baseline, 1, 2, and 3  
4  
5 months after randomization.  
6

### 7 ***Adverse events***

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10 Adverse events such as syncope, dizziness, and light headiness will be measured  
11  
12 during all study periods.  
13

### 14 ***Co-variables***

15  
16 Other covariables will be collected as follows.  
17

- 18  
19 1. Demographic data including age, sex, educational level, and marital status
- 20  
21 2. Underlying diseases such as hypertension, dyslipidaemia, fatty liver
- 22  
23 disease, and history of gestational diabetes mellitus
- 24  
25 3. Health risk behaviours including smoking and alcohol intake
- 26  
27 4. Family history of DM in the first degree relatives
- 28  
29 5. Sleep factors including sleep duration, sleep quality measured by the Thai
- 30  
31 version of the Pittsburgh Sleep Quality Index<sup>30</sup>, and morningness and
- 32  
33 eveningness preference using the validated Thai version of the Composite
- 34  
35 Scale of Morningness (CSM)<sup>31</sup>
- 36  
37 6. Physical activity level measured by Global Physical Activity
- 38  
39 Questionnaire (GPAQ)<sup>32</sup>
- 40  
41 7. Details of food and caloric intakes assessed by 24-hour food recall and
- 42  
43 food frequency questionnaires (FFQs)
- 44  
45 8. Time and risk preference assessed by multiple price list method<sup>33-38</sup>
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### 51 ***Study protocol and data collection***

52  
53 Schedule matrix consisting of data collections and time at measurements are  
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55 presented in Table 1. At the first visit, trained investigator and research assistants will  
56  
57 explained about the study protocol, process of data collection, and detail of TRE, behavioural  
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3 economic interventions, and comparator. At one week after enrolment (2<sup>nd</sup> visit), participants  
4 will be interviewed by research assistants about demographic data, underlying diseases,  
5  
6 health risk behaviours, 24-hour food recall, sleep factors, physical activity level, and time and  
7  
8 risk preference questionnaire. Physical examination including blood pressure, body weight,  
9  
10 and height will be measured by trained research assistants. Laboratory measurement (i.e.,  
11  
12 FPG, HbA1c, serum triglyceride, total cholesterol, LDL-C, HDL-C, fasting insulin, and hs-  
13  
14 CRP) will be performed after fasting at least 8 hours or longer. After that participant will be  
15  
16 randomly assigned to any of 3 groups as behavioural economic intervention plus TRE, TRE  
17  
18 alone, and usual care.  
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23  
24 Physical activity level, sleep factors, 24-hour food recall, body weight, SBP, DBP,  
25  
26 and laboratory measurement will be obtained at 3<sup>rd</sup> visit (4<sup>th</sup> weeks after randomization), 4<sup>th</sup>  
27  
28 visit (8<sup>th</sup> weeks after randomization), and 5<sup>th</sup> visit (12<sup>th</sup> weeks after randomization or the end  
29  
30 of the study).  
31  
32

### 33 ***Data management***

34  
35 All data will be collected and filled in hard case record forms (CRF). All CRFs will  
36  
37 be checked by researchers for completeness and correction before data entry. Hard CRFs will  
38  
39 be independently computerised by two research assistants using Epidata version 3.1 software.  
40  
41 Data will be cleaned and checked every month by investigators (US and TA). Any unclear or  
42  
43 missing information will be cross-checked against the source documents of CRFs and  
44  
45 medical records if required. Hospital number will be encrypted and keep confidentiality,  
46  
47 unique identification number (ID) will be assigned instead to each patient. All data will be  
48  
49 backed up using Google drive to prevent data loss.  
50  
51  
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53

### 54 ***Data monitoring***

55  
56 A formal data and safety monitoring board (DSMB) is not required because of no  
57  
58 expected major adverse event from study's interventions. If adverse events are occurred, these  
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3 will be managed by the trial committee, including all authors of this protocol. Recruitment and  
4 retention rates, and any protocol violations will be monitored by the trial committee via regular  
5 meeting every month.  
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### 9 ***Sample size calculation***

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12 Sample size is calculated based on a superiority trial using one way analysis of  
13 variance method in STATA version 17.0. Baseline mean and standard deviation (SD) of FPG  
14 in patients of prediabetes cohort conducted in the OFM was 105 and 9 mg/dl. We expected  
15 that receiving behavioural economic interventions plus TRE and TRE alone should be able to  
16 decrease FPG around 7% and 5% relative to the control, i.e., the FBGs were about 98 and  
17 100 mg/dl, respectively. Type I error, power, and follow up are set at 0.05, 0.8, and 20%; a  
18 total of 114 participants with 38 per group will be required to detect these differences.  
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### 28 ***Statistical analysis***

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31 Baseline characteristics and outcomes among 3 groups will be described using mean  
32 (SD) or median (range) where appropriate for continuous data, and frequency (percentage)  
33 for categorical data. Means of primary and secondary outcomes will be compared among  
34 three groups using a mixed-effect linear regression model by regress outcome on intervention  
35 and time considering patients as a random effect (i.e., repeated measured at 4, 8, and 12  
36 weeks) and the intervention arms (TRE with behavioral economic interventions and TRE  
37 alone versus usual care) as a fixed-effect. Marginal means and differences between any pair  
38 of the three interventions will be then estimated accordingly.  
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50 Protocol violation will be dealt using an intention to treat analysis (ITT) and per-  
51 protocol analysis (PPA). For the PPA, patients in the TRE plus behavioral economic  
52 interventions and TRE alone who do not comply with TRE (i.e., comply < 5 days per week)  
53 throughout the study or patients in the usual care group who take TRE 5 days of more per  
54 week will be excluded from analysis.  
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3 All analyses will be performed using STATA 17.0. P value of less than 0.05 will be  
4 considered as a statistical significance.  
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### 7 **Ethics and dissemination**

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9  
10 The study protocol is approved by the Ethics Committee of Ramathibodi Hospital,  
11 Mahidol University, (MURA 2021/389) and will be conducted in agreement with the Helsinki  
12 declaration. All participants will sign informed consent at the baseline of the study (see  
13 Supplementary Appendix). Protocol amendments will be reported to the institutional ethics  
14 committee. Identification numbers will be used instead of hospital number to protect the  
15 confidentiality of study's participants. All data will be stored in database with password  
16 protection and can be accessed by only authorized staff.  
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26 Results of this study will be presented at national or international conferences and will  
27 be published in peer review journal. We plan to disseminate the results to participants,  
28 endocrinologists, and primary care physicians.  
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### 33 **Patient and Public Involvement**

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35 There was no patient or public involvement in the study.  
36  
37

### 38 **Discussion**

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40 Patients with IFG have a significant increased risk of DM. Diet interventions focused  
41 mainly on caloric restriction has been proved to decrease DM risk in this population. TRE is  
42 one type of diet intervention that has positive effects on many metabolic signal pathways  
43 from animal studies but evidence in human is limited especially in patients with IFG.  
44  
45 Therefore, this RCT is the first study that evaluate the effect of TRE on blood sugar levels  
46 and other cardiometabolic risk factors in patients with IFG. In addition, this is the first study  
47 that assess the impact of behavioural economic interventions such as financial incentive and  
48 text reminder on adherence to TRE intervention.  
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3 Our study design has some critical issues. First, our interventions cannot be blinded;  
4 hence, the results may be affected by observer and information bias. However, most of our  
5 outcomes are objectively measured, thus measurement or ascertainment bias should be less  
6 likely. Second, although our study has longer term follow up than previous studies, 3-month  
7 assessment is still conserved as a short-term follow-up. Therefore, only surrogate outcomes  
8 as FBG, HbA1c, body weight, and other laboratory tests will be assessed; either a long-term  
9 effect of TRE on cardiometabolic risk factors or permanent change of participant's behaviour  
10 cannot be evaluated. Third, adherence to TRE will be measured through self-reported  
11 logbook which can be upwardly biased. However, concerning study outcomes, we consider  
12 only biological measures which will be objectively measured, e.g., FPG, HbA1c, body  
13 weight, etc. Fourth, there may be contamination of TRE in patients randomized to usual care  
14 group because TRE has been promoted in some social media in Thailand. Therefore, patients  
15 in usual care group can adopt TRE by themselves. In contrast, patients randomized to the  
16 TRE group may not comply to the TRE protocol due to intolerance to the long fasting period  
17 and will drop-out from the study. These drawbacks may dilute the effect of TRE in our study.  
18 However, we hope that these contaminations should be minimized because we will carefully  
19 assess patients who may have already performed TRE before the beginning of this study; but  
20 once occur, this protocol violation will be dealt with ITT/PPA.  
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45 In conclusion, we will conduct an opened labeled randomized controlled trial to  
46 evaluate the efficacy of behavioral economic interventions plus TRE, TRE alone, and usual  
47 care in improving FPG, HbA1c, and other cardiometabolic risk factors in patients with  
48 prediabetes. The findings from this study will be applied for the recommendation of lifestyle  
49 modification used for diabetes prevention in patients with prediabetes. Findings about the  
50 efficacy of behavioral economic intervention will inform policy makers about the novel method  
51 to help people change and maintain their healthy behaviour.  
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3 **Authors' contributions:** US and TA are the principal investigators. US, TA, SB, SP, AC, SR,  
4 and AT designed the study. US and TA drafted the manuscript. US, TA, SB, SP, AC, SR, and  
5  
6 AT critically revised the study protocol and the manuscript. The entire project will be  
7  
8 supervised by TA, SR, and AT.  
9  
10

11  
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13  
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15  
16

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For peer review only

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**Table 1.** Schedule matrix including activities and time at measurements/data collection

Activity	Time point				
	Screening visit	Visit 1 (baseline)	Visit 2 (4 week)	Visit 3 (8 week)	Visit 4 (12 week)
<b><i>Enrolment</i></b>					
- Eligibility screen	√				
- Informed consent		√			
- Allocation		√			
<b><i>Intervention</i></b>					
- TRE with economic behavioural intervention		√	√	√	√
- TRE		√	√	√	√
- Usual care		√	√	√	√
<b><i>Assessment</i></b>					
- Demographic data		√			
- Underlying diseases		√			
- Health risk behaviour		√			
- Family history of DM		√			
- Physical activity		√	√	√	√
- Sleep factors		√	√	√	√
- 24-hour food recall		√	√	√	√
- Time and risk preference		√			√
<b><i>Primary outcomes</i></b>					

- FPG		√	√	√	√
- HbA1c		√	√	√	√
<i>Secondary outcomes</i>					
- Body weight		√	√	√	√
- Blood pressure		√	√	√	√
- Fasting insulin		√	√	√	√
- Serum triglyceride		√	√	√	√
- Serum cholesterol		√	√	√	√
- LDL-cholesterol		√	√	√	√
- HDL-cholesterol		√	√	√	√
- hs-CRP		√	√	√	√

## Patient/Participant Information Sheet

**Project title:** Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

**Researcher's name:** Dr. Unyaporn Suthutvoravut

**Research location:** Ramathibodi Hospital Mahidol University

**Who and how to contact when there is an emergency or disorder associated with research:**

Dr. Unyaporn Suthutvoravut                      Tel. 0869041556

Dr. Thunyarat Anothaisintawee                Tel. 0813725424

**Sponsor for this research:** National Research Council of Thailand

### Project Background

Diabetes is a major health problem in Thailand. Diabetes is a major risk factor for cardiovascular and cerebrovascular disease. Therefore, the prevention of diabetes in the Thai population is important in reducing the mortality and disability of the Thai population in the future.

Prediabetes is a condition in which the blood sugar level is higher than normal but does not reach the diagnostic criteria for diabetes. People with pre-diabetes comparing to people with normal sugar levels are at greater risk of developing diabetes. Behavior modification through diet and exercise can reduce the risk of diabetes in people with pre-diabetes. Most dietary intervention will focus on limiting the amount of energy you get from your diet each day. Other dietary approaches other than energy restriction, such as the Intermittent time restricted eating (TRE) are now being developed to help patients make permanent behavioral changes. It is an eating style with short eating periods. and increase the duration of fasting each day to increase with or without limiting the amount of energy received from food

Previous literature shows that there have been studies on the effect of diet restriction on eating periods. It was found that diet control by having an 8-hour eating period and 16-hour fasting per day can significantly reduce body weight in people with abdominal obesity.

### Objective

To study the efficacy of a time restricted-eating together with the use of behavioral economic tools to reduce blood sugar levels in people with pre-diabetes compared to time restricted-eating alone and usual care

### Details to be treated with research participants

After received information about the project details, the participants sign the documents, consented to participate in this research. One week later, research assistants will conduct interviews to collect general information, history of underlying disease, risky behavior, family history of diabetes, physical activity level, diet history together with physical examination and blood test would be done to check the levels of sugar, fat and hormone. Participants will be required to fast 8-10 hours prior to the blood draw, after which they will randomly be assigned to a restricted diet, together with the use of socio-economic tool or those who received a restricted diet only for a period of time or a group that eats normally.

1  
2  
3  
4 A time-restricted diet is a way of limiting the amount of time you eat during the day. In  
5 this study, participants will have their first meal at 8:00 AM and the last meal no later than 5:00  
6 PM, without eating any food, snacks, fruit and beverages except water after 17: 00 until 8:00 the  
7 next day. The tool for behavioral economics is to create incentives to encourage more behavior  
8 change. The behavioral economics tool of the study was to award 1,000 baht to research  
9 participants who can maintain a restricted diet of greater than or equal to five days a week for one  
10 month in a row. Prize money will be given every month for 3 months until graduation. Participants  
11 were also given messages to encourage them to adopt a time restricted diet. The researcher will  
12 send a message every 3 days via the Line application.

13  
14 After participants participated in the study at 4 weeks, 8 weeks, and 12 weeks.  
15 Blood samples will be collected. Participants will be required to fast 8-10 hours before the blood  
16 draw and interview about their eating habits. physical activity level together with physical  
17 examination by research assistant There is a compensation for the patient's time during the follow-  
18 up visit, 500 baht per time.

### 19 **Benefits to the research participants**

20 Participants will gain knowledge about diet to prevent future diabetes risk.

### 21 **Side effects for the participants**

22 There may be symptoms of low blood sugar, but the likelihood of occurrence is low Because the  
23 measures given are only recommendations for time retracted diet only, not compulsory. The patient  
24 may or may not follow the instructions. Risks associated with blood test may include pain,  
25 bleeding.

### 26 **Confidentiality**

27  
28  
29 The data will be collected with confidentiality. No name of number of hospital record will be  
30 collected. The data will be presented as a whole and no individual identification. Only researchers  
31 will have access to information. This study will inform patients that they are in research and able  
32 to decide whether to join or not. Patients can withdraw from research at any time and has no effect  
33 on the treatment of patients in any way.

34  
35  
36 If you have questions or concerns about participating in this research project. You can  
37 contact the chairman of the Human Research Ethics Board at Faculty Research Office,  
38 Research and Welfare Building, Faculty of Medicine Ramathibodi Hospital.  
39 Tel. 02-2011544  
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## Informed Consent Form

**Project title:** Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Researcher's name, Dr. Unyaporn Suthutvoravut

Name of research participant.....

Age.....medical record number.....

### Research Participant Consent

I, Mr./Mrs./Ms..... have known the details of the research project as well as the benefits and the risks that will arise to me from the researcher clearly and consents to be involved in the above research project. And I know that if there are any problems or questions I could ask the researchers. Also, I could quit this research project at any time, without affecting the treatment that I deserve. In addition, the researchers will keep the specific information about me confidential and will only disclose it in the form of a summary of the research. Disclosure of information about me to relevant agencies could only be done in cases of necessity for academic reasons.

Signed.....

(Research participant)

.....  
(witness)

.....  
(witness)

Date .....

### Description of the doctor or researcher

I have explained the details of the project. as well as the benefits of research and the potential risks were clearly known to the participants without any hidden objection.

Signed.....

(Doctor or Researcher)

date.....



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

## SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1__
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__3,8__
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	__3__
Funding	4	Sources and types of financial, material, and other support	__16__
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1, 16__
	5b	Name and contact information for the trial sponsor	__16__
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__16__
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__16__

## 1 Introduction

2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	___ 5-7 ___
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	___ 5-7 ___
7				
8	Objectives	7	Specific objectives or hypotheses	___ 7 ___
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___ 8 ___
12				
13				

## 14 Methods: Participants, interventions, and outcomes

15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	___ 8 ___
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	___ 8 ___
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	___ 9-10 ___
23			administered	
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	___ NA ___
25			change in response to harms, participant request, or improving/worsening disease)	
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	___ 10,13 ___
27			(eg, drug tablet return, laboratory tests)	
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___ 10 ___
29				
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	___ 10-11 ___
31			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
32			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
33			efficacy and harm outcomes is strongly recommended	
34	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	___ 11-12 ___
35			participants. A schematic diagram is highly recommended (see Figure)	
36				
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____ 13 _____
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____ 8-9 _____
5				
6				
7	<b>Methods: Assignment of interventions (for controlled trials)</b>			
8	Allocation:			
9				
10	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____ 8-9 _____
11				
12				
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16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____ 9 _____
17				
18				
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____ 9 _____
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____ 9 _____
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____ 9 _____
28				
29				
30				
31	<b>Methods: Data collection, management, and analysis</b>			
32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____ 11-13 _____
34				
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38		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____ - _____
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1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	___ 12 ___
2				
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4				
5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___ 13 ___
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___ 13 ___
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___ 13 ___
11				
12				
13				
14	<b>Methods: Monitoring</b>			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___ 12-13 ___
17				
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___ NA ___
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___ 12-13 ___
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___ 13 ___
29				
30				
31				
32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___ 14 ___
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___ 14 ___
38				
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 8 _____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ NA _____
5				
6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, stored, and maintained in order to protect confidentiality before, during, and after the trial	_____ 14 _____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 16 _____
11				
12				
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____ 14 _____
14				
15				
16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____ NA _____
17				
18				
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____ 14 _____
21				
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23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ NA _____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ NA _____
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Appendix
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____ NA _____
35				
36				

37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by/4.0/)" license.  
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# BMJ Open

## Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

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<b>Primary Subject Heading</b>:	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, NUTRITION & DIETETICS

SCHOLARONE™  
Manuscripts

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3 **Efficacy of time restricted eating and behavioral economic intervention in reducing**  
4 **fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time**  
5 **restricted eating alone or usual care in patients with impaired fasting glucose: Protocol**  
6 **for a randomized controlled trial**  
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## Abstract

**Introduction:** Impaired fasting glucose(IFG) is a significant risk factor for diabetes mellitus(DM). Time restricted eating(TRE) is one type of diet that showed positive effects on many metabolic signal pathways. However, the effects of TRE on cardiometabolic risk factors in humans are still limited. In addition, compliance with TRE remains problematic for some people despite their intention to follow the diet control. Therefore, this study aims to investigate the efficacy of TRE with behavioral economic interventions, compared to TRE alone and usual care, in reducing fasting plasma glucose(FPG), hemoglobin A1c(HbA1c), and other cardiometabolic risk factors in patients with IFG.

**Methods and analysis:** This parallel randomized controlled trial will be conducted at the outpatient clinic of the Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. Patients aged 18-65 years with IFG defined as FPG 100-125 mg/dl and having body mass index(BMI)  $\geq 25$  kg/m<sup>2</sup> will be recruited between October 2021 and October 2022. Patients will be randomly allocated to 3 groups (1:1:1 ratio) as 1) TRE with behavioral economic interventions which include financial incentives and text reminders, 2) TRE alone, or 3) usual care. The number of participants will be 38 per group (a total of 114). The duration of the intervention will be 12 weeks. Primary outcomes are FPG and HbA1c levels measured at 12 weeks after randomization. Secondary outcomes are body weight, systolic and diastolic blood pressure, fasting insulin, serum triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and high sensitivity C-reactive protein.

**Ethics and dissemination:** The study protocol has been approved by the Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University(MURA2021/389). All patients will be informed about the details of the study and sign written informed consent before enrollment in the study. Results from this study will be published in peer-reviewed

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3 journal.  
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5 **Trial registration number:** TCTR20210520002 (18 January 2022, version 2) from Thai  
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8 Clinical Trial Registry (TCTR) (<https://thaiclinicaltrials.org>)  
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For peer review only

### Strengths and limitations of this study

- First randomized controlled trial that assesses the efficacy of time restricted eating on blood sugar levels and other cardiometabolic risk factors in patients with impaired fasting glucose.
- The study has longer-term follow-up than previous studies.
- The interventions cannot be blinded; hence, the results may be affected by observer and information bias.
- Contamination of time restricted eating in the usual care group might be occurred due to the promotion of time restricted eating on some social media in Thailand.

## Background and rationale

Diabetes mellitus (DM) is one of the important health problems in Thailand. The results from the National health examination survey reported that the prevalence of DM in the Thai population has increased from 7.7% in 2004 to 9.9% in 2014<sup>1</sup>. Diabetes is a risk factor for cardiovascular diseases (CVD) and also the cause of microvascular complications such as chronic kidney disease (CKD) and diabetic retinopathy. Moreover, around 4% of mortality in the Thai population is caused by DM<sup>2</sup>. Hence, the prevention of DM in the Thai population is critical to decreasing further morbidity and mortality in the future.

Impaired fasting glucose (IFG) or intermediate hyperglycemia is the condition in which blood sugar level is higher than normal but does not reach the DM threshold. A person with IFG has a higher risk for DM about 13 times than a person with a normal blood glucose level<sup>3</sup>. Evidence from a previous umbrella review found that lifestyle modifications by diet control and exercise significantly decreased the risk of DM in persons with IFG<sup>4</sup>. Most diet interventions including low and very low-calorie diets are mainly focused on caloric restriction (CR) with the main objective of body weight reduction. Although the efficacy of these diet interventions in decreasing DM risk is well established, most patients could not sustain their healthy behaviors or maintain their healthy lifestyle permanently<sup>5</sup>. As a result, other methods of diet control such as time restricted eating (TRE) have been introduced as an alternative, which may help patients permanently maintain their behaviors.

TRE is one type of dietary approach that limits the daily eating window to commonly lower than 10 h/day and prolongs fasting time<sup>6-8</sup>. Previous literature found that increased fasting time has positive effects on many metabolic signal pathways, i.e., prolonged fasting stimulated autophagy and cell repair including mitochondria biogenesis resulting in better metabolic signal pathways in animals. In a human study, the TRE could significantly lower body weight but could not decline fasting plasma glucose (FPG), fasting insulin, and



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3 hemoglobin A1c (HbA1c) when compared to the normal eating style in patients with  
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5 metabolic syndrome<sup>9</sup>. Likewise, a study in patients with obesity also found that TRE could  
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7 reduce body weight, blood pressure, low-density lipoprotein cholesterol (LDL-C), and non-  
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9 high-density lipoprotein (HDL-C) cholesterol but could not reduce FPG, fasting insulin and  
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11 HbA1c<sup>10</sup>, while the study of Schroder et al found the significant reduction of body mass  
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13 index, body fat percentage, and waist circumference in middle-aged women with obesity  
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15 receiving TRE but FPG, HbA1c, fasting insulin, LDL-C, HDL-C, serum uric acid, and blood  
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17 pressure were not significantly different between TRE and control groups<sup>11</sup>. Contrastingly,  
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19 meta-analyses found beneficial of TRE in lowering not only body weight but also FPG, blood  
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21 pressure, and triglyceride levels<sup>12 13</sup>. Until now, there are few small randomized controlled  
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23 trials (RCT) that examined the effect of TRE in patients with prediabetes. A cross-over RCT  
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25 assessing the effects of early or delayed TRE in 15 men at risk for type 2 DM found that both  
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27 early and delayed TRE improved glycemic response, but only early TRE could lower mean  
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29 FPG in men with a high risk of DM<sup>14</sup>. Another RCT assessed the effect of early TRE in 8  
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31 men with prediabetes and found that early TRE could reduce insulin level, blood pressure,  
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33 and food appetite, increase insulin sensitivity and beta-cell responsiveness but could not  
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35 reduce FPG<sup>15</sup>. However, these RCTs focused on only men with very short follow-up times  
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37 (i.e., 7 days and 5 weeks). Therefore, further RCT investigating the longer-term effect of  
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39 TRE in both male and female patients is still needed.  
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47 Although several studies found that TRE was well accepted by study  
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49 participants<sup>16</sup> and well-tolerated even in older adults<sup>17</sup> but the long-term adherence to TRE is  
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51 still questionable in the real life of some people. Such a gap occurs because the benefits of  
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53 reducing cardiometabolic risks are intangible and will occur in the far future, whereas the  
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55 cost of adherence to this diet control, namely being disciplined on diet time instead of eating  
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57 freely whenever desired, happens immediately. Thus, some people who place much greater  
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3 weight on the present than on the future will be less likely to adhere to diet control. This is  
4 called present bias from behavioral economics perspective<sup>18 19</sup>. Behavioral economics is a  
5 field that integrates insights and methods from psychology and economics to understand  
6 human decision-making<sup>20-22</sup>.  
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12 A few behavioral economics tools have been used to deal with a present bias to  
13 promote adherence to diet control, i.e., financial incentives and text reminder<sup>23</sup>. Previous  
14 studies show that financial incentive was an effective tool to promote a healthy lifestyle such  
15 as smoking cessation, physical activity<sup>24</sup>, and weight loss<sup>25</sup>. Text reminders about an  
16 individual commitment, performance, or goal can immediately remind them of the priority.  
17 Such reminders have been proven effective in many domains, such as for the promotion of  
18 savings<sup>26</sup>, weight loss<sup>27 28</sup>, and medication adherence<sup>29</sup>. As a result, using behavioral  
19 economics might help increase compliance with lifestyle modification such as TRE or even  
20 maintaining behavioral change and finally improve the efficacy of lifestyle intervention in  
21 people with IFG who require a lifelong healthy lifestyle to prevention of DM conversion.  
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36 Nevertheless, there has been no study that assesses the efficacy of combined TRE  
37 with behavioral economic interventions in patients with IFG. Therefore, this RCT protocol is  
38 developed which aims to compare the efficacy of additional behavioral economic  
39 interventions in TRE to TRE alone and usual care in patients with IFG with the following  
40 objectives: First, to compare FPG and HbA1c levels between patients with IFG who receive  
41 behavioral economic interventions plus TRE, TRE alone, and usual care. Second, to compare  
42 body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting insulin,  
43 serum triglyceride, total cholesterol, LDL-C, HDL-C, and high sensitivity C-reactive protein  
44 (hs-CRP) between these three interventions.  
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## 55 **Methods and analysis**

### 56 *Study design*

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3 This study is a parallel RCT, which will be conducted at the outpatient clinic of the  
4 Department of Family Medicine (OFM), Faculty of Medicine, Ramathibodi Hospital, during  
5 October 2021 to October 2022. This research method complies with the Consolidated  
6 Standards of Reporting Trials (CONSORT) statement. The trial protocol has been registered  
7 at the Thai Clinical Trials Registry (TCTR20210520002).  
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### 10 11 12 13 14 ***Patient recruitment***

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16 Patients and staffs of Ramathibodi Hospital who are diagnosed with IFG will be  
17 recruited from October 2021 to October 2022, and they will be followed up until the 12<sup>th</sup>  
18 week after receiving interventions. Trained investigators and research assistants will  
19 approach and inform patients about the study protocol, randomization process, and details of  
20 intervention and comparisons. Participants will sign informed consent before participating.  
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### 28 29 ***Participants***

30 Patients will be included in this study, if they meet all of the following criteria: 1) age  
31 18 to 65 years, 2) having FPG of 100-125 mg/dl with or without HbA1c of 5.7-6.49%, and 3)  
32 body mass index  $\geq 25$  kg/m<sup>2</sup>. The Patients will be ineligible if 1) they are currently on  
33 Ketogenic or vegetarian diets, 2) doing night shift work at least  $\geq 3$  hours during 10:00 PM-  
34 5:00 AM more than 1 day/week, 3) having more than 5 kg body weight changes during the 3  
35 months before enrolment to the study, 4) taking medicines that must be taken with food in the  
36 early morning (i.e., before 8:00 AM) or late evening (i.e., after 5:00 PM), 5) pregnancy or  
37 breastfeeding, 6) having psychiatric disorders such as eating disorder or mood disorder but  
38 not including depression, 7) taking corticosteroid or anti-diabetic drugs, 8) having a history of  
39 bariatric surgery, and 9) having impaired nutrients absorption.  
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### 54 ***Randomizations***

55 Patients will be randomly assigned to any of three interventions including behavioural  
56 economic interventions plus TRE, TRE alone, and usual care with a ratio of 1:1:1. Block  
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3 randomization with varying block sizes of 6 and 9 will be generated by a biostatistician who  
4 does not involve in the trial using STATA program version 16. Randomization will be  
5 stratified according to age groups (i.e., 18-59 years and 60-65 years). A random sequence list  
6 will be then concealed using sequential opaque sealed envelopes, which will be kept at the  
7 OFM. A research assistant will administer and open the sealed envelope once patients are  
8 eligible.  
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### 16 ***Blinding***

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19 Participants and clinicians cannot be blinded due to the nature of interventions.  
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21 However, data collectors and a biostatistician will be blinded about the intervention  
22 allocation. In addition, the outcomes of this study will be objectively measured that will not  
23 be affected by the unblinded intervention.  
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### 28 ***Study interventions***

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30 Interested interventions are TRE and behavioural economic interventions. TRE is a  
31 limitation of the daily time of food intake to 9 hours with prolonged fasting in the night time  
32 of 15 hours. Participants will be requested to limit their periods of food intake from 8:00 AM  
33 to 5:00 PM without restriction on types of food and beverages. Participants will be asked for  
34 complying with TRE as much as they can.  
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42 Behavioural economic interventions will consist of financial incentives and text  
43 reminders. For financial incentive, the participant will receive monetary compensation of  
44 1000 Baths per month (23 £) if they self-report that they can adhere to TRE at least 5  
45 days/week for 4 weeks. TRE adherence will be evaluated every week by asking participants  
46 to record their first and last mealtime every day via logbook and financial incentives will be  
47 provided on 4<sup>th</sup>, 8<sup>th</sup>, and 12<sup>th</sup> week after randomisation. In addition, text reminders will be  
48 sent to participants every 2 days to remind them about their commitment (Your goal is to  
49 stick to the TRE plan for at least 5 days a week.), performance (Last week you have  
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3 successfully stuck to the TRE plan for 5 days.), and also about the TRE interval. The TRE  
4 alone group will be advised about the benefit of TRE without any additional support.  
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7 However, the participants in TRE alone group will be asked to record the adherence of TRE  
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10 via logbook.  
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12         Comparator of the study is a usual care according to the current practice guideline of  
13 diabetes prevention. Patients will be educated about their conditions and disease progression,  
14 dietary control, and exercise to prevent disease progression. Participants in TRE and  
15 behavioural economic interventions and TRE alone groups also will receive the education  
16 about dietary control and exercise similar to patients in the usual care group. In addition,  
17 patients will be asked to record their first and last mealtime every day, which will be the same  
18 as patients in the other two interventions to evaluate protocol violation. All patients in 3  
19 groups will received a leaflet that provides knowledge about healthy food and lifestyle  
20 modification to control their weight and reduce the risk of progression to DM.  
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### 32 ***Outcomes***

33         The primary outcomes of this study are FPG and HbA1c levels which will be  
34 measured at the end of the study, i.e., 3 months after randomisation. Fasting plasma glucose  
35 and HbA1c will be measured by hexokinase glucose-6 phosphate dehydrogenase and turbid  
36 metric inhibition immunoassay certified by the National Glycohemoglobin Standardization  
37 Program (NGSP).  
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46         Secondary outcomes are body weight, SBP, DBP, fasting insulin, serum triglyceride,  
47 total cholesterol, LDL-C, HDL-C, and hs-CRP. Body weight and blood pressure  
48 measurement will be taken by trained research assistants. Body weight will be measured  
49 without shoes to the nearest 100 g. Blood pressure will measured after the resting for at least  
50 15 minutes with an automatic blood pressure monitoring. Fasting insulin, serum triglyceride,  
51 total cholesterol, LDL-C, HDL-C, and hs-CRP will be measured by chemiluminescent  
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3 microparticle immunoassay, glycerol phosphate oxidase, enzymatic method, liquid selective  
4 detergent, accelerator selective detergent, and immunonephelometry, respectively.  
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7 All primary and secondary outcomes will be measured at the baseline, 1, 2, and 3  
8 months after randomization.  
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### 10 *Adverse events*

11 Adverse events such as syncope, dizziness, and light headiness will be measured  
12 during all study periods.  
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### 14 *Co-variables*

15 Other covariables will be collected as follows.  
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- 17 1. Demographic data including age, sex, educational level, and marital status
- 18 2. Underlying diseases such as hypertension, dyslipidaemia, fatty liver  
19 disease, and history of gestational diabetes mellitus
- 20 3. Health risk behaviours including smoking and alcohol intake
- 21 4. Family history of DM in the first degree relatives
- 22 5. Sleep factors including sleep duration, sleep quality measured by the Thai  
23 version of the Pittsburgh Sleep Quality Index<sup>30</sup>, and morningness and  
24 eveningness preference using the validated Thai version of the Composite  
25 Scale of Morningness (CSM)<sup>31</sup>
- 26 6. Physical activity level measured by Global Physical Activity  
27 Questionnaire (GPAQ)<sup>32</sup>
- 28 7. Details of food and caloric intakes assessed by 24-hour food recall and  
29 food frequency questionnaires (FFQs)
- 30 8. Time and risk preference assessed by multiple price list method<sup>33-38</sup>

### 31 *Study protocol and data collection*

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3 Schedule matrix consisting of data collections and time at measurements are  
4 presented in Table 1. At the first visit, trained investigator and research assistants will recruit  
5 the patient by screening FPG and other inclusion criteria (i.e., age and BMI). If the patient  
6 meets all the inclusion criteria, the research assistants will explain about the study protocol,  
7 process of data collection, and detail of TRE, behavioural economic interventions, and  
8 comparator. The patient will be asked to sign the informed consent if they are willing to  
9 participate the study.

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12 At one week after enrolment (2<sup>nd</sup> visit), participants will be interviewed by research  
13 assistants about demographic data, underlying diseases, health risk behaviours, 24-hour food  
14 recall, sleep factors, physical activity level, and time and risk preference questionnaire.  
15 Physical examination including blood pressure, body weight, and height will be measured by  
16 trained research assistants. Laboratory measurement (i.e., FPG, HbA1c, serum triglyceride,  
17 total cholesterol, LDL-C, HDL-C, fasting insulin, and hs-CRP) will be performed after  
18 fasting at least 8 hours or longer. After that participant will be randomly assigned to any of 3  
19 groups as behavioural economic intervention plus TRE, TRE alone, and usual care.

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22 Physical activity level, sleep factors, 24-hour food recall, body weight, SBP, DBP,  
23 and laboratory measurement will be obtained at 3<sup>rd</sup> visit (4<sup>th</sup> weeks after randomization), 4<sup>th</sup>  
24 visit (8<sup>th</sup> weeks after randomization), and 5<sup>th</sup> visit (12<sup>th</sup> weeks after randomization or the end  
25 of the study). 24-hour food recall will be collected using food diary for 7 days at each visit.  
26 INMUCAL-nutrients version 4.0 (<https://inmu2.mahidol.ac.th/inmucal/index.php>) will be  
27 used to calculate the dietary data to nutrient intakes. This program was developed by the  
28 Institute of Nutrition, Mahidol University, Thailand.

### 29 ***Data management***

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31 All data will be collected and filled in hard case record forms (CRF). All CRFs will  
32 be checked by researchers for completeness and correction before data entry. Hard CRFs will  
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3 be independently computerised by two research assistants using Epidata version 3.1 software.  
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5 Data will be cleaned and checked every month by investigators (US and TA). Any unclear or  
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7 missing information will be cross-checked against the source documents of CRFs and  
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9 medical records if required. Hospital numbers will be encrypted and kept confidentiality;  
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11 unique identification number (ID) will be assigned instead to each patient. All data will be  
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13 backed up using Google drive to prevent data loss.  
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### 16 17 ***Data monitoring***

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19 A formal data and safety monitoring board (DSMB) is not required because of no  
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21 expected major adverse event from study's interventions. If adverse events are occurred, these  
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23 will be managed by the trial committee, including all authors of this protocol. Recruitment and  
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25 retention rates, and any protocol violations will be monitored by the trial committee via regular  
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27 meeting every month.  
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### 30 31 ***Sample size calculation***

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33 Sample size is calculated based on a superiority trial using one way analysis of  
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35 variance method in STATA version 17.0. Baseline mean and standard deviation (SD) of FPG  
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37 in patients of prediabetes cohort conducted in the OFM was 105 and 9 mg/dl. We expected  
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39 that receiving behavioural economic interventions plus TRE and TRE alone should be able to  
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41 decrease FPG around 7% and 5% relative to the control, i.e., the FBGs were about 98 and  
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43 100 mg/dl, respectively. Type I error, power, and follow up are set at 0.05, 0.8, and 20%; a  
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45 total of 114 participants with 38 per group will be required to detect these differences.  
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### 49 50 ***Statistical analysis***

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52 Baseline characteristics and outcomes among 3 groups will be described using mean  
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54 (SD) or median (range) where appropriate for continuous data, and frequency (percentage)  
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56 for categorical data. Means of primary and secondary outcomes will be compared among  
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58 three groups using a mixed-effect linear regression model by regress outcome on intervention  
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3 and time considering patients as a random effect (i.e., repeated measured at 4, 8, and 12  
4 weeks) and the intervention arms (TRE with behavioral economic interventions and TRE  
5 alone versus usual care) as a fixed-effect. Marginal means and differences between any pair  
6 of the three interventions will be then estimated accordingly.  
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12 Protocol violation will be dealt using an intention to treat analysis (ITT) and per-  
13 protocol analysis (PPA). For the PPA, patients in the TRE plus behavioral economic  
14 interventions and TRE alone who do not comply with TRE (i.e., comply < 5 days per week)  
15 throughout the study or patients in the usual care group who take TRE 5 days of more per  
16 week will be excluded from analysis. Multivariate linear regression analysis will be applied,  
17 if there is the difference in baseline characteristics between 3 groups.  
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26 All analyses will be performed using STATA 17.0. P value of less than 0.05 will be  
27 considered as a statistical significance.  
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### 30 **Ethics and dissemination**

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32 The study protocol is approved by the Ethics Committee of Ramathibodi Hospital,  
33 Mahidol University, (MURA 2021/389) and will be conducted in agreement with the Helsinki  
34 declaration. All participants will sign informed consent at the baseline of the study (see  
35 Supplementary Appendix). Protocol amendments will be reported to the institutional ethics  
36 committee. Identification numbers will be used instead of hospital number to protect the  
37 confidentiality of study's participants. All data will be stored in database with password  
38 protection and can be accessed by only authorized staff.  
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49 Results of this study will be presented at national or international conferences and will  
50 be published in peer review journal. We plan to disseminate the results to participants,  
51 endocrinologists, and primary care physicians.  
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### 55 **Patient and Public Involvement**

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57 There was no patient or public involvement in the study.  
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## Discussion

Patients with IFG have a significant increased risk of DM. Diet interventions focused mainly on caloric restriction has been proved to decrease DM risk in this population. TRE is one type of diet intervention that has positive effects on many metabolic signal pathways from animal studies but evidence in human is limited especially in patients with IFG. Therefore, this RCT is the first study that evaluate the effect of TRE on blood sugar levels and other cardiometabolic risk factors in patients with IFG. In addition, this is the first study that assesses the impact of behavioural economic interventions such as financial incentive and text reminder on adherence to TRE intervention.

Our study design has some critical issues. First, our interventions cannot be blinded; hence, the results may be affected by observer and information bias. However, most of our outcomes are laboratory values that are objectively measured and are blinded from the outcome assessors, thus measurement error or ascertainment bias should be reduced. Second, although our study has longer term follow up than previous studies, 3-month assessment is still conserved as a short-term follow-up. Therefore, only surrogate outcomes as FPG, HbA1c, body weight, and other laboratory tests will be assessed; either a long-term effect of TRE on cardiometabolic risk factors or permanent change of participant's behaviour cannot be evaluated. Third, adherence to TRE will be measured through self-reported logbook which can be upwardly biased. However, concerning study outcomes, we consider only biological measures which will be objectively measured, e.g., FPG, HbA1c, body weight, etc. Fourth, there may be contamination of TRE in patients randomized to usual care group because TRE has been promoted in some social media in Thailand. Therefore, patients in usual care group can adopt TRE by themselves. In contrast, patients randomized to the TRE group may not comply to the TRE protocol due to intolerance to the long fasting period and will drop-out from the study. These drawbacks may dilute the effect of TRE in our study. However, we

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3 hope that these contaminations should be minimized because we will carefully assess patients  
4 who may have already performed TRE before the beginning of this study; but once occur,  
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6 this protocol violation will be dealt with ITT/PPA.  
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10 In conclusion, we will conduct an opened labeled randomized controlled trial to  
11 evaluate the efficacy of behavioral economic interventions plus TRE, TRE alone, and usual  
12 care in improving FPG, HbA1c, and other cardiometabolic risk factors in patients with  
13 prediabetes. The findings from this study will be applied for the recommendation of lifestyle  
14 modification used for diabetes prevention in patients with prediabetes. Findings about the  
15 efficacy of behavioral economic intervention will inform policy makers about the novel method  
16 to help people change and maintain their healthy behaviour.  
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26 **Authors' contributions:** US and TA are the principal investigators. US, TA, SB, SP, AC, SR,  
27 and AT designed the study. US and TA drafted the manuscript. US, TA, SB, SP, AC, SR, and  
28 AT critically revised the study protocol and the manuscript. The entire project will be  
29 supervised by TA, SR, and AT.  
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36 grant number 186/2564. The funder has no role in this study.  
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40 **Competing interest statement:** none  
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**Table 1.** Schedule matrix including activities and time at measurements/data collection

Activity	Time point				
	Screening visit	Visit 1 (baseline)	Visit 2 (4 week)	Visit 3 (8 week)	Visit 4 (12 week)
<b><i>Enrolment</i></b>					
- Eligibility screen	√				
- Informed consent		√			
- Allocation		√			
<b><i>Intervention</i></b>					
- TRE with economic behavioural intervention		√	√	√	√
- TRE		√	√	√	√
- Usual care		√	√	√	√
<b><i>Assessment</i></b>					
- Demographic data		√			
- Underlying diseases		√			
- Health risk behaviour		√			
- Family history of DM		√			
- Physical activity		√	√	√	√
- Sleep factors		√	√	√	√
- 24-hour food recall		√	√	√	√
- Time and risk preference		√			√
<b><i>Primary outcomes</i></b>					

- FPG		√	√	√	√
- HbA1c		√	√	√	√
<i>Secondary outcomes</i>					
- Body weight		√	√	√	√
- Blood pressure		√	√	√	√
- Fasting insulin		√	√	√	√
- Serum triglyceride		√	√	√	√
- Serum cholesterol		√	√	√	√
- LDL-cholesterol		√	√	√	√
- HDL-cholesterol		√	√	√	√
- hs-CRP		√	√	√	√

## Patient/Participant Information Sheet

**Project title:** Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

**Researcher's name:** Dr. Unyaporn Suthutvoravut

**Research location:** Ramathibodi Hospital Mahidol University

**Who and how to contact when there is an emergency or disorder associated with research:**

Dr. Unyaporn Suthutvoravut                      Tel. 0869041556

Dr. Thunyarat Anothaisintawee                Tel. 0813725424

**Sponsor for this research:** National Research Council of Thailand

### Project Background

Diabetes is a major health problem in Thailand. Diabetes is a major risk factor for cardiovascular and cerebrovascular disease. Therefore, the prevention of diabetes in the Thai population is important in reducing the mortality and disability of the Thai population in the future.

Prediabetes is a condition in which the blood sugar level is higher than normal but does not reach the diagnostic criteria for diabetes. People with pre-diabetes comparing to people with normal sugar levels are at greater risk of developing diabetes. Behavior modification through diet and exercise can reduce the risk of diabetes in people with pre-diabetes. Most dietary intervention will focus on limiting the amount of energy you get from your diet each day. Other dietary approaches other than energy restriction, such as the Intermittent time restricted eating (TRE) are now being developed to help patients make permanent behavioral changes. It is an eating style with short eating periods. and increase the duration of fasting each day to increase with or without limiting the amount of energy received from food

Previous literature shows that there have been studies on the effect of diet restriction on eating periods. It was found that diet control by having an 8-hour eating period and 16-hour fasting per day can significantly reduce body weight in people with abdominal obesity.

### Objective

To study the efficacy of a time restricted-eating together with the use of behavioral economic tools to reduce blood sugar levels in people with pre-diabetes compared to time restricted-eating alone and usual care

### Details to be treated with research participants

After received information about the project details, the participants sign the documents, consented to participate in this research. One week later, research assistants will conduct interviews to collect general information, history of underlying disease, risky behavior, family history of diabetes, physical activity level, diet history together with physical examination and blood test would be done to check the levels of sugar, fat and hormone. Participants will be required to fast 8-10 hours prior to the blood draw, after which they will randomly be assigned to a restricted diet, together with the use of socio-economic tool or those who received a restricted diet only for a period of time or a group that eats normally.

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4 A time-restricted diet is a way of limiting the amount of time you eat during the day. In  
5 this study, participants will have their first meal at 8:00 AM and the last meal no later than 5:00  
6 PM, without eating any food, snacks, fruit and beverages except water after 17: 00 until 8:00 the  
7 next day. The tool for behavioral economics is to create incentives to encourage more behavior  
8 change. The behavioral economics tool of the study was to award 1,000 baht to research  
9 participants who can maintain a restricted diet of greater than or equal to five days a week for one  
10 month in a row. Prize money will be given every month for 3 months until graduation. Participants  
11 were also given messages to encourage them to adopt a time restricted diet. The researcher will  
12 send a message every 3 days via the Line application.

13  
14 After participants participated in the study at 4 weeks, 8 weeks, and 12 weeks.  
15 Blood samples will be collected. Participants will be required to fast 8-10 hours before the blood  
16 draw and interview about their eating habits. physical activity level together with physical  
17 examination by research assistant There is a compensation for the patient's time during the follow-  
18 up visit, 500 baht per time.

### 19 **Benefits to the research participants**

20 Participants will gain knowledge about diet to prevent future diabetes risk.

### 21 **Side effects for the participants**

22 There may be symptoms of low blood sugar, but the likelihood of occurrence is low Because the  
23 measures given are only recommendations for time retracted diet only, not compulsory. The patient  
24 may or may not follow the instructions. Risks associated with blood test may include pain,  
25 bleeding.

### 26 **Confidentiality**

27  
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29 The data will be collected with confidentiality. No name of number of hospital record will be  
30 collected. The data will be presented as a whole and no individual identification. Only researchers  
31 will have access to information. This study will inform patients that they are in research and able  
32 to decide whether to join or not. Patients can withdraw from research at any time and has no effect  
33 on the treatment of patients in any way.

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If you have questions or concerns about participating in this research project. You can  
contact the chairman of the Human Research Ethics Board at Faculty Research Office,  
Research and Welfare Building, Faculty of Medicine Ramathibodi Hospital.  
Tel. 02-2011544

## Informed Consent Form

**Project title:** Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Researcher's name, Dr. Unyaporn Suthutvoravut

Name of research participant.....

Age.....medical record number.....

### Research Participant Consent

I, Mr./Mrs./Ms..... have known the details of the research project as well as the benefits and the risks that will arise to me from the researcher clearly and consents to be involved in the above research project. And I know that if there are any problems or questions I could ask the researchers. Also, I could quit this research project at any time, without affecting the treatment that I deserve. In addition, the researchers will keep the specific information about me confidential and will only disclose it in the form of a summary of the research. Disclosure of information about me to relevant agencies could only be done in cases of necessity for academic reasons.

Signed.....

(Research participant)

.....  
(witness)

.....  
(witness)

Date .....

### Description of the doctor or researcher

I have explained the details of the project. as well as the benefits of research and the potential risks were clearly known to the participants without any hidden objection.

Signed.....

(Doctor or Researcher)

date.....



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__ 1 __
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__ 3,8 __
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	__ 3 __
Funding	4	Sources and types of financial, material, and other support	__ 16 __
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__ 1, 16 __
	5b	Name and contact information for the trial sponsor	__ 16 __
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__ 16 __
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__ 16 __

## 1 Introduction

2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	___ 5-7 ___
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	___ 5-7 ___
7				
8	Objectives	7	Specific objectives or hypotheses	___ 7 ___
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___ 8 ___
12				
13				

## 14 Methods: Participants, interventions, and outcomes

15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	___ 8 ___
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	___ 8 ___
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	___ 9-10 ___
23			administered	
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	___ NA ___
25			change in response to harms, participant request, or improving/worsening disease)	
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	___ 10,13 ___
27			(eg, drug tablet return, laboratory tests)	
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___ 10 ___
29				
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	___ 10-11 ___
31			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
32			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
33			efficacy and harm outcomes is strongly recommended	
34	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	___ 11-12 ___
35			participants. A schematic diagram is highly recommended (see Figure)	
36				
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____ 13 _____
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____ 8-9 _____
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7	<b>Methods: Assignment of interventions (for controlled trials)</b>			
8	Allocation:			
9				
10	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____ 8-9 _____
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16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____ 9 _____
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____ 9 _____
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____ 9 _____
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____ 9 _____
28				
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31	<b>Methods: Data collection, management, and analysis</b>			
32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____ 11-13 _____
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38		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____ - _____
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1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
2				
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4				
5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
11				
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13				
14	<b>Methods: Monitoring</b>			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12-13
17				
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
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32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
35				
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37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 8 _____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ NA _____
5				
6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, stored, and maintained in order to protect confidentiality before, during, and after the trial	_____ 14 _____
8				
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 16 _____
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13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____ 14 _____
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16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____ NA _____
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____ 14 _____
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ NA _____
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26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ NA _____
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29	<b>Appendices</b>			
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31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Appendix
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34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____ NA _____
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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by/4.0/)" license.

# BMJ Open

## Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

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Manuscripts

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3 **Efficacy of time restricted eating and behavioral economic intervention in reducing**  
4 **fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time**  
5 **restricted eating alone or usual care in patients with impaired fasting glucose: Protocol**  
6 **for a randomized controlled trial**  
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## Abstract

**Introduction:** Impaired fasting glucose(IFG) is a significant risk factor for diabetes mellitus(DM). Time restricted eating(TRE) is one type of diet that showed positive effects on many metabolic signal pathways. However, the effects of TRE on cardiometabolic risk factors in humans are still limited. In addition, compliance with TRE remains problematic for some people despite their intention to follow the diet control. Therefore, this study aims to investigate the efficacy of TRE with behavioral economic interventions, compared to TRE alone and usual care, in reducing fasting plasma glucose(FPG), hemoglobin A1c(HbA1c), and other cardiometabolic risk factors in patients with IFG.

**Methods and analysis:** This parallel randomized controlled trial will be conducted at the outpatient clinic of the Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. Patients aged 18-65 years with IFG defined as FPG 100-125 mg/dl and having body mass index(BMI)  $\geq 25$  kg/m<sup>2</sup> will be recruited between October 2021 and October 2022. Patients will be randomly allocated to 3 groups (1:1:1 ratio) as 1) TRE with behavioral economic interventions which include financial incentives and text reminders, 2) TRE alone, or 3) usual care. The number of participants will be 38 per group (a total of 114). The duration of the intervention will be 12 weeks. Primary outcomes are FPG and HbA1c levels measured at 12 weeks after randomization. Secondary outcomes are body weight, systolic and diastolic blood pressure, fasting insulin, serum triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and high sensitivity C-reactive protein.

**Ethics and dissemination:** The study protocol has been approved by the Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University(MURA2021/389). All patients will be informed about the details of the study and sign written informed consent before enrollment in the study. Results from this study will be published in peer-reviewed

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3 journal.  
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5 **Trial registration number:** TCTR20210520002 (18 January 2022, version 2) from Thai  
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8 Clinical Trial Registry (TCTR) (<https://thaiclinicaltrials.org>)  
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For peer review only

### Strengths and limitations of this study

- First randomized controlled trial that assesses the efficacy of time restricted eating on blood sugar levels and other cardiometabolic risk factors in patients with impaired fasting glucose.
- The study has longer-term follow-up than previous studies.
- The interventions cannot be blinded; hence, the results may be affected by observer and information bias.
- Contamination of time restricted eating in the usual care group might be occurred due to the promotion of time restricted eating on some social media in Thailand.

## Background and rationale

Diabetes mellitus (DM) is one of the important health problems in Thailand. The results from the National health examination survey reported that the prevalence of DM in the Thai population has increased from 7.7% in 2004 to 9.9% in 2014<sup>1</sup>. Diabetes is a risk factor for cardiovascular diseases (CVD) and also the cause of microvascular complications such as chronic kidney disease (CKD) and diabetic retinopathy. Moreover, around 4% of mortality in the Thai population is caused by DM<sup>2</sup>. Hence, the prevention of DM in the Thai population is critical to decreasing further morbidity and mortality in the future.

Impaired fasting glucose (IFG) or intermediate hyperglycemia is the condition in which blood sugar level is higher than normal but does not reach the DM threshold. A person with IFG has a higher risk for DM about 13 times than a person with a normal blood glucose level<sup>3</sup>. Evidence from a previous umbrella review found that lifestyle modifications by diet control and exercise significantly decreased the risk of DM in persons with IFG<sup>4</sup>. Most diet interventions including low and very low-calorie diets are mainly focused on caloric restriction (CR) with the main objective of body weight reduction. Although the efficacy of these diet interventions in decreasing DM risk is well established, most patients could not sustain their healthy behaviors or maintain their healthy lifestyle permanently<sup>5</sup>. As a result, other methods of diet control such as time restricted eating (TRE) have been introduced as an alternative, which may help patients permanently maintain their behaviors.

TRE is one type of dietary approach that limits the daily eating window to commonly lower than 10 h/day and prolongs fasting time<sup>6-8</sup>. Previous literature found that increased fasting time has positive effects on many metabolic signal pathways, i.e., prolonged fasting stimulated autophagy and cell repair including mitochondria biogenesis resulting in better metabolic signal pathways in animals. In a human study, the TRE could significantly lower body weight but could not decline fasting plasma glucose (FPG), fasting insulin, and



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3 hemoglobin A1c (HbA1c) when compared to the normal eating style in patients with  
4 metabolic syndrome<sup>9</sup>. Likewise, a study in patients with obesity also found that TRE could  
5 reduce body weight, blood pressure, low-density lipoprotein cholesterol (LDL-C), and non-  
6 high-density lipoprotein (HDL-C) cholesterol but could not reduce FPG, fasting insulin and  
7 HbA1c<sup>10</sup>, while the study of Schroder et al found the significant reduction of body mass  
8 index, body fat percentage, and waist circumference in middle-aged women with obesity  
9 receiving TRE but FPG, HbA1c, fasting insulin, LDL-C, HDL-C, serum uric acid, and blood  
10 pressure were not significantly different between TRE and control groups<sup>11</sup>. Contrastingly,  
11 meta-analyses found beneficial of TRE in lowering not only body weight but also FPG, blood  
12 pressure, and triglyceride levels<sup>12 13</sup>. Until now, there are few small randomized controlled  
13 trials (RCT) that examined the effect of TRE in patients with prediabetes. A cross-over RCT  
14 assessing the effects of early or delayed TRE in 15 men at risk for type 2 DM found that both  
15 early and delayed TRE improved glycemic response, but only early TRE could lower mean  
16 FPG in men with a high risk of DM<sup>14</sup>. Another RCT assessed the effect of early TRE in 8  
17 men with prediabetes and found that early TRE could reduce insulin level, blood pressure,  
18 and food appetite, increase insulin sensitivity and beta-cell responsiveness but could not  
19 reduce FPG<sup>15</sup>. However, these RCTs focused on only men with very short follow-up times  
20 (i.e., 7 days and 5 weeks). Therefore, further RCT investigating the longer-term effect of  
21 TRE in both male and female patients is still needed.

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47 Although several studies found that TRE was well accepted by study  
48 participants<sup>16</sup> and well-tolerated even in older adults<sup>17</sup> but the long-term adherence to TRE is  
49 still questionable in the real life of some people. Such a gap occurs because the benefits of  
50 reducing cardiometabolic risks are intangible and will occur in the far future, whereas the  
51 cost of adherence to this diet control, namely being disciplined on diet time instead of eating  
52 freely whenever desired, happens immediately. Thus, some people who place much greater  
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3 weight on the present than on the future will be less likely to adhere to diet control. This is  
4 called present bias from behavioral economics perspective<sup>18 19</sup>. Behavioral economics is a  
5 field that integrates insights and methods from psychology and economics to understand  
6 human decision-making<sup>20-22</sup>.  
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12 A few behavioral economics tools have been used to deal with a present bias to  
13 promote adherence to diet control, i.e., financial incentives and text reminder<sup>23</sup>. Previous  
14 studies show that financial incentive was an effective tool to promote a healthy lifestyle such  
15 as smoking cessation, physical activity<sup>24</sup>, and weight loss<sup>25</sup>. Text reminders about an  
16 individual commitment, performance, or goal can immediately remind them of the priority.  
17 Such reminders have been proven effective in many domains, such as for the promotion of  
18 savings<sup>26</sup>, weight loss<sup>27 28</sup>, and medication adherence<sup>29</sup>. As a result, using behavioral  
19 economics might help increase compliance with lifestyle modification such as TRE or even  
20 maintaining behavioral change and finally improve the efficacy of lifestyle intervention in  
21 people with IFG who require a lifelong healthy lifestyle to prevention of DM conversion.  
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36 Nevertheless, there has been no study that assesses the efficacy of combined TRE  
37 with behavioral economic interventions in patients with IFG. Therefore, this RCT protocol is  
38 developed which aims to compare the efficacy of additional behavioral economic  
39 interventions in TRE to TRE alone and usual care in patients with IFG with the following  
40 objectives: First, to compare FPG and HbA1c levels between patients with IFG who receive  
41 behavioral economic interventions plus TRE, TRE alone, and usual care. Second, to compare  
42 body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting insulin,  
43 serum triglyceride, total cholesterol, LDL-C, HDL-C, and high sensitivity C-reactive protein  
44 (hs-CRP) between these three interventions.  
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## 55 **Methods and analysis**

### 56 *Study design*

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3 This study is a parallel RCT, which will be conducted at the outpatient clinic of the  
4 Department of Family Medicine (OFM), Faculty of Medicine, Ramathibodi Hospital, during  
5 October 2021 to October 2022. This research method complies with the Consolidated  
6 Standards of Reporting Trials (CONSORT) statement. The trial protocol has been registered  
7 at the Thai Clinical Trials Registry (TCTR20210520002).  
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### 10 11 12 13 14 ***Patient recruitment***

15  
16 Patients and staffs of Ramathibodi Hospital who are diagnosed with IFG will be  
17 recruited from October 2021 to October 2022, and they will be followed up until the 12<sup>th</sup>  
18 week after receiving interventions. Trained investigators and research assistants will  
19 approach and inform patients about the study protocol, randomization process, and details of  
20 intervention and comparisons. Participants will sign informed consent before participating.  
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### 28 29 ***Participants***

30 Patients will be included in this study, if they meet all of the following criteria: 1) age  
31 18 to 65 years, 2) having FPG of 100-125 mg/dl with HbA1c less than 6.5%, and 3) body  
32 mass index  $\geq 25$  kg/m<sup>2</sup>. The Patients will be ineligible if 1) they are currently on Ketogenic or  
33 vegetarian diets, 2) doing night shift work at least  $\geq 3$  hours during 10:00 PM-5:00 AM more  
34 than 1 day/week, 3) having more than 5 kg body weight changes during the 3 months before  
35 enrolment to the study, 4) taking medicines that must be taken with food in the early morning  
36 (i.e., before 8:00 AM) or late evening (i.e., after 5:00 PM), 5) pregnancy or breastfeeding, 6)  
37 having psychiatric disorders such as eating disorder or mood disorder but not including  
38 depression, 7) taking corticosteroid or anti-diabetic drugs, 8) having a history of bariatric  
39 surgery, and 9) having impaired nutrients absorption.  
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### 54 ***Randomizations***

55 Patients will be randomly assigned to any of three interventions including behavioural  
56 economic interventions plus TRE, TRE alone, and usual care with a ratio of 1:1:1. Block  
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3 randomization with varying block sizes of 6 and 9 will be generated by a biostatistician who  
4 does not involve in the trial using STATA program version 16. Randomization will be  
5 stratified according to age groups (i.e., 18-59 years and 60-65 years). A random sequence list  
6 will be then concealed using sequential opaque sealed envelopes, which will be kept at the  
7 OFM. A research assistant will administer and open the sealed envelope once patients are  
8 eligible.  
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### 16 ***Blinding***

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19 Participants and clinicians cannot be blinded due to the nature of interventions.  
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21 However, data collectors and a biostatistician will be blinded about the intervention  
22 allocation. In addition, the outcomes of this study will be objectively measured that will not  
23 be affected by the unblinded intervention.  
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### 28 ***Study interventions***

29  
30 Interested interventions are TRE and behavioural economic interventions. TRE is a  
31 limitation of the daily time of food intake to 9 hours with prolonged fasting in the night time  
32 of 15 hours. Participants will be requested to limit their periods of food intake from 8:00 AM  
33 to 5:00 PM without restriction on types of food and beverages. Participants will be asked for  
34 complying with TRE as much as they can.  
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42 Behavioural economic interventions will consist of financial incentives and text  
43 reminders. For financial incentive, the participant will receive monetary compensation of  
44 1000 Baths per month (23 £) if they self-report that they can adhere to TRE at least 5  
45 days/week for 4 weeks. TRE adherence will be evaluated every week by asking participants  
46 to record their first and last mealtime every day via logbook and financial incentives will be  
47 provided on 4<sup>th</sup>, 8<sup>th</sup>, and 12<sup>th</sup> week after randomisation. In addition, text reminders will be  
48 sent to participants every 2 days to remind them about their commitment (Your goal is to  
49 stick to the TRE plan for at least 5 days a week.), performance (Last week you have  
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3 successfully stucked to the TRE plan for 5 days.), and also about the TRE interval. The TRE  
4 alone group will be advised about the benefit of TRE without any additional support.  
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7 However, the participants in TRE alone group will be asked to record the adherence of TRE  
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10 via logbook.  
11

12           Comparator of the study is a usual care according to the current practice guideline of  
13 diabetes prevention. Patients will be educated about their conditions and disease progression,  
14 dietary control, and exercise to prevent disease progression. Participants in TRE and  
15 behavioural economic interventions and TRE alone groups also will receive the education  
16 about dietary control and exercise similar to patients in the usual care group. In addition,  
17 patients will be asked to record their first and last mealtime every day, which will be the same  
18 as patients in the other two interventions to evaluate protocol violation. All patients in 3  
19 groups will received a leaflet that provides knowledge about healthy food and lifestyle  
20 modification to control their weight and reduce the risk of progression to DM.  
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### 32 ***Outcomes***

33           The primary outcomes of this study are FPG and HbA1c levels which will be  
34 measured at the end of the study, i.e., 3 months after randomisation. Fasting plasma glucose  
35 and HbA1c will be measured by hexokinase glucose-6 phosphate dehydrogenase and turbid  
36 metric inhibition immunoassay certified by the National Glycohemoglobin Standardization  
37 Program (NGSP).  
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46           Secondary outcomes are body weight, SBP, DBP, fasting insulin, serum triglyceride,  
47 total cholesterol, LDL-C, HDL-C, and hs-CRP. Body weight and blood pressure  
48 measurement will be taken by trained research assistants. Body weight will be measured  
49 without shoes to the nearest 100 g. Blood pressure will measured after the resting for at least  
50 15 minutes with an automatic blood pressure monitoring. Fasting insulin, serum triglyceride,  
51 total cholesterol, LDL-C, HDL-C, and hs-CRP will be measured by chemiluminescent  
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3 microparticle immunoassay, glycerol phosphate oxidase, enzymatic method, liquid selective  
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5 detergent, accelerator selective detergent, and immunonephelometry, respectively.  
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8 All primary and secondary outcomes will be measured at the baseline, 1, 2, and 3  
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10 months after randomization.  
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### 12 *Adverse events*

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14 Adverse events such as syncope, dizziness, and light headiness will be measured  
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16 during all study periods.  
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### 19 *Co-variables*

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21 Other covariables will be collected as follows.  
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23

- 24 1. Demographic data including age, sex, educational level, and marital status
- 25 2. Underlying diseases such as hypertension, dyslipidaemia, fatty liver
- 26 3. Health risk behaviours including smoking and alcohol intake
- 27 4. Family history of DM in the first degree relatives
- 28 5. Sleep factors including sleep duration, sleep quality measured by the Thai
- 29 6. Physical activity level measured by Global Physical Activity
- 30 7. Details of food and caloric intakes assessed by 24-hour food recall and
- 31 8. Time and risk preference assessed by multiple price list method<sup>33-38</sup>
- 32 8. Health risk behaviours including smoking and alcohol intake
- 33 4. Family history of DM in the first degree relatives
- 34 5. Sleep factors including sleep duration, sleep quality measured by the Thai
- 35 version of the Pittsburgh Sleep Quality Index<sup>30</sup>, and morningness and
- 36 eveningness preference using the validated Thai version of the Composite
- 37 Scale of Morningness (CSM)<sup>31</sup>
- 38 6. Physical activity level measured by Global Physical Activity
- 39 Questionnaire (GPAQ)<sup>32</sup>
- 40 7. Details of food and caloric intakes assessed by 24-hour food recall and
- 41 food frequency questionnaires (FFQs)
- 42 8. Time and risk preference assessed by multiple price list method<sup>33-38</sup>
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### 57 *Study protocol and data collection*

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3 Schedule matrix consisting of data collections and time at measurements are  
4 presented in Table 1. At the first visit, trained investigator and research assistants will recruit  
5 the patient by screening FPG and other inclusion criteria (i.e., age and BMI). If the patient  
6 meets all the inclusion criteria, the research assistants will explain about the study protocol,  
7 process of data collection, and detail of TRE, behavioural economic interventions, and  
8 comparator. The patient will be asked to sign the informed consent if they are willing to  
9 participate the study.

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19 At one week after enrolment (2<sup>nd</sup> visit), participants will be interviewed by research  
20 assistants about demographic data, underlying diseases, health risk behaviours, 24-hour food  
21 recall, sleep factors, physical activity level, and time and risk preference questionnaire.  
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Physical examination including blood pressure, body weight, and height will be measured by  
trained research assistants. Laboratory measurement (i.e., FPG, HbA1c, serum triglyceride,  
total cholesterol, LDL-C, HDL-C, fasting insulin, and hs-CRP) will be performed after  
fasting at least 8 hours or longer. After that participant will be randomly assigned to any of 3  
groups as behavioural economic intervention plus TRE, TRE alone, and usual care.

Physical activity level, sleep factors, 24-hour food recall, body weight, SBP, DBP,  
and laboratory measurement will be obtained at 3<sup>rd</sup> visit (4<sup>th</sup> weeks after randomization), 4<sup>th</sup>  
visit (8<sup>th</sup> weeks after randomization), and 5<sup>th</sup> visit (12<sup>th</sup> weeks after randomization or the end  
of the study). 24-hour food recall will be collected using food diary for 7 days at each visit.  
INMUCAL-nutrients version 4.0 (<https://inmu2.mahidol.ac.th/inmucal/index.php>) will be  
used to calculate the dietary data to nutrient intakes. This program was developed by the  
Institute of Nutrition, Mahidol University, Thailand.

### ***Data management***

All data will be collected and filled in hard case record forms (CRF). All CRFs will  
be checked by researchers for completeness and correction before data entry. Hard CRFs will

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3 be independently computerised by two research assistants using Epidata version 3.1 software.  
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5 Data will be cleaned and checked every month by investigators (US and TA). Any unclear or  
6  
7 missing information will be cross-checked against the source documents of CRFs and  
8  
9 medical records if required. Hospital numbers will be encrypted and kept confidentiality;  
10  
11 unique identification number (ID) will be assigned instead to each patient. All data will be  
12  
13 backed up using Google drive to prevent data loss.  
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### 16 17 ***Data monitoring***

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19 A formal data and safety monitoring board (DSMB) is not required because of no  
20  
21 expected major adverse event from study's interventions. If adverse events are occurred, these  
22  
23 will be managed by the trial committee, including all authors of this protocol. Recruitment and  
24  
25 retention rates, and any protocol violations will be monitored by the trial committee via regular  
26  
27 meeting every month.  
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### 30 31 ***Sample size calculation***

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33 Sample size is calculated based on a superiority trial using one way analysis of  
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35 variance method in STATA version 17.0. Baseline mean and standard deviation (SD) of FPG  
36  
37 in patients of prediabetes cohort conducted in the OFM was 105 and 9 mg/dl. We expected  
38  
39 that receiving behavioural economic interventions plus TRE and TRE alone should be able to  
40  
41 decrease FPG around 7% and 5% relative to the control, i.e., the FBGs were about 98 and  
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43 100 mg/dl, respectively. Type I error, power, and follow up are set at 0.05, 0.8, and 20%; a  
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45 total of 114 participants with 38 per group will be required to detect these differences.  
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### 49 50 ***Statistical analysis***

51  
52 Baseline characteristics and outcomes among 3 groups will be described using mean  
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54 (SD) or median (range) where appropriate for continuous data, and frequency (percentage)  
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56 for categorical data. Means of primary and secondary outcomes will be compared among  
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58 three groups using a mixed-effect linear regression model by regress outcome on intervention  
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3 and time considering patients as a random effect (i.e., repeated measured at 4, 8, and 12  
4 weeks) and the intervention arms (TRE with behavioral economic interventions and TRE  
5 alone versus usual care) as a fixed-effect. Marginal means and differences between any pair  
6 of the three interventions will be then estimated accordingly.  
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12 Protocol violation will be dealt using an intention to treat analysis (ITT) and per-  
13 protocol analysis (PPA). For the PPA, patients in the TRE plus behavioral economic  
14 interventions and TRE alone who do not comply with TRE (i.e., comply < 5 days per week)  
15 throughout the study or patients in the usual care group who take TRE 5 days of more per  
16 week will be excluded from analysis. Multivariate regression analysis will be applied, if there  
17 is the difference in baseline characteristics between 3 groups.  
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26 All analyses will be performed using STATA 17.0. P value of less than 0.05 will be  
27 considered as a statistical significance.  
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### 30 **Ethics and dissemination**

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32 The study protocol is approved by the Ethics Committee of Ramathibodi Hospital,  
33 Mahidol University, (MURA 2021/389) and will be conducted in agreement with the Helsinki  
34 declaration. All participants will sign informed consent at the baseline of the study (see  
35 Supplementary Appendix). Protocol amendments will be reported to the institutional ethics  
36 committee. Identification numbers will be used instead of hospital number to protect the  
37 confidentiality of study's participants. All data will be stored in database with password  
38 protection and can be accessed by only authorized staff.  
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49 Results of this study will be presented at national or international conferences and will  
50 be published in peer review journal. We plan to disseminate the results to participants,  
51 endocrinologists, and primary care physicians.  
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### 55 **Patient and Public Involvement**

56  
57 There was no patient or public involvement in the study.  
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## Discussion

Patients with IFG have a significant increased risk of DM. Diet interventions focused mainly on caloric restriction has been proved to decrease DM risk in this population. TRE is one type of diet intervention that has positive effects on many metabolic signal pathways from animal studies but evidence in human is limited especially in patients with IFG. Therefore, this RCT is the first study that evaluate the effect of TRE on blood sugar levels and other cardiometabolic risk factors in patients with IFG. In addition, this is the first study that assesses the impact of behavioural economic interventions such as financial incentive and text reminder on adherence to TRE intervention.

Our study design has some critical issues. First, our interventions cannot be blinded; hence, the results may be affected by observer and information bias. However, most of our outcomes are laboratory values that are objectively measured and are blinded from the outcome assessors, thus measurement error or ascertainment bias should be reduced. Second, although our study has longer term follow up than previous studies, 3-month assessment is still conserved as a short-term follow-up. Therefore, only surrogate outcomes as FPG, HbA1c, body weight, and other laboratory tests will be assessed; either a long-term effect of TRE on cardiometabolic risk factors or permanent change of participant's behaviour cannot be evaluated. Third, adherence to TRE will be measured through self-reported logbook which can be upwardly biased. However, concerning study outcomes, we consider only biological measures which will be objectively measured, e.g., FPG, HbA1c, body weight, etc. Fourth, there may be contamination of TRE in patients randomized to usual care group because TRE has been promoted in some social media in Thailand. Therefore, patients in usual care group can adopt TRE by themselves. In contrast, patients randomized to the TRE group may not comply to the TRE protocol due to intolerance to the long fasting period and will drop-out from the study. These drawbacks may dilute the effect of TRE in our study. However, we

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3 hope that these contaminations should be minimized because we will carefully assess patients  
4 who may have already performed TRE before the beginning of this study; but once occur,  
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6 this protocol violation will be dealt with ITT/PPA.  
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10 In conclusion, we will conduct an opened labeled randomized controlled trial to  
11 evaluate the efficacy of behavioral economic interventions plus TRE, TRE alone, and usual  
12 care in improving FPG, HbA1c, and other cardiometabolic risk factors in patients with  
13 prediabetes. The findings from this study will be applied for the recommendation of lifestyle  
14 modification used for diabetes prevention in patients with prediabetes. Findings about the  
15 efficacy of behavioral economic intervention will inform policy makers about the novel method  
16 to help people change and maintain their healthy behaviour.  
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26 **Authors' contributions:** US and TA are the principal investigators. US, TA, SB, SP, AC, SR,  
27 and AT designed the study. US and TA drafted the manuscript. US, TA, SB, SP, AC, SR, and  
28 AT critically revised the study protocol and the manuscript. The entire project will be  
29 supervised by TA, SR, and AT.  
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36 grant number 186/2564. The funder has no role in this study.  
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40 **Competing interest statement:** none  
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**Table 1.** Schedule matrix including activities and time at measurements/data collection

Activity	Time point				
	Screening visit	Visit 1 (baseline)	Visit 2 (4 week)	Visit 3 (8 week)	Visit 4 (12 week)
<b><i>Enrolment</i></b>					
- Eligibility screen including assessment of age, FPG, BMI, and HbA1c	√				
- Informed consent		√			
- Allocation		√			
<b><i>Intervention</i></b>					
- TRE with economic behavioural intervention		√	√	√	√
- TRE		√	√	√	√
- Usual care		√	√	√	√
<b><i>Assessment</i></b>					
- Demographic data		√			
- Underlying diseases		√			
- Health risk behaviour		√			
- Family history of DM		√			
- Physical activity		√	√	√	√
- Sleep factors		√	√	√	√
- 24-hour food recall		√	√	√	√

- Time and risk preference		√			√
<i>Primary outcomes</i>					
- FPG		√	√	√	√
- HbA1c		√	√	√	√
<i>Secondary outcomes</i>					
- Body weight		√	√	√	√
- Blood pressure		√	√	√	√
- Fasting insulin		√	√	√	√
- Serum triglyceride		√	√	√	√
- Serum cholesterol		√	√	√	√
- LDL-cholesterol		√	√	√	√
- HDL-cholesterol		√	√	√	√
- hs-CRP		√	√	√	√

## Patient/Participant Information Sheet

**Project title:** Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

**Researcher's name:** Dr. Unyaporn Suthutvoravut

**Research location:** Ramathibodi Hospital Mahidol University

**Who and how to contact when there is an emergency or disorder associated with research:**

Dr. Unyaporn Suthutvoravut                      Tel. 0869041556

Dr. Thunyarat Anothaisintawee                Tel. 0813725424

**Sponsor for this research:** National Research Council of Thailand

### Project Background

Diabetes is a major health problem in Thailand. Diabetes is a major risk factor for cardiovascular and cerebrovascular disease. Therefore, the prevention of diabetes in the Thai population is important in reducing the mortality and disability of the Thai population in the future.

Prediabetes is a condition in which the blood sugar level is higher than normal but does not reach the diagnostic criteria for diabetes. People with pre-diabetes comparing to people with normal sugar levels are at greater risk of developing diabetes. Behavior modification through diet and exercise can reduce the risk of diabetes in people with pre-diabetes. Most dietary intervention will focus on limiting the amount of energy you get from your diet each day. Other dietary approaches other than energy restriction, such as the Intermittent time restricted eating (TRE) are now being developed to help patients make permanent behavioral changes. It is an eating style with short eating periods. and increase the duration of fasting each day to increase with or without limiting the amount of energy received from food

Previous literature shows that there have been studies on the effect of diet restriction on eating periods. It was found that diet control by having an 8-hour eating period and 16-hour fasting per day can significantly reduce body weight in people with abdominal obesity.

### Objective

To study the efficacy of a time restricted-eating together with the use of behavioral economic tools to reduce blood sugar levels in people with pre-diabetes compared to time restricted-eating alone and usual care

### Details to be treated with research participants

After received information about the project details, the participants sign the documents, consented to participate in this research. One week later, research assistants will conduct interviews to collect general information, history of underlying disease, risky behavior, family history of diabetes, physical activity level, diet history together with physical examination and blood test would be done to check the levels of sugar, fat and hormone. Participants will be required to fast 8-10 hours prior to the blood draw, after which they will randomly be assigned to a restricted diet, together with the use of socio-economic tool or those who received a restricted diet only for a period of time or a group that eats normally.

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A time-restricted diet is a way of limiting the amount of time you eat during the day. In this study, participants will have their first meal at 8:00 AM and the last meal no later than 5:00 PM, without eating any food, snacks, fruit and beverages except water after 17:00 until 8:00 the next day. The tool for behavioral economics is to create incentives to encourage more behavior change. The behavioral economics tool of the study was to award 1,000 baht to research participants who can maintain a restricted diet of greater than or equal to five days a week for one month in a row. Prize money will be given every month for 3 months until graduation. Participants were also given messages to encourage them to adopt a time restricted diet. The researcher will send a message every 3 days via the Line application.

After participants participated in the study at 4 weeks, 8 weeks, and 12 weeks. Blood samples will be collected. Participants will be required to fast 8-10 hours before the blood draw and interview about their eating habits, physical activity level together with physical examination by research assistant. There is a compensation for the patient's time during the follow-up visit, 500 baht per time.

#### **Benefits to the research participants**

Participants will gain knowledge about diet to prevent future diabetes risk.

#### **Side effects for the participants**

There may be symptoms of low blood sugar, but the likelihood of occurrence is low. Because the measures given are only recommendations for time restricted diet only, not compulsory. The patient may or may not follow the instructions. Risks associated with blood test may include pain, bleeding.

#### **Confidentiality**

The data will be collected with confidentiality. No name or number of hospital record will be collected. The data will be presented as a whole and no individual identification. Only researchers will have access to information. This study will inform patients that they are in research and able to decide whether to join or not. Patients can withdraw from research at any time and has no effect on the treatment of patients in any way.

If you have questions or concerns about participating in this research project. You can contact the chairman of the Human Research Ethics Board at Faculty Research Office, Research and Welfare Building, Faculty of Medicine Ramathibodi Hospital.  
Tel. 02-2011544

## Informed Consent Form

**Project title:** Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Researcher's name, Dr. Unyaporn Suthutvoravut

Name of research participant.....

Age.....medical record number.....

### Research Participant Consent

I, Mr./Mrs./Ms..... have known the details of the research project as well as the benefits and the risks that will arise to me from the researcher clearly and consents to be involved in the above research project. And I know that if there are any problems or questions I could ask the researchers. Also, I could quit this research project at any time, without affecting the treatment that I deserve. In addition, the researchers will keep the specific information about me confidential and will only disclose it in the form of a summary of the research. Disclosure of information about me to relevant agencies could only be done in cases of necessity for academic reasons.

Signed.....

(Research participant)

.....  
(witness)

.....  
(witness)

Date .....

### Description of the doctor or researcher

I have explained the details of the project. as well as the benefits of research and the potential risks were clearly known to the participants without any hidden objection.

Signed.....

(Doctor or Researcher)

date.....



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

## SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1__
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__3,8__
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	__3__
Funding	4	Sources and types of financial, material, and other support	__16__
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1, 16__
	5b	Name and contact information for the trial sponsor	__16__
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__16__
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__16__

## 1 Introduction

2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	___ 5-7 ___
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
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6		6b	Explanation for choice of comparators	___ 5-7 ___
7				
8	Objectives	7	Specific objectives or hypotheses	___ 7 ___
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___ 8 ___
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## 14 Methods: Participants, interventions, and outcomes

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16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	___ 8 ___
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	___ 8 ___
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
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22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	___ 9-10 ___
23			administered	
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	___ NA ___
25			change in response to harms, participant request, or improving/worsening disease)	
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	___ 10,13 ___
27			(eg, drug tablet return, laboratory tests)	
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___ 10 ___
29				
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	___ 10-11 ___
31			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
32			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
33			efficacy and harm outcomes is strongly recommended	
34	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	___ 11-12 ___
35			participants. A schematic diagram is highly recommended (see Figure)	
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____ 13 _____
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____ 8-9 _____
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6				
7	<b>Methods: Assignment of interventions (for controlled trials)</b>			
8	Allocation:			
9				
10	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____ 8-9 _____
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16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____ 9 _____
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____ 9 _____
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____ 9 _____
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____ 9 _____
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31	<b>Methods: Data collection, management, and analysis</b>			
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33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____ 11-13 _____
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38		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____ - _____
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1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	___ 12 ___
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5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___ 13 ___
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___ 13 ___
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10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___ 13 ___
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14	<b>Methods: Monitoring</b>			
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16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___ 12-13 ___
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___ NA ___
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___ 12-13 ___
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___ 13 ___
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32	<b>Ethics and dissemination</b>			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___ 14 ___
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37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___ 14 ___
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 8 _____
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ NA _____
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7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, stored, and maintained in order to protect confidentiality before, during, and after the trial	_____ 14 _____
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 16 _____
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13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____ 14 _____
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16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____ NA _____
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____ 14 _____
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ NA _____
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26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ NA _____
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29	<b>Appendices</b>			
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31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Appendix
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34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____ NA _____
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37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 39 “[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by/4.0/)” license.  
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# BMJ Open

## Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, NUTRITION & DIETETICS

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Manuscripts

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3 **Efficacy of time restricted eating and behavioral economic intervention in reducing**  
4 **fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time**  
5 **restricted eating alone or usual care in patients with impaired fasting glucose: Protocol**  
6 **for a randomized controlled trial**  
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## Abstract

**Introduction:** Impaired fasting glucose(IFG) is a significant risk factor for diabetes mellitus(DM). Time restricted eating(TRE) is one type of diet that showed positive effects on many metabolic signal pathways. However, the effects of TRE on cardiometabolic risk factors in humans are still limited. In addition, compliance with TRE remains problematic for some people despite their intention to follow the diet control. Therefore, this study aims to investigate the efficacy of TRE with behavioral economic interventions or TRE alone relative to usual care, in reducing fasting plasma glucose(FPG), hemoglobin A1c(HbA1c), and other cardiometabolic risk factors in patients with IFG.

**Methods and analysis:** This parallel randomized controlled trial will be conducted at the outpatient clinic of the Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. Patients aged 18-65 years with IFG defined as FPG 100-125 mg/dl and having body mass index(BMI)  $\geq 25$  kg/m<sup>2</sup> will be recruited between October 2021 and October 2022. Patients will be randomly allocated to 3 groups (1:1:1 ratio) as 1) TRE with behavioral economic interventions which include financial incentives and text reminders, 2) TRE alone, or 3) usual care. The number of participants will be 38 per group (a total of 114). The duration of the intervention will be 12 weeks. Primary outcome is FPG levels measured at 12 weeks after randomization. Secondary outcomes are HbA1c, body weight, systolic and diastolic blood pressure, fasting insulin, serum triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and high sensitivity C-reactive protein.

**Ethics and dissemination:** The study protocol has been approved by the Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University(MURA2021/389). All patients will be informed about the details of the study and sign written informed consent before enrollment in the study. Results from this study will be published in peer-reviewed

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3 journal.  
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5 **Trial registration number:** TCTR20210520002 (18 January 2022, version 2) from Thai  
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8 Clinical Trial Registry (TCTR) (<https://thaiclinicaltrials.org>)  
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For peer review only

### Strengths and limitations of this study

- First randomized controlled trial that assesses the efficacy of time restricted eating on blood sugar levels and other cardiometabolic risk factors in patients with impaired fasting glucose.
- The study has longer-term follow-up than previous studies.
- The interventions cannot be blinded; hence, the results may be affected by observer and information bias.
- Contamination of time restricted eating in the usual care group might be occurred due to the promotion of time restricted eating on some social media in Thailand.

## Background and rationale

Diabetes mellitus (DM) is one of the important health problems in Thailand. The results from the National health examination survey reported that the prevalence of DM in the Thai population has increased from 7.7% in 2004 to 9.9% in 2014<sup>1</sup>. Diabetes is a risk factor for cardiovascular diseases (CVD) and also the cause of microvascular complications such as chronic kidney disease (CKD) and diabetic retinopathy. Moreover, around 4% of mortality in the Thai population is caused by DM<sup>2</sup>. Hence, the prevention of DM in the Thai population is critical to decreasing further morbidity and mortality in the future.

Impaired fasting glucose (IFG) or intermediate hyperglycemia is the condition in which blood sugar level is higher than normal but does not reach the DM threshold. A person with IFG has a higher risk for DM about 13 times than a person with a normal blood glucose level<sup>3</sup>. Evidence from a previous umbrella review found that lifestyle modifications by diet control and exercise significantly decreased the risk of DM in persons with IFG<sup>4</sup>. Most diet interventions including low and very low-calorie diets are mainly focused on caloric restriction (CR) with the main objective of body weight reduction. Although the efficacy of these diet interventions in decreasing DM risk is well established, most patients could not sustain their healthy behaviors or maintain their healthy lifestyle permanently<sup>5</sup>. As a result, other methods of diet control such as time restricted eating (TRE) have been introduced as an alternative, which may help patients permanently maintain their behaviors.

TRE is one type of dietary approach that limits the daily eating window to commonly lower than 10 h/day and prolongs fasting time<sup>6-8</sup>. Previous literature found that increased fasting time has positive effects on many metabolic signal pathways, i.e., prolonged fasting stimulated autophagy and cell repair including mitochondria biogenesis resulting in better metabolic signal pathways in animals. In a human study, the TRE could significantly lower body weight but could not decline fasting plasma glucose (FPG), fasting insulin, and



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3 hemoglobin A1c (HbA1c) when compared to the normal eating style in patients with  
4 metabolic syndrome<sup>9</sup>. Likewise, a study in patients with obesity also found that TRE could  
5 reduce body weight, blood pressure, low-density lipoprotein cholesterol (LDL-C), and non-  
6 high-density lipoprotein (HDL-C) cholesterol but could not reduce FPG, fasting insulin and  
7 HbA1c<sup>10</sup>, while the study of Schroder et al found the significant reduction of body mass  
8 index, body fat percentage, and waist circumference in middle-aged women with obesity  
9 receiving TRE but FPG, HbA1c, fasting insulin, LDL-C, HDL-C, serum uric acid, and blood  
10 pressure were not significantly different between TRE and control groups<sup>11</sup>. Contrastingly,  
11 meta-analyses found beneficial of TRE in lowering not only body weight but also FPG, blood  
12 pressure, and triglyceride levels<sup>12 13</sup>. Until now, there are few small randomized controlled  
13 trials (RCT) that examined the effect of TRE in patients with prediabetes. A cross-over RCT  
14 assessing the effects of early or delayed TRE in 15 men at risk for type 2 DM found that both  
15 early and delayed TRE improved glycemic response, but only early TRE could lower mean  
16 FPG in men with a high risk of DM<sup>14</sup>. Another RCT assessed the effect of early TRE in 8  
17 men with prediabetes and found that early TRE could reduce insulin level, blood pressure,  
18 and food appetite, increase insulin sensitivity and beta-cell responsiveness but could not  
19 reduce FPG<sup>15</sup>. However, these RCTs focused on only men with very short follow-up times  
20 (i.e., 7 days and 5 weeks). Therefore, further RCT investigating the longer-term effect of  
21 TRE in both male and female patients is still needed.

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47 Although several studies found that TRE was well accepted by study  
48 participants<sup>16</sup> and well-tolerated even in older adults<sup>17</sup> but the long-term adherence to TRE is  
49 still questionable in the real life of some people. Such a gap occurs because the benefits of  
50 reducing cardiometabolic risks are intangible and will occur in the far future, whereas the  
51 cost of adherence to this diet control, namely being disciplined on diet time instead of eating  
52 freely whenever desired, happens immediately. Thus, some people who place much greater  
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3 weight on the present than on the future will be less likely to adhere to diet control. This is  
4 called present bias from behavioral economics perspective<sup>18 19</sup>. Behavioral economics is a  
5 field that integrates insights and methods from psychology and economics to understand  
6 human decision-making<sup>20-22</sup>.  
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12 A few behavioral economics tools have been used to deal with a present bias to  
13 promote adherence to diet control, i.e., financial incentives and text reminder<sup>23</sup>. Previous  
14 studies show that financial incentive was an effective tool to promote a healthy lifestyle such  
15 as smoking cessation, physical activity<sup>24</sup>, and weight loss<sup>25</sup>. Text reminders about an  
16 individual commitment, performance, or goal can immediately remind them of the priority.  
17 Such reminders have been proven effective in many domains, such as for the promotion of  
18 savings<sup>26</sup>, weight loss<sup>27 28</sup>, and medication adherence<sup>29</sup>. As a result, using behavioral  
19 economics might help increase compliance with lifestyle modification such as TRE or even  
20 maintaining behavioral change and finally improve the efficacy of lifestyle intervention in  
21 people with IFG who require a lifelong healthy lifestyle to prevention of DM conversion.  
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36 Nevertheless, there has been no study that assesses the efficacy of combined TRE  
37 with behavioral economic interventions in patients with IFG. Therefore, this RCT protocol is  
38 developed which aims to determine the efficacy of TRE plus behavioral economic  
39 interventions or TRE, when compare with usual care alone in patients with IFG with the  
40 following objectives. First, to investigate whether providing TRE plus behavioral economic  
41 interventions or TRE in addition to usual care for patients with IFG will provide additional  
42 benefit in reducing FPG when compared with usual care alone? Second, to compare HbA1c,  
43 body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting insulin,  
44 serum triglyceride, total cholesterol, LDL-C, HDL-C, and high sensitivity C-reactive protein  
45 (hs-CRP) between these three interventions.  
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## 58 **Methods and analysis**

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### ***Study design***

This study is a parallel RCT, which will be conducted at the outpatient clinic of the Department of Family Medicine (OFM), Faculty of Medicine, Ramathibodi Hospital, during October 2021 to October 2022. This research method complies with the Consolidated Standards of Reporting Trials (CONSORT) statement extension for multi-arm trials. The trial protocol has been registered at the Thai Clinical Trials Registry (TCTR20210520002).

### ***Patient recruitment***

Patients and staffs of Ramathibodi Hospital who are diagnosed with IFG will be recruited from October 2021 to October 2022, and they will be followed up until the 12<sup>th</sup> week after receiving interventions. Trained investigators and research assistants will approach and inform patients about the study protocol, randomization process, and details of intervention and comparisons. Participants will sign informed consent before participating.

### ***Participants***

Patients will be included in this study, if they meet all of the following criteria: 1) age 18 to 65 years, 2) having FPG of 100-125 mg/dl with HbA1c less than 6.5%, and 3) body mass index  $\geq 25$  kg/m<sup>2</sup>. The Patients will be ineligible if 1) they are currently on Ketogenic or vegetarian diets, 2) doing night shift work at least  $\geq 3$  hours during 10:00 PM-5:00 AM more than 1 day/week, 3) having more than 5 kg body weight changes during the 3 months before enrolment to the study, 4) taking medicines that must be taken with food in the early morning (i.e., before 8:00 AM) or late evening (i.e., after 5:00 PM), 5) pregnancy or breastfeeding, 6) having psychiatric disorders such as eating disorder or mood disorder but not including depression, 7) taking corticosteroid or anti-diabetic drugs, 8) having a history of bariatric surgery, and 9) having impaired nutrients absorption.

### ***Randomizations***

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3 Patients will be randomly assigned to any of three interventions including behavioural  
4 economic interventions plus TRE, TRE alone, and usual care with a ratio of 1:1:1. Block  
5 randomization with varying block sizes of 6 and 9 will be generated by a biostatistician who  
6 does not involve in the trial using STATA program version 16. Randomization will be  
7 stratified according to age groups (i.e., 18-59 years and 60-65 years). A random sequence list  
8 will be then concealed using sequential opaque sealed envelopes, which will be kept at the  
9 OFM. A research assistant will administer and open the sealed envelope once patients are  
10 eligible.  
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### 22 ***Blinding***

23 Participants and clinicians cannot be blinded due to the nature of interventions.  
24 However, data collectors and a biostatistician will be blinded about the intervention  
25 allocation. In addition, the outcomes of this study will be objectively measured that will not  
26 be affected by the unblinded intervention.  
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### 33 ***Study interventions***

34 Interested interventions are TRE and behavioural economic interventions. TRE is a  
35 limitation of the daily time of food intake to 9 hours with prolonged fasting in the night time  
36 of 15 hours. Participants will be requested to limit their periods of food intake from 8:00 AM  
37 to 5:00 PM without restriction on types of food and beverages. Participants will be asked for  
38 complying with TRE as much as they can.  
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47 Behavioural economic interventions will consist of financial incentives and text  
48 reminders. For financial incentive, the participant will receive monetary compensation of  
49 1000 Baths per month (23 £) if they self-report that they can adhere to TRE at least 5  
50 days/week for 4 weeks. TRE adherence will be evaluated every week by asking participants  
51 to record their first and last mealtime every day via logbook and financial incentives will be  
52 provided on 4<sup>th</sup>, 8<sup>th</sup>, and 12<sup>th</sup> week after randomisation. In addition, text reminders will be  
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3 sent to participants every 2 days to remind them about their commitment (Your goal is to  
4 stick to the TRE plan for at least 5 days a week.), performance (Last week you have  
5 successfully stuck to the TRE plan for 5 days.), and also about the TRE interval. The TRE  
6 alone group will be advised about the benefit of TRE without any additional support.  
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8 However, the participants in TRE alone group will be asked to record the adherence of TRE  
9 via logbook.  
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Comparator of the study is a usual care according to the current practice guideline of diabetes prevention. Patients will be educated about their conditions and disease progression, dietary control, and exercise to prevent disease progression. Participants in TRE and behavioural economic interventions and TRE alone groups also will receive the education about dietary control and exercise similar to patients in the usual care group. In addition, patients will be asked to record their first and last mealtime every day, which will be the same as patients in the other two interventions to evaluate protocol violation. All patients in 3 groups will received a leaflet that provides knowledge about healthy food and lifestyle modification to control their weight and reduce the risk of progression to DM.

### **Outcomes**

The primary outcome of this study is FPG which will be measured at the end of the study, i.e., 3 months after randomisation. Fasting plasma glucose will be measured by hexokinase glucose-6 phosphate dehydrogenase.

Secondary outcomes are HbA1c, body weight, SBP, DBP, fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and hs-CRP. HbA1c will be measured by turbid metric inhibition immunoassay certified by the National Glycohemoglobin Standardization Program (NGSP). Body weight and blood pressure measurement will be taken by trained research assistants. Body weight will be measured without shoes to the nearest 100 g. Blood pressure will measured after the resting for at least 15 minutes with an

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3 automatic blood pressure monitoring. Fasting insulin, serum triglyceride, total cholesterol,  
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5 LDL-C, HDL-C, and hs-CRP will be measured by chemiluminescent microparticle  
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7 immunoassay, glycerol phosphate oxidase, enzymatic method, liquid selective detergent,  
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9 accelerator selective detergent, and immunonephelometry, respectively.  
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12 All primary and secondary outcomes will be measured at the baseline, 1, 2, and 3  
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14 months after randomization.  
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### 16 *Adverse events*

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18 Adverse events such as syncope, dizziness, and light headiness will be measured  
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20 during all study periods.  
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### 23 *Co-variables*

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25 Other covariables will be collected as follows.  
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- 28 1. Demographic data including age, sex, educational level, and marital status
- 29 2. Underlying diseases such as hypertension, dyslipidaemia, fatty liver  
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31 disease, and history of gestational diabetes mellitus
- 32 3. Health risk behaviours including smoking and alcohol intake
- 33 4. Family history of DM in the first degree relatives
- 34 5. Sleep factors including sleep duration, sleep quality measured by the Thai  
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36 version of the Pittsburgh Sleep Quality Index<sup>30</sup>, and morningness and  
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38 eveningness preference using the validated Thai version of the Composite  
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40 Scale of Morningness (CSM)<sup>31</sup>
- 41 6. Physical activity level measured by Global Physical Activity  
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43 Questionnaire (GPAQ)<sup>32</sup>
- 44 7. Details of food and caloric intakes assessed by 24-hour food recall and  
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46 food frequency questionnaires (FFQs)
- 47 8. Time and risk preference assessed by multiple price list method<sup>33-38</sup>
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### ***Study protocol and data collection***

Schedule matrix consisting of data collections and time at measurements are presented in Table 1. At the first visit, trained investigator and research assistants will recruit the patient by screening FPG and other inclusion criteria (i.e., age and BMI). If the patient meets all the inclusion criteria, the research assistants will explain about the study protocol, process of data collection, and detail of TRE, behavioural economic interventions, and comparator. The patient will be asked to sign the informed consent if they are willing to participate the study.

At one week after enrolment (2<sup>nd</sup> visit), participants will be interviewed by research assistants about demographic data, underlying diseases, health risk behaviours, 24-hour food recall, sleep factors, physical activity level, and time and risk preference questionnaire. Physical examination including blood pressure, body weight, and height will be measured by trained research assistants. Laboratory measurement (i.e., FPG, HbA1c, serum triglyceride, total cholesterol, LDL-C, HDL-C, fasting insulin, and hs-CRP) will be performed after fasting at least 8 hours or longer. After that participant will be randomly assigned to any of 3 groups as behavioural economic intervention plus TRE, TRE alone, and usual care.

Physical activity level, sleep factors, 24-hour food recall, body weight, SBP, DBP, and laboratory measurement will be obtained at 3<sup>rd</sup> visit (4<sup>th</sup> weeks after randomization), 4<sup>th</sup> visit (8<sup>th</sup> weeks after randomization), and 5<sup>th</sup> visit (12<sup>th</sup> weeks after randomization or the end of the study). 24-hour food recall will be collected using food diary for 7 days at each visit. INMUCAL-nutrients version 4.0 (<https://inmu2.mahidol.ac.th/inmucal/index.php>) will be used to calculate the dietary data to nutrient intakes. This program was developed by the Institute of Nutrition, Mahidol University, Thailand.

### ***Data management***

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3 All data will be collected and filled in hard case record forms (CRF). All CRFs will  
4 be checked by researchers for completeness and correction before data entry. Hard CRFs will  
5 be independently computerised by two research assistants using Epidata version 3.1 software.  
6  
7 Data will be cleaned and checked every month by investigators (US and TA). Any unclear or  
8 missing information will be cross-checked against the source documents of CRFs and  
9  
10 medical records if required. Hospital numbers will be encrypted and kept confidentiality;  
11  
12 unique identification number (ID) will be assigned instead to each patient. All data will be  
13  
14 backed up using Google drive to prevent data loss.  
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### 21 ***Data monitoring***

22  
23 A formal data and safety monitoring board (DSMB) is not required because of no  
24 expected major adverse event from study's interventions. If adverse events are occurred, these  
25 will be managed by the trial committee, including all authors of this protocol. Recruitment and  
26 retention rates, and any protocol violations will be monitored by the trial committee via regular  
27 meeting every month.  
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### 35 ***Sample size calculation***

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37 Sample size is calculated based on a superiority trial using one way analysis of  
38 variance method in STATA version 17.0. Baseline mean and standard deviation (SD) of FPG  
39 in patients of prediabetes cohort conducted in the OFM was 105 and 9 mg/dl. We expected  
40 that receiving behavioural economic interventions plus TRE and TRE alone should be able to  
41 decrease FPG around 7% and 5% relative to the control, i.e., the FBGs were about 98 and  
42 100 mg/dl, respectively. Type I error, power, and follow up are set at 0.05, 0.8, and 20%; a  
43 total of 114 participants with 38 per group will be required to detect these differences.  
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### 53 ***Statistical analysis***

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55 Baseline characteristics and outcomes among 3 groups will be described using mean  
56 (SD) or median (range) where appropriate for continuous data, and frequency (percentage)  
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3 for categorical data. Means of primary and secondary outcomes will be compared among  
4  
5 three groups using a mixed-effect linear regression model by regress outcome on intervention  
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7 and time considering patients as a random effect (i.e., repeated measured at 4, 8, and 12  
8  
9 weeks) and the intervention arms (TRE with behavioral economic interventions and TRE  
10  
11 alone versus usual care) as a fixed-effect. Marginal means and differences between any pair  
12  
13 of the three interventions will be then estimated accordingly. Sensitivity analysis will be  
14  
15 performed to check the robustness of the primary analyses. Independent T-test will be applied  
16  
17 to compare means of primary and secondary outcomes at the end of the study between TRE  
18  
19 plus behavioural economic interventions and usual care groups and to compare mean of  
20  
21 primary and secondary outcomes between TRE and usual care groups. Last observation  
22  
23 carried forward (LOCF) will be applied to impute the missing outcome data for patients who  
24  
25 are loss to follow up.  
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31 Protocol violation will be dealt using an intention to treat analysis (ITT) and per-  
32  
33 protocol analysis (PPA). For the PPA, patients in the TRE plus behavioral economic  
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35 interventions and TRE alone who do not comply with TRE (i.e., comply < 5 days per week)  
36  
37 throughout the study or patients in the usual care group who take TRE 5 days of more per  
38  
39 week will be excluded from analysis. Multivariate regression analysis will be applied, if there  
40  
41 is the difference in baseline characteristics between 3 groups.  
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44  
45 All analyses will be performed using STATA 17.0. P value of less than 0.05 will be  
46  
47 considered as a statistical significance.  
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### 49 **Ethics and dissemination**

50  
51 The study protocol is approved by the Ethics Committee of Ramathibodi Hospital,  
52  
53 Mahidol University, (MURA 2021/389) and will be conducted in agreement with the Helsinki  
54  
55 declaration. All participants will sign informed consent at the baseline of the study (see  
56  
57 Supplementary Appendix). Protocol amendments will be reported to the institutional ethics  
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3 committee. Identification numbers will be used instead of hospital number to protect the  
4 confidentiality of study's participants. All data will be stored in database with password  
5 protection and can be accessed by only authorized staff.  
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10 Results of this study will be presented at national or international conferences and will  
11 be published in peer review journal. We plan to disseminate the results to participants,  
12 endocrinologists, and primary care physicians.  
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### 16 **Patient and Public Involvement**

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19 There was no patient or public involvement in the study.  
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### 21 **Discussion**

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24 Patients with IFG have a significant increased risk of DM. Diet interventions focused  
25 mainly on caloric restriction has been proved to decrease DM risk in this population. TRE is  
26 one type of diet intervention that has positive effects on many metabolic signal pathways  
27 from animal studies but evidence in human is limited especially in patients with IFG.  
28  
29 Therefore, this RCT is the first study that evaluate the effect of TRE on blood sugar levels  
30 and other cardiometabolic risk factors in patients with IFG. In addition, this is the first study  
31 that assesses the impact of behavioural economic interventions such as financial incentive  
32 and text reminder on adherence to TRE intervention.  
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42 Our study design has some critical issues. First, our interventions cannot be blinded;  
43 hence, the results may be affected by observer and information bias. However, most of our  
44 outcomes are laboratory values that are objectively measured and are blinded from the  
45 outcome assessors, thus measurement error or ascertainment bias should be reduced. Second,  
46 although our study has longer term follow up than previous studies, 3-month assessment is  
47 still conserved as a short-term follow-up. Therefore, only surrogate outcomes as FPG,  
48 HbA1c, body weight, and other laboratory tests will be assessed; either a long-term effect of  
49 TRE on cardiometabolic risk factors or permanent change of participant's behaviour cannot  
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3 be evaluated. Third, adherence to TRE will be measured through self-reported logbook which  
4 can be upwardly biased. However, concerning study outcomes, we consider only biological  
5 measures which will be objectively measured, e.g., FPG, HbA1c, body weight, etc. Fourth,  
6 there may be contamination of TRE in patients randomized to usual care group because TRE  
7 has been promoted in some social media in Thailand. Therefore, patients in usual care group  
8 can adopt TRE by themselves. In contrast, patients randomized to the TRE group may not  
9 comply to the TRE protocol due to intolerance to the long fasting period and will drop-out  
10 from the study. These drawbacks may dilute the effect of TRE in our study. However, we  
11 hope that these contaminations should be minimized because we will carefully assess patients  
12 who may have already performed TRE before the beginning of this study; but once occur,  
13 this protocol violation will be dealt with ITT/PPA.  
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28 In conclusion, we will conduct an opened labeled randomized controlled trial to  
29 evaluate the efficacy of behavioral economic interventions plus TRE, TRE alone, and usual  
30 care in improving FPG, HbA1c, and other cardiometabolic risk factors in patients with  
31 prediabetes. The findings from this study will be applied for the recommendation of lifestyle  
32 modification used for diabetes prevention in patients with prediabetes. Findings about the  
33 efficacy of behavioral economic intervention will inform policy makers about the novel method  
34 to help people change and maintain their healthy behaviour.  
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44 **Authors' contributions:** US and TA are the principal investigators. US, TA, SB, SP, AC, SR,  
45 and AT designed the study. US and TA drafted the manuscript. US, TA, SB, SP, AC, SR, and  
46 AT critically revised the study protocol and the manuscript. The entire project will be  
47 supervised by TA, SR, and AT.  
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54 grant number 186/2564. The funder has no role in this study.  
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58 **Competing interest statement:** none **References**  
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**Table 1.** Schedule matrix including activities and time at measurements/data collection

Activity	Time point				
	Screening visit	Visit 1 (baseline)	Visit 2 (4 week)	Visit 3 (8 week)	Visit 4 (12 week)
<b><i>Enrolment</i></b>					
- Eligibility screen including assessment of age, FPG, BMI, and HbA1c	√				
- Informed consent		√			
- Allocation		√			
<b><i>Intervention</i></b>					
- TRE with economic behavioural intervention		√	√	√	√
- TRE		√	√	√	√
- Usual care		√	√	√	√
<b><i>Assessment</i></b>					
- Demographic data		√			
- Underlying diseases		√			
- Health risk behaviour		√			
- Family history of DM		√			
- Physical activity		√	√	√	√
- Sleep factors		√	√	√	√
- 24-hour food recall		√	√	√	√

- Time and risk preference		√			√
<i>Primary outcomes</i>					
- FPG		√	√	√	√
- HbA1c		√	√	√	√
<i>Secondary outcomes</i>					
- Body weight		√	√	√	√
- Blood pressure		√	√	√	√
- Fasting insulin		√	√	√	√
- Serum triglyceride		√	√	√	√
- Serum cholesterol		√	√	√	√
- LDL-cholesterol		√	√	√	√
- HDL-cholesterol		√	√	√	√
- hs-CRP		√	√	√	√

## Patient/Participant Information Sheet

**Project title:** Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

**Researcher's name:** Dr. Unyaporn Suthutvoravut

**Research location:** Ramathibodi Hospital Mahidol University

**Who and how to contact when there is an emergency or disorder associated with research:**

Dr. Unyaporn Suthutvoravut                      Tel. 0869041556

Dr. Thunyarat Anothaisintawee                Tel. 0813725424

**Sponsor for this research:** National Research Council of Thailand

### Project Background

Diabetes is a major health problem in Thailand. Diabetes is a major risk factor for cardiovascular and cerebrovascular disease. Therefore, the prevention of diabetes in the Thai population is important in reducing the mortality and disability of the Thai population in the future.

Prediabetes is a condition in which the blood sugar level is higher than normal but does not reach the diagnostic criteria for diabetes. People with pre-diabetes comparing to people with normal sugar levels are at greater risk of developing diabetes. Behavior modification through diet and exercise can reduce the risk of diabetes in people with pre-diabetes. Most dietary intervention will focus on limiting the amount of energy you get from your diet each day. Other dietary approaches other than energy restriction, such as the Intermittent time restricted eating (TRE) are now being developed to help patients make permanent behavioral changes. It is an eating style with short eating periods. and increase the duration of fasting each day to increase with or without limiting the amount of energy received from food

Previous literature shows that there have been studies on the effect of diet restriction on eating periods. It was found that diet control by having an 8-hour eating period and 16-hour fasting per day can significantly reduce body weight in people with abdominal obesity.

### Objective

To study the efficacy of a time restricted-eating together with the use of behavioral economic tools to reduce blood sugar levels in people with pre-diabetes compared to time restricted-eating alone and usual care

### Details to be treated with research participants

After received information about the project details, the participants sign the documents, consented to participate in this research. One week later, research assistants will conduct interviews to collect general information, history of underlying disease, risky behavior, family history of diabetes, physical activity level, diet history together with physical examination and blood test would be done to check the levels of sugar, fat and hormone. Participants will be required to fast 8-10 hours prior to the blood draw, after which they will randomly be assigned to a restricted diet, together with the use of socio-economic tool or those who received a restricted diet only for a period of time or a group that eats normally.

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A time-restricted diet is a way of limiting the amount of time you eat during the day. In this study, participants will have their first meal at 8:00 AM and the last meal no later than 5:00 PM, without eating any food, snacks, fruit and beverages except water after 17:00 until 8:00 the next day. The tool for behavioral economics is to create incentives to encourage more behavior change. The behavioral economics tool of the study was to award 1,000 baht to research participants who can maintain a restricted diet of greater than or equal to five days a week for one month in a row. Prize money will be given every month for 3 months until graduation. Participants were also given messages to encourage them to adopt a time restricted diet. The researcher will send a message every 3 days via the Line application.

After participants participated in the study at 4 weeks, 8 weeks, and 12 weeks. Blood samples will be collected. Participants will be required to fast 8-10 hours before the blood draw and interview about their eating habits, physical activity level together with physical examination by research assistant. There is a compensation for the patient's time during the follow-up visit, 500 baht per time.

#### **Benefits to the research participants**

Participants will gain knowledge about diet to prevent future diabetes risk.

#### **Side effects for the participants**

There may be symptoms of low blood sugar, but the likelihood of occurrence is low. Because the measures given are only recommendations for time restricted diet only, not compulsory. The patient may or may not follow the instructions. Risks associated with blood test may include pain, bleeding.

#### **Confidentiality**

The data will be collected with confidentiality. No name or number of hospital record will be collected. The data will be presented as a whole and no individual identification. Only researchers will have access to information. This study will inform patients that they are in research and able to decide whether to join or not. Patients can withdraw from research at any time and has no effect on the treatment of patients in any way.

If you have questions or concerns about participating in this research project. You can contact the chairman of the Human Research Ethics Board at Faculty Research Office, Research and Welfare Building, Faculty of Medicine Ramathibodi Hospital.  
Tel. 02-2011544

**Informed Consent Form**

**Project title:** Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Researcher's name, Dr. Unyaporn Suthutvoravut

Name of research participant.....

Age.....medical record number.....

**Research Participant Consent**

I, Mr./Mrs./Ms..... have known the details of the research project as well as the benefits and the risks that will arise to me from the researcher clearly and consents to be involved in the above research project. And I know that if there are any problems or questions I could ask the researchers. Also, I could quit this research project at any time, without affecting the treatment that I deserve. In addition, the researchers will keep the specific information about me confidential and will only disclose it in the form of a summary of the research. Disclosure of information about me to relevant agencies could only be done in cases of necessity for academic reasons.

Signed.....

(Research participant)

.....

(witness)

.....

(witness)

Date .....

**Description of the doctor or researcher**

I have explained the details of the project. as well as the benefits of research and the potential risks were clearly known to the participants without any hidden objection.

Signed.....

(Doctor or Researcher)

date.....



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__ 1 __
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__ 3,8 __
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	__ 3 __
Funding	4	Sources and types of financial, material, and other support	__ 16 __
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__ 1, 16 __
	5b	Name and contact information for the trial sponsor	__ 16 __
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__ 16 __
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__ 16 __

## 1 Introduction

2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	___ 5-7 ___
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	___ 5-7 ___
7				
8	Objectives	7	Specific objectives or hypotheses	___ 7 ___
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___ 8 ___
12				
13				

## 14 Methods: Participants, interventions, and outcomes

15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	___ 8 ___
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	___ 8 ___
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	___ 9-10 ___
23			administered	
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	___ NA ___
25			change in response to harms, participant request, or improving/worsening disease)	
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	___ 10,13 ___
27			(eg, drug tablet return, laboratory tests)	
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___ 10 ___
29				
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	___ 10-11 ___
31			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
32			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
33			efficacy and harm outcomes is strongly recommended	
34	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	___ 11-12 ___
35			participants. A schematic diagram is highly recommended (see Figure)	
36				
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____ 13 _____
2				
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____ 8-9 _____
5				
6				
7	<b>Methods: Assignment of interventions (for controlled trials)</b>			
8	Allocation:			
9				
10	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____ 8-9 _____
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16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____ 9 _____
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____ 9 _____
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____ 9 _____
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____ 9 _____
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31	<b>Methods: Data collection, management, and analysis</b>			
32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____ 11-13 _____
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38		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____ - _____
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1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	___ 12 ___
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5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___ 13 ___
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___ 13 ___
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___ 13 ___
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14	<b>Methods: Monitoring</b>			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___ 12-13 ___
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___ NA ___
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___ 12-13 ___
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___ 13 ___
29				
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32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___ 14 ___
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36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___ 14 ___
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 8 _____
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ NA _____
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7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, stored, and maintained in order to protect confidentiality before, during, and after the trial	_____ 14 _____
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 16 _____
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13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____ 14 _____
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16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____ NA _____
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____ 14 _____
21				
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ NA _____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ NA _____
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29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Appendix
32				
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34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____ NA _____
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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by/4.0/)" license.

# BMJ Open

## **Efficacy of time restricted eating and behavioural economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared with time restricted eating alone or usual care in patients with impaired fasting glucose: protocol for an open-label randomized controlled trial**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-058954.R5
Article Type:	Protocol
Date Submitted by the Author:	25-Aug-2022
Complete List of Authors:	Suthutvoravut, Unyaporn; Mahidol University, Department of Family Medicine Anothaisintawee, Thunyarat; Mahidol University, Department of Family Medicine; Mahidol University, Department of Clinical Epidemiology and Biostatistics Boonmanunt, Suparee; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Clinical Epidemiology and Biostatistics Pramyothin, Sarunporn; Mahidol University Chaithanasarn, Arthit; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Family Medicine Reutrakul, Sirimon; University of Illinois, Department of Medicine Thakkestian, Ammarin ; Mahidol University Faculty of Medicine Ramathibodi Hospital
<b>Primary Subject Heading</b>:	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, NUTRITION & DIETETICS

SCHOLARONE™  
Manuscripts

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3 **Efficacy of time restricted eating and behavioural economic intervention in reducing**  
4 **fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared with time**  
5 **restricted eating alone or usual care in patients with impaired fasting glucose: protocol**  
6 **for an open-label randomized controlled trial**  
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55 **Abstract**

56  
57 **Introduction:** Impaired fasting glucose (IFG) is a significant risk factor for diabetes mellitus  
58 (DM). Time restricted eating (TRE) is one type of diet showing positive effects on metabolic  
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3 signal pathways. However, effects of TRE on cardiometabolic risk factors in humans are  
4 limited. Additionally, compliance with TRE remains problematic despite having intention to  
5 follow the diet control. Therefore, this study aims to investigate the efficacy of TRE with  
6 behavioural economic interventions or TRE alone relative to usual care, in reducing fasting  
7 plasma glucose (FPG), haemoglobin A1c (HbA1c), and other cardiometabolic risk factors in  
8 patients with IFG.  
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12 **Methods and analysis:** This parallel-group, open-label randomized controlled trial will be  
13 conducted at the outpatient clinic of the Department of Family Medicine, Faculty of  
14 Medicine, Ramathibodi Hospital, Bangkok, Thailand. Patients aged 18-65 years with IFG  
15 defined as FPG 100-125 mg/dl and body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup> will be recruited  
16 between October 2021 and October 2022. Patients will be randomly allocated to 3 groups  
17 (1:1:1 ratio) as 1) TRE with behavioural economic interventions including financial  
18 incentives and text reminders, 2) TRE alone, or 3) usual care. The number of participants will  
19 be 38 per group (a total of 114). The duration of the intervention will be 12 weeks. Primary  
20 outcome is FPG levels measured at 12 weeks after randomization. Secondary outcomes are  
21 HbA1c, body weight, systolic and diastolic blood pressure, fasting insulin, serum triglyceride,  
22 total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol,  
23 and high sensitivity C-reactive protein. P-value<0.05 of 2-sided test will be considered as  
24 statistical significance.  
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47 **Ethics and dissemination:** The study protocol has been approved by the Ethics Committee  
48 of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University (MURA2021/389).  
49 All patients will be informed about the details of the study and sign written informed consent  
50 before enrolment in the study. Results from this study will be published in peer-reviewed  
51 journal.  
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3 **Trial registration number:** Thai Clinical Trial Registry, TCTR20210520002 (18 January  
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5 2022, version 2).  
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8 **Strengths and limitations of this study**  
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- 11 • The study uses a randomized controlled trial design to assesses the efficacy of time  
12 restricted eating on blood sugar levels and other cardiometabolic risk factors in  
13 patients with impaired fasting glucose.  
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  - 15 • The study has longer-term follow-up than previous studies.  
16
  - 17 • The interventions cannot be blinded; hence, the results may be affected by observer  
18 and information bias.  
19
  - 20 • Contamination of time restricted eating in the usual care group might occur due to the  
21 promotion of time restricted eating on some social media in Thailand.  
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## Introduction

Diabetes mellitus (DM) is one of the important health problems in Thailand. The results from the National health examination survey reported that the prevalence of DM in the Thai population has increased from 7.7% in 2004 to 9.9% in 2014<sup>1</sup>. Diabetes is a risk factor for cardiovascular diseases (CVD) and also the cause of microvascular complications such as chronic kidney disease (CKD) and diabetic retinopathy. Moreover, around 4% of mortality in the Thai population is caused by DM<sup>2</sup>. Hence, the prevention of DM in the Thai population is critical to decreasing further morbidity and mortality in the future.

Impaired fasting glucose (IFG) or intermediate hyperglycaemia is the condition in which blood sugar level is higher than normal but does not reach the DM threshold. A person with IFG has a higher risk for DM about 13 times than a person with a normal blood glucose level<sup>3</sup>. Evidence from a previous umbrella review found that lifestyle modifications by diet control and exercise significantly decreased the risk of DM in persons with IFG<sup>4</sup>. Most diet interventions including low and very low-calorie diets are mainly focused on caloric restriction (CR) with the main objective of body weight reduction. Although the efficacy of these diet interventions in decreasing DM risk is well established, most patients could not sustain their healthy behaviours or maintain their healthy lifestyle permanently<sup>5</sup>. As a result, other methods of diet control such as time restricted eating (TRE) have been introduced as an alternative, which may help patients permanently maintain their behaviours.

TRE is one type of dietary approach that limits the daily eating window to commonly lower than 10 h/day and prolongs fasting time<sup>6-8</sup>. Previous literature found that increased fasting time has positive effects on many metabolic signal pathways, i.e., prolonged fasting stimulated autophagy and cell repair including mitochondria biogenesis resulting in better metabolic signal pathways in animals. In a human study, the TRE could significantly lower body weight but could not decline fasting plasma glucose (FPG), fasting insulin, and

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3 haemoglobin A1c (HbA1c) when compared to the normal eating style in patients with  
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5 metabolic syndrome<sup>9</sup>. Likewise, a study in patients with obesity also found that TRE could  
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7 reduce body weight, blood pressure, low-density lipoprotein cholesterol (LDL-C), and non-  
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9 high-density lipoprotein (HDL-C) cholesterol but could not reduce FPG, fasting insulin and  
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11 HbA1c<sup>10</sup>, while the study of Schroder et al found the significant reduction of body mass  
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13 index, body fat percentage, and waist circumference in middle-aged women with obesity  
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15 receiving TRE but FPG, HbA1c, fasting insulin, LDL-C, HDL-C, serum uric acid, and blood  
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17 pressure were not significantly different between TRE and control groups<sup>11</sup>. Contrastingly,  
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19 meta-analyses found beneficial of TRE in lowering not only body weight but also FPG, blood  
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21 pressure, and triglyceride levels<sup>12 13</sup>. Until now, there are few small randomized controlled  
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23 trials (RCT) that examined the effect of TRE in patients with prediabetes. A cross-over RCT  
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25 assessing the effects of early or delayed TRE in 15 men at risk for type 2 DM found that both  
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27 early and delayed TRE improved glycaemic response, but only early TRE could lower mean  
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29 FPG in men with a high risk of DM<sup>14</sup>. Another RCT assessed the effect of early TRE in 8  
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31 men with prediabetes and found that early TRE could reduce insulin level, blood pressure,  
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33 and food appetite, increase insulin sensitivity and beta-cell responsiveness but could not  
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35 reduce FPG<sup>15</sup>. However, these RCTs focused on only men with very short follow-up times  
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37 (i.e., 7 days and 5 weeks). Therefore, further RCT investigating the longer-term effect of  
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39 TRE in both male and female patients is still needed.

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42 Although several studies found that TRE was well accepted by study  
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44 participants<sup>16</sup> and well-tolerated even in older adults<sup>17</sup> but the long-term adherence to TRE is  
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46 still questionable in the real life of some people. Such a gap occurs because the benefits of  
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48 reducing cardiometabolic risks are intangible and will occur in the far future, whereas the  
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50 cost of adherence to this diet control, namely being disciplined on diet time instead of eating  
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52 freely whenever desired, happens immediately. Thus, some people who place much greater  
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3 weight on the present than on the future will be less likely to adhere to diet control. This is  
4 called present bias from behavioural economics perspective<sup>18 19</sup>. Behavioural economics is a  
5 field that integrates insights and methods from psychology and economics to understand  
6 human decision-making<sup>20-22</sup>.  
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12 A few behavioural economics tools have been used to deal with a present bias to  
13 promote adherence to diet control, i.e., financial incentives and text reminder<sup>23</sup>. Previous  
14 studies show that financial incentive was an effective tool to promote a healthy lifestyle such  
15 as smoking cessation, physical activity<sup>24</sup>, and weight loss<sup>25</sup>. Text reminders about an  
16 individual commitment, performance, or goal can immediately remind them of the priority.  
17 Such reminders have been proven effective in many domains, such as for the promotion of  
18 savings<sup>26</sup>, weight loss<sup>27 28</sup>, and medication adherence<sup>29</sup>. As a result, using behavioural  
19 economics might help increase compliance with lifestyle modification such as TRE or even  
20 maintaining behavioural change and finally improve the efficacy of lifestyle intervention in  
21 people with IFG who require a lifelong healthy lifestyle to prevention of DM conversion.  
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36 Nevertheless, there has been no study that assesses the efficacy of combined TRE  
37 with behavioural economic interventions in patients with IFG. Therefore, this RCT protocol  
38 is developed which aims to determine the efficacy of TRE plus behavioural economic  
39 interventions or TRE alone, when compare with usual care in patients with IFG with the  
40 following objectives. First, to investigate whether providing TRE plus behavioural economic  
41 interventions or TRE alone for patients with IFG will provide additional benefit in reducing  
42 FPG when compared with usual care? Second, to compare HbA1c, body weight, systolic  
43 blood pressure (SBP), diastolic blood pressure (DBP), fasting insulin, serum triglyceride,  
44 total cholesterol, LDL-C, HDL-C, and high sensitivity C-reactive protein (hs-CRP) between  
45 TRE plus behavioural economic interventions or TRE alone with usual care.  
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## Methods and analysis

### *Study design*

This study is a parallel RCT, which will be conducted at the outpatient clinic of the Department of Family Medicine (OFM), Faculty of Medicine, Ramathibodi Hospital, during October 2021 to October 2022. This research method complies with the Consolidated Standards of Reporting Trials (CONSORT) statement extension for multi-arm trials. The trial protocol has been registered at the Thai Clinical Trials Registry (TCTR20210520002).

### *Participants*

Patients and staffs of Ramathibodi Hospital who are diagnosed with IFG will be recruited from October 2021 to October 2022, and they will be followed up until the 12<sup>th</sup> week after receiving interventions. Trained investigators and research assistants will approach and inform patients about the study protocol, randomization process, and details of intervention and comparisons. Participants will sign informed consent before participating.

Patients will be included in this study, if they meet all of the following criteria: 1) age 18 to 65 years, 2) having FPG of 100-125 mg/dl with HbA1c less than 6.5%, and 3) body mass index  $\geq 25$  kg/m<sup>2</sup>. The Patients will be ineligible if 1) they are currently on Ketogenic or vegetarian diets, 2) doing night shift work at least  $\geq 3$  hours during 10:00 PM-5:00 AM more than 1 day/week, 3) having more than 5 kg body weight changes during the 3 months before enrolment to the study, 4) taking medicines that must be taken with food in the early morning (i.e., before 8:00 AM) or late evening (i.e., after 5:00 PM), 5) pregnancy or breastfeeding, 6) having psychiatric disorders such as eating disorder or mood disorder but not including depression, 7) taking corticosteroid or anti-diabetic drugs, 8) having a history of bariatric surgery, and 9) having impaired nutrients absorption.

### *Randomization*

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3 Patients will be randomly assigned to any of three interventions including behavioural  
4 economic interventions plus TRE, TRE alone, and usual care with a ratio of 1:1:1. Block  
5 randomization with varying block sizes of 6 and 9 will be generated by a biostatistician who  
6 does not involve in the trial using STATA program version 16. Randomization will be  
7 stratified according to age groups (i.e., 18-59 years and 60-65 years). A random sequence list  
8 will be then concealed using sequential opaque sealed envelopes, which will be kept at the  
9 OFM. A research assistant will administer and open the sealed envelope once patients are  
10 eligible.  
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### 22 ***Blinding***

23  
24 The study is open label as participants and clinicians cannot be blinded due to the nature of  
25 interventions. However, data collectors and a biostatistician will be blinded about the  
26 intervention allocation. In addition, the outcomes of this study will be objectively measured  
27 that will not be affected by the unblinded intervention.  
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### 33 ***Study interventions***

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35 Interested interventions are TRE and behavioural economic interventions. TRE is a limitation  
36 of the daily time of food intake to 9 hours with prolonged fasting in the night time of 15  
37 hours. Participants will be requested to limit their periods of food intake from 8:00 AM to  
38 5:00 PM without restriction on types of food and beverages. Participants will be asked for  
39 complying with TRE as much as they can.  
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47 Behavioural economic interventions will consist of financial incentives and text  
48 reminders. For financial incentive, the participant will receive monetary compensation of  
49 1000 Baths per month (23 £) if they self-report that they can adhere to TRE at least 5  
50 days/week for 4 weeks. TRE adherence will be evaluated every week by asking participants  
51 to record their first and last mealtime every day via logbook and financial incentives will be  
52 provided on 4<sup>th</sup>, 8<sup>th</sup>, and 12<sup>th</sup> week after randomisation. In addition, text reminders will be  
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3 sent to participants every 2 days to remind them about their commitment (Your goal is to  
4 stick to the TRE plan for at least 5 days a week.), performance (Last week you have  
5 successfully stuck to the TRE plan for 5 days.), and also about the TRE interval. The TRE  
6 alone group will be advised about the benefit of TRE without any additional support.  
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8 However, the participants in TRE alone group will be asked to record the adherence of TRE  
9 via logbook.  
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Comparator of the study is a usual care according to the current practice guideline of diabetes prevention. Patients will be educated about their conditions and disease progression, dietary control, and exercise to prevent disease progression. Participants in TRE and behavioural economic interventions and TRE alone groups also will receive the education about dietary control and exercise similar to patients in the usual care group. In addition, patients will be asked to record their first and last mealtime every day, which will be the same as patients in the other two interventions to evaluate protocol violation. All patients in 3 groups will received a leaflet that provides knowledge about healthy food and lifestyle modification to control their weight and reduce the risk of progression to DM.

### ***Outcomes***

The primary outcome of this study is FPG which will be measured at the end of the study, i.e., 3 months (12 weeks) after randomisation. Fasting plasma glucose will be measured by hexokinase glucose-6 phosphate dehydrogenase.

Secondary outcomes are HbA1c, body weight, SBP, DBP, fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and hs-CRP. HbA1c will be measured by turbid metric inhibition immunoassay certified by the National Glycohemoglobin Standardization Program (NGSP). Body weight and blood pressure measurement will be taken by trained research assistants. Body weight will be measured without shoes to the nearest 100 g. Blood pressure will measured after the resting for at least 15 minutes with an

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3 automatic blood pressure monitoring. Fasting insulin, serum triglyceride, total cholesterol,  
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5 LDL-C, HDL-C, and hs-CRP will be measured by chemiluminescent microparticle  
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7 immunoassay, glycerol phosphate oxidase, enzymatic method, liquid selective detergent,  
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9 accelerator selective detergent, and immunonephelometry, respectively.  
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12 All primary and secondary outcomes will be measured at the baseline, 1, 2, and 3  
13  
14 months after randomization.  
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### 16 *Adverse events*

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18 Adverse events such as syncope, dizziness, and light headiness will be measured during all  
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20 study periods.  
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### 23 *Covariables*

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25 Other covariables will be collected as follows.  
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- 28 1. Demographic data including age, sex, educational level, and marital status
  - 29 2. Underlying diseases such as hypertension, dyslipidaemia, fatty liver  
30 disease, and history of gestational diabetes mellitus
  - 31 3. Health risk behaviours including smoking and alcohol intake
  - 32 4. Family history of DM in the first degree relatives
  - 33 5. Sleep factors including sleep duration, sleep quality measured by the Thai  
34 version of the Pittsburgh Sleep Quality Index<sup>30</sup>, and morningness and  
35 eveningness preference using the validated Thai version of the Composite  
36 Scale of Morningness (CSM)<sup>31</sup>
  - 37 6. Physical activity level measured by Global Physical Activity  
38 Questionnaire (GPAQ)<sup>32</sup>
  - 39 7. Details of food and caloric intakes assessed by 24-hour food recall and  
40 food frequency questionnaires (FFQs)
  - 41 8. Time and risk preference assessed by multiple price list method<sup>33-38</sup>
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### ***Study protocol and data collection***

Schedule matrix consisting of data collections and time at measurements are presented in Table 1. At the first visit, trained investigator and research assistants will recruit the patient by screening FPG and other inclusion criteria (i.e., age and BMI). If the patient meets all the inclusion criteria, the research assistants will explain about the study protocol, process of data collection, and detail of TRE, behavioural economic interventions, and comparator. The patient will be asked to sign the informed consent if they are willing to participate the study.

**Table 1. Study assessment schedule**

Activity	Time point				
	Screening visit	Visit 1 (baseline)	Visit 2 (4 week)	Visit 3 (8 week)	Visit 4 (12 week)
<b><i>Enrolment</i></b>					
- Eligibility screen including assessment of age, FPG, BMI, and HbA1c	√				
- Informed consent		√			
- Allocation		√			
<b><i>Intervention</i></b>					
- TRE with economic behavioural intervention		√	√	√	√
- TRE		√	√	√	√
- Usual care		√	√	√	√
<b><i>Assessment</i></b>					

- Demographic data		√			
- Underlying diseases		√			
- Health risk behaviour		√			
- Family history of DM		√			
- Physical activity		√	√	√	√
- Sleep factors		√	√	√	√
- 24-hour food recall		√	√	√	√
- Time and risk preference		√			√
<i>Outcomes</i>					
- FPG		√	√	√	√
- HbA1c		√	√	√	√
- Body weight		√	√	√	√
- Blood pressure		√	√	√	√
- Fasting insulin		√	√	√	√
- Serum triglyceride		√	√	√	√
- Serum cholesterol		√	√	√	√
- LDL-cholesterol		√	√	√	√
- HDL-cholesterol		√	√	√	√
- hs-CRP		√	√	√	√

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2  
3 At one week after enrolment (2<sup>nd</sup> visit), participants will be interviewed by research  
4 assistants about demographic data, underlying diseases, health risk behaviours, 24-hour food  
5 recall, sleep factors, physical activity level, and time and risk preference questionnaire.  
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10 Physical examination including blood pressure, body weight, and height will be measured by  
11 trained research assistants. Laboratory measurement (i.e., FPG, HbA1c, serum triglyceride,  
12 total cholesterol, LDL-C, HDL-C, fasting insulin, and hs-CRP) will be performed after  
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Physical activity level, sleep factors, 24-hour food recall, body weight, SBP, DBP,  
and laboratory measurement will be obtained at 3<sup>rd</sup> visit (4<sup>th</sup> weeks after randomization), 4<sup>th</sup>  
visit (8<sup>th</sup> weeks after randomization), and 5<sup>th</sup> visit (12<sup>th</sup> weeks after randomization or the end  
of the study). 24-hour food recall will be collected using food diary for 7 days at each visit.  
INMUCAL-nutrients version 4.0 (<https://inmu2.mahidol.ac.th/inmucal/index.php>) will be  
used to calculate the dietary data to nutrient intakes. This program was developed by the  
Institute of Nutrition, Mahidol University, Thailand.

### ***Data management***

All data will be collected and filled in hard case record forms (CRF). All CRFs will be  
checked by researchers for completeness and correction before data entry. Hard CRFs will be  
independently computerised by two research assistants using Epidata version 3.1 software.  
Data will be cleaned and checked every month by investigators (US and TA). Any unclear or  
missing information will be cross-checked against the source documents of CRFs and  
medical records if required. Hospital numbers will be encrypted and kept confidentiality;  
unique identification number (ID) will be assigned instead to each patient. All data will be  
backed up using Google drive to prevent data loss.

### ***Data monitoring***



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3 A formal data and safety monitoring board (DSMB) is not required because of no expected  
4 major adverse event from study's interventions. If adverse events are occurred, these will be  
5 managed by the trial committee, including all authors of this protocol. Recruitment and  
6 retention rates, and any protocol violations will be monitored by the trial committee via regular  
7 meeting every month.  
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### 14 ***Sample size calculation***

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16 Sample size is calculated based on a superiority trial using one way analysis of variance  
17 method in STATA version 17.0. Baseline mean and standard deviation (SD) of FPG in  
18 patients of prediabetes cohort conducted in the OFM was 105 and 9 mg/dl. We expected that  
19 receiving behavioural economic interventions plus TRE and TRE alone should be able to  
20 decrease FPG around 7% and 5% relative to the control, i.e., the FBGs were about 98 and  
21 100 mg/dl, respectively. Type I error, power, and follow up are set at 0.05, 0.8, and 20%; a  
22 total of 114 participants with 38 per group will be required to detect these differences.  
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### 33 ***Statistical analysis***

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35 Baseline characteristics and outcomes among 3 groups will be described using mean (SD) or  
36 median (range) where appropriate for continuous data, and frequency (percentage) for  
37 categorical data. Means of primary and secondary outcomes will be compared among three  
38 groups using a mixed-effect linear regression model by regress outcome on intervention and  
39 time considering patients as a random effect (i.e., repeated measured at 4, 8, and 12 weeks)  
40 and the intervention arms (TRE with behavioural economic interventions and TRE alone  
41 versus usual care) as a fixed-effect. Marginal means and differences between any pair of the  
42 three interventions will be then estimated accordingly. Sensitivity analysis will be performed  
43 to check the robustness of the primary analyses. Independent T-test will be applied to  
44 compare means of primary and secondary outcomes at the end of the study between TRE plus  
45 behavioural economic interventions and usual care groups and to compare mean of primary  
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3 and secondary outcomes between TRE and usual care groups. Last observation carried  
4 forward (LOCF) will be applied to impute the missing outcome data for patients who are loss  
5 to follow up.  
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10 Protocol violation will be dealt using an intention to treat analysis (ITT) and per-  
11 protocol analysis (PPA). For the PPA, patients in the TRE plus behavioural economic  
12 interventions and TRE alone who do not comply with TRE (i.e., comply < 5 days per week)  
13 throughout the study or patients in the usual care group who take TRE 5 days of more per  
14 week will be excluded from analysis. Multivariate regression analysis will be applied, if there  
15 is the difference in baseline characteristics between 3 groups.  
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24 All analyses will be performed using STATA 17.0. P value less than 0.05 of 2-sided  
25 test will be considered as a statistical significance.  
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### 28 ***Patient and public involvement***

29  
30 None.  
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### 35 **Ethics and dissemination**

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37 The study protocol is approved by the Ethics Committee of Ramathibodi Hospital, Mahidol  
38 University, (MURA 2021/389) and will be conducted in agreement with the Helsinki  
39 declaration. All participants will sign informed consent at the baseline of the study (see  
40 Supplementary Appendix). Protocol amendments will be reported to the institutional ethics  
41 committee. Identification numbers will be used instead of hospital number to protect the  
42 confidentiality of study's participants. All data will be stored in database with password  
43 protection and can be accessed by only authorized staff.  
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54 Results of this study will be presented at national or international conferences and will  
55 be published in peer review journal. We plan to disseminate the results to participants,  
56 endocrinologists, and primary care physicians.  
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## Discussion

Patients with IFG have a significant increased risk of DM. Diet interventions focused mainly on caloric restriction has been proved to decrease DM risk in this population. TRE is one type of diet intervention that has positive effects on many metabolic signal pathways from animal studies but evidence in human is limited especially in patients with IFG. Therefore, this RCT is the first study that evaluate the effect of TRE on blood sugar levels and other cardiometabolic risk factors in patients with IFG. In addition, this is the first study that assesses the impact of behavioural economic interventions such as financial incentive and text reminder on adherence to TRE intervention.

Our study design has some critical issues. First, our interventions cannot be blinded; hence, the results may be affected by observer and information bias. However, most of our outcomes are laboratory values that are objectively measured and are blinded from the outcome assessors, thus measurement error or ascertainment bias should be reduced. Second, although our study has longer term follow up than previous studies, 3-month assessment is still conserved as a short-term follow-up. Therefore, only surrogate outcomes as FPG, HbA1c, body weight, and other laboratory tests will be assessed; either a long-term effect of TRE on cardiometabolic risk factors or permanent change of participant's behaviour cannot be evaluated. Third, adherence to TRE will be measured through self-reported logbook which can be upwardly biased. However, concerning study outcomes, we consider only biological measures which will be objectively measured, e.g., FPG, HbA1c, body weight, etc. Fourth, there may be contamination of TRE in patients randomized to usual care group because TRE has been promoted in some social media in Thailand. Therefore, patients in usual care group can adopt TRE by themselves. In contrast, patients randomized to the TRE group may not comply to the TRE protocol due to intolerance to the long fasting period and will drop-out

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3 from the study. These drawbacks may dilute the effect of TRE in our study. However, we  
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5 hope that these contaminations should be minimized because we will carefully assess patients  
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7 who may have already performed TRE before the beginning of this study; but once occur,  
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9 this protocol violation will be dealt with ITT/PPA.  
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12 In conclusion, we will conduct a randomized controlled trial to evaluate the efficacy of  
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14 behavioural economic interventions plus TRE, TRE alone, and usual care in improving FPG,  
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16 HbA1c, and other cardiometabolic risk factors in patients with prediabetes. The findings from  
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18 this study will be applied for the recommendation of lifestyle modification used for diabetes  
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20 prevention in patients with prediabetes. Findings about the efficacy of behavioural economic  
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22 intervention will inform policy makers about the novel method to help people change and  
23  
24 maintain their healthy behaviour.  
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33 **Contributors:** US and TA are the principal investigators. US, TA, SB, SP, AC, SR, and AT  
34  
35 designed the study. US and TA drafted the manuscript. US, TA, SB, SP, AC, SR, and AT  
36  
37 critically revised the study protocol and the manuscript. The entire project will be supervised  
38  
39 by TA, SR, and AT.  
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45  
46

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## Patient/Participant Information Sheet

**Project title:** Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

**Researcher's name:** Dr. Unyaporn Suthutvoravut

**Research location:** Ramathibodi Hospital Mahidol University

**Who and how to contact when there is an emergency or disorder associated with research:**

Dr. Unyaporn Suthutvoravut                      Tel. 0869041556

Dr. Thunyarat Anothaisintawee                Tel. 0813725424

**Sponsor for this research:** National Research Council of Thailand

### Project Background

Diabetes is a major health problem in Thailand. Diabetes is a major risk factor for cardiovascular and cerebrovascular disease. Therefore, the prevention of diabetes in the Thai population is important in reducing the mortality and disability of the Thai population in the future.

Prediabetes is a condition in which the blood sugar level is higher than normal but does not reach the diagnostic criteria for diabetes. People with pre-diabetes comparing to people with normal sugar levels are at greater risk of developing diabetes. Behavior modification through diet and exercise can reduce the risk of diabetes in people with pre-diabetes. Most dietary intervention will focus on limiting the amount of energy you get from your diet each day. Other dietary approaches other than energy restriction, such as the Intermittent time restricted eating (TRE) are now being developed to help patients make permanent behavioral changes. It is an eating style with short eating periods. and increase the duration of fasting each day to increase with or without limiting the amount of energy received from food

Previous literature shows that there have been studies on the effect of diet restriction on eating periods. It was found that diet control by having an 8-hour eating period and 16-hour fasting per day can significantly reduce body weight in people with abdominal obesity.

### Objective

To study the efficacy of a time restricted-eating together with the use of behavioral economic tools to reduce blood sugar levels in people with pre-diabetes compared to time restricted-eating alone and usual care

### Details to be treated with research participants

After received information about the project details, the participants sign the documents, consented to participate in this research. One week later, research assistants will conduct interviews to collect general information, history of underlying disease, risky behavior, family history of diabetes, physical activity level, diet history together with physical examination and blood test would be done to check the levels of sugar, fat and hormone. Participants will be required to fast 8-10 hours prior to the blood draw, after which they will randomly be assigned to a restricted diet, together with the use of socio-economic tool or those who received a restricted diet only for a period of time or a group that eats normally.

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A time-restricted diet is a way of limiting the amount of time you eat during the day. In this study, participants will have their first meal at 8:00 AM and the last meal no later than 5:00 PM, without eating any food, snacks, fruit and beverages except water after 17:00 until 8:00 the next day. The tool for behavioral economics is to create incentives to encourage more behavior change. The behavioral economics tool of the study was to award 1,000 baht to research participants who can maintain a restricted diet of greater than or equal to five days a week for one month in a row. Prize money will be given every month for 3 months until graduation. Participants were also given messages to encourage them to adopt a time restricted diet. The researcher will send a message every 3 days via the Line application.

After participants participated in the study at 4 weeks, 8 weeks, and 12 weeks. Blood samples will be collected. Participants will be required to fast 8-10 hours before the blood draw and interview about their eating habits, physical activity level together with physical examination by research assistant. There is a compensation for the patient's time during the follow-up visit, 500 baht per time.

#### **Benefits to the research participants**

Participants will gain knowledge about diet to prevent future diabetes risk.

#### **Side effects for the participants**

There may be symptoms of low blood sugar, but the likelihood of occurrence is low. Because the measures given are only recommendations for time restricted diet only, not compulsory. The patient may or may not follow the instructions. Risks associated with blood test may include pain, bleeding.

#### **Confidentiality**

The data will be collected with confidentiality. No name or number of hospital record will be collected. The data will be presented as a whole and no individual identification. Only researchers will have access to information. This study will inform patients that they are in research and able to decide whether to join or not. Patients can withdraw from research at any time and has no effect on the treatment of patients in any way.

<p>If you have questions or concerns about participating in this research project. You can contact the chairman of the Human Research Ethics Board at Faculty Research Office, Research and Welfare Building, Faculty of Medicine Ramathibodi Hospital. Tel. 02-2011544</p>
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### Informed Consent Form

**Project title:** Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Researcher's name, Dr. Unyaporn Suthutvoravut

Name of research participant.....

Age.....medical record number.....

#### Research Participant Consent

I, Mr./Mrs./Ms..... have known the details of the research project as well as the benefits and the risks that will arise to me from the researcher clearly and consents to be involved in the above research project. And I know that if there are any problems or questions I could ask the researchers. Also, I could quit this research project at any time, without affecting the treatment that I deserve. In addition, the researchers will keep the specific information about me confidential and will only disclose it in the form of a summary of the research. Disclosure of information about me to relevant agencies could only be done in cases of necessity for academic reasons.

Signed.....

(Research participant)

.....

(witness)

.....

(witness)

Date .....

#### Description of the doctor or researcher

I have explained the details of the project. as well as the benefits of research and the potential risks were clearly known to the participants without any hidden objection.

Signed.....

(Doctor or Researcher)

date.....



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1__
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__3,8__
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	__3__
Funding	4	Sources and types of financial, material, and other support	__16__
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1, 16__
	5b	Name and contact information for the trial sponsor	__16__
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__16__
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__16__

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1	<b>Introduction</b>			
2				
3	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	___ 5-7 ___
4				
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6		6b	Explanation for choice of comparators	___ 5-7 ___
7				
8	Objectives	7	Specific objectives or hypotheses	___ 7 ___
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___ 8 ___
11				
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14	<b>Methods: Participants, interventions, and outcomes</b>			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	___ 8 ___
17				
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19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___ 8 ___
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22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___ 9-10 ___
23				
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	___ NA ___
25				
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	___ 10,13 ___
27				
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___ 10 ___
29				
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	___ 10-11 ___
31				
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34	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	___ 11-12 ___
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____ 13 _____
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____ 8-9 _____
5				

### 6 **Methods: Assignment of interventions (for controlled trials)**

#### 7 Allocation:

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10	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____ 8-9 _____
11				
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16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____ 9 _____
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____ 9 _____
21				
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____ 9 _____
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____ 9 _____
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### 31 **Methods: Data collection, management, and analysis**

32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____ 11-13 _____
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38		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____ - _____
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1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	___ 12 ___
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5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___ 13 ___
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___ 13 ___
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10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___ 13 ___
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13				
14	<b>Methods: Monitoring</b>			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___ 12-13 ___
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___ NA ___
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___ 12-13 ___
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___ 13 ___
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32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___ 14 ___
35				
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37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___ 14 ___
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, stored, and maintained in order to protect confidentiality before, during, and after the trial	14
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
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13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
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16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	NA
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26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
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29	<b>Appendices</b>			
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31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Appendix
32				
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34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA
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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.

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