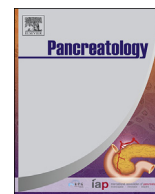




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The EFFECT of dietary fat content on the recurrence of pancreatitis (EFFORT): Protocol of a multicenter randomized controlled trial



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ABSTRACT

Background: Around 20% of patients with acute pancreatitis (AP) will develop acute recurrent pancreatitis (ARP) and 10% will progress to chronic pancreatitis. While interventions to avoid recurrences exist for the two most common causes – abstinence for alcoholic and cholecystectomy for biliary pancreatitis – the are no known preventive measures in idiopathic ARP. Though it is not included in any of the guidelines, a low-fat diet is often recommended.

Our aim is to test dietary fat reduction's effect on AP recurrence in a randomized controlled setting, in order to provide high-quality evidence for the validity of such an intervention.

Methods, design: Participants with at least 2 episodes of AP in the preceding 2 years of which the last episode was idiopathic will be randomized to one of two diets with different fat contents: a 'reduced fat diet' (15% fat, 65% carbohydrate, 20% protein) and a 'standard healthy diet' (30% fat, 50% carbohydrate, 20% protein; based on WHO recommendations). Participants will be followed-up for 2 years (visits will be scheduled for months 3, 6, 12, 18 and 24) during which they will receive a repeated session of nutritional guidance, complete food frequency questionnaires and data on relapse, mortality, BMI, cardiovascular parameters and serum lipid values will be collected.

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Discussion: This study will determine the effect of modifying the dietary fat content on AP recurrence, mortality, serum lipids and weight loss in idiopathic cases.

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Trial registration: The study is registered at clinicaltrials.gov under registration number NCT04761523

Ethical approval number: 40304-11/2020/EÜIG

1. Introduction

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas, most frequently caused by excessive alcohol consumption and gallstones [1]. Around 20% of patients with AP will develop acute recurrent pancreatitis (ARP) and 10% progress to chronic pancreatitis (CP) [2]. While interventions exist to avoid recurrences in the case of the two major etiologies – abstinence in alcoholic AP and cholecystectomy in biliary AP – there are no preventive therapeutic options for patients with idiopathic ARP. One possibility would be to comply with a low-fat diet, which is widely recommended to AP patients, regardless of etiology.

Though it is indeed frequently recommended, maintaining a low-fat diet after AP is not included in any of the guidelines [3–5] and evidence is scarce. In a prospective cohort of more than 36,000 participants, Prizment et al. found increased total and saturated fat intake to be associated with AP [6]. Setiawan et al. observed a positive association between saturated fat intake and gallstone-related AP, but not with non-gallstone-related AP, ARP or CP [7]. Oskarsson et al. prospectively studied a cohort of non-gallstone-related AP patients with no clear associations between overall diet quality and pancreatitis recurrence or progression [8]. Aside from the recognized connection between high fat intake and gallstone formation, thus biliary AP [9,10], there are hypotheses as to why fat excess could be a risk factor for non-biliary pancreatitis as well. One possible reason can be the elevated serum triglyceride (TG) levels, a known etiological factor for AP, stimulating free fatty acid production which is believed to be pancreatotoxic [6,11–13]. Zhang et al. found that a chronic high-fat diet in rats increased levels of pancreatic free fatty acids and lipid peroxidation, associated with pancreatic injuries and collagen synthesis via activated pancreatic stellate cells [14]. Animal experiments have also described a more severe AP course in animals on high-fat diets [15].

While the aforementioned cohort trials boast an impressive number of participants the study design is not suitable to determine a cause-effect relationship between dietary fat content and pancreatitis recurrence.

Our aim was to conduct a randomized controlled trial (RCT) comparing two low-fat diets that contain the same amount of calories and protein but have different fat contents (15 and 30% respectively) in order to determine the effect of dietary fat content reduction on AP recurrence. We wanted to include patients with idiopathic ARP as this is the group without a preventive therapeutic option. Our hypothesis is that while patients on both arms will benefit from receiving nutritional guidance, those with less fat in their diet will see an additional benefit due to the further reduction in serum lipids.

2. Methods, design

2.1. Trial design, study setting

This study will be a multicenter, prospective, parallel-group RCT

with a superiority framework. Participants will be randomly assigned in a 1:1 ratio to one of 2 different dietary interventions which are: a 'reduced fat diet'-arm and a 'standard healthy diet'-arm (largely based on WHO recommendations) to be further detailed in the 'Interventions'-section of this protocol.

The chief study site will be an academic hospital (1st Department of Medicine, Medical School, University of Pécs in Pécs, Hungary), other academic hospitals and hospitals with internal medicine departments regularly treating AP both in and out of Hungary will be invited to join the study. List of study sites can be obtained at clinicaltrials.gov.

2.2. Eligibility criteria

The inclusion and exclusion criteria for this trial are detailed in Table 1. A participant must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for enrolment.

2.3. Interventions

2.3.1. Description of interventions

Participants will be randomly assigned in a 1:1 ratio to one of 2 different dietary interventions which are as follows: (1) a 'reduced fat diet' in which the daily calorie intake will be composed of 15% fat, 65% carbohydrates, 20% proteins; (2) a 'standard healthy diet' (which also qualifies as a low-fat diet and is largely based on WHO recommendations) in which the daily calorie intake will be composed of 30% fat, 50% carbohydrates and 20% proteins.

Diets will be individualized to each participant. We will provide, for both arms, recommendations and meal-plans prepared every 200 kcals between 1800 and 3000 kcal. Before performing the dietary intervention, study dietitians will be required to use one of these sample diets and tailor it to the exact calorie needs of the participant (and if necessary, make alterations based on the country of the enrolling center).

Consultations will take place in an outpatient setting. When assigned to an intervention, first, patients will complete a food frequency questionnaire (FFQ – the National Health and Nutrition Examination Survey FFQ) to assess their eating habits. Then, based on their assigned intervention group they will receive recommendations according to the given diet. These consultations will be conducted by study dietitians centrally trained and evaluated by a qualified dietician coordinator. Relatives of the participants will also be allowed to attend these consultations, since the cooperation and involvement of family members can augment adherence and it is possible that the participant is not personally involved with the alimentation of the household.

The FFQ applied in this study is not only capable of assessing fat, carbohydrate and protein consumption but will provide a more detailed breakdown of dietary intake. Such detail is needed to account for other dietary variables possibly skewing data (not very likely due to randomization) and to conduct subgroup analyses – for details, see 'Statistical analysis plan'.

2.3.2. Discontinuation criteria

Participants will be advised to discontinue their allocated intervention (through personal communication or if impossible,

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
<ol style="list-style-type: none"> 1. Individuals with at least two episodes of acute pancreatitis in the 2 years preceding the inclusion with 2. The last episode being idiopathic, who are 3. At least 14 years old.
Exclusion criteria
<ol style="list-style-type: none"> 1. Individuals already receiving regular nutritional guidance (with medical indication), 2. Individuals in critical condition or in terminal stage of cancer (with an expected survival <2 years), 3. Individuals undergoing treatment for active malignancy, 4. Individuals with known cholecystolithiasis, 5. Individuals with uncontrolled diabetes mellitus (admitted lack of compliance with antidiabetic therapy/HbA1c $\geq 7\%$/indication of uncontrolled diabetes mellitus in last 24 months' anamnesis/newly discovered diabetes mellitus) 6. Individuals who are pregnant or nursing 7. Individuals with a BMI < 18.5 8. Individuals who are regularly receiving systemic corticosteroids 9. Individuals consuming more alcohol than: 5 units per day or 15 units per week for men; 4 units per day or 8 units per week for women.

One unit of alcohol equals 10 ml or 8 g of pure alcohol. HbA1c: hemoglobin A1c; BMI: body mass index.

other means – phone, e-mail, mail) if any of the following happens:

- (1) The participant withdraws his/her consent, (2) fails to attend two consecutive visits (3) develops one of the conditions mentioned in the exclusion criteria, or (4) completes the study. In these cases, participants will be advised to keep a balanced diet (according to WHO recommendations) with appropriate amount of calories to their age, gender, body weight and physical activity [16].

Based on any positive results of our study, dietary recommendation for this patient population might change and testing the long-term effect of these diets on pancreatitis recurrence, progression to CP and mortality might become necessary in form of a separate controlled trial.

2.3.3. Adherence

Compliance with dietary interventions is often problematic, this was taken into account when estimating the required sample size. We will, however, attempt to augment adherence via a repeated dietary intervention at the second visit, by completing FFQs with participants with the explicit purpose of estimating adherence and by reminding participants that through the evaluation of their BMI, laboratory results and FFQs we will have a good overview on whether or not they complied with the recommendations. These data will also be used to give motivational feed-back to the participants at the second visit.

Additionally, before participants consent to take part in the study they will be provided with detailed information on the composition and fiscal aspects of both diets so as to reduce drop-outs after-randomization. Our center will also maintain a “hot-line” – a telephone number that can be reached during working hours to answer questions that emerged regarding the diet.

2.3.4. Concomitant care

Concomitant interventions that do not categorically alter the diet of participants will not be limited.

2.4. Outcomes

2.4.1. Primary outcome measures

The primary outcome measure for this trial will be (1) a composite endpoint: the recurrence of AP (given as a rate of event) AND/OR all-cause mortality.

2.4.2. Secondary outcome measures

Secondary outcome measures will be the following: (1) Pancreas-specific mortality; (2) Cardiovascular cause mortality, (3) newly diagnosed CP, (4) changes in BMI compared to baseline (both total and percentage), serum lipid parameters (values and change from baseline), including: (5) total cholesterol, (6) TG, (7) HDL-cholesterol and (8) LDL-cholesterol; (9) serum albumin value and change from baseline, levels of (10–13) vitamins A, D, E and K (value and change from baseline); (14) blood pressure (systolic and diastolic) values and change compared to baseline. We will also assess (15) current smoking at the time of each visit, (16) adherence to dietary recommendations (as determined by the results of a food frequency questionnaire); (17) adverse events (given as rate of events). We will also assess (18) quality of life with the EQ-5D-5L questionnaire (see in supplementary material) and (19) muscle strength using a handgrip dynamometer (value and change from baseline for both).

2.4.3. Additional data collected at baseline

The index visit will entail an additional patient questionnaire and retrospective chart review collecting data on: comorbidities (diabetes, hypertension, chronic heart disease, chronic kidney disease, chronic liver disease, stroke, etc.), socioeconomic status (education, occupation, income, subjective social status) and past pancreatic history: how many episodes of AP, etiology of former episodes, is CP present. In case the patient has a new episode of AP during the study period, its etiology will also be recorded.

Data collection forms are available in our supplementary material.

2.4.4. Biologic sample collection

At enrollment and every visit, basic laboratory tests from blood will be carried out and participants will provide blood for storage in the biobank.

Laboratory parameters measured are shown on the data collection forms in our supplementary material. In case of alarming laboratory results, a physician will be notified, who will decide whether further medical attention is necessary. All patients will receive the results of their laboratory tests in written form.

The samples in the biobank will be stored at -80°C and identified by the personal identification number (PIN) given at study entry. All samples will be collected and sent together to the laboratory when the patient number reached the pre-set goal for analysis.

From the collected biological samples, we will – for not diagnostic, but research purposes – conduct genetic analyses. In case the result of these analyses contains information that impacts the health of either the participant or their relatives, we will inform them via one of the provided methods of availability.

2.4.5. Participant timeline

All participants will appear at the study site according to the study schedule (Table 2).

To determine eligibility, physical examination, BMI measurement, laboratory testing and a review of the individuals' medical history and documentation in order to rule out AP with an established etiology will be performed. At the time of allocation and before receivable of the intervention baseline values for outcomes (4–15, 18, 19) will be collected and participants will be physically examined as well as a FFQ will be completed with the help of a study administrator, all in an outpatient setting. All outcomes will be assessed at 3, 6, 12, 18 and 24 month visits. Participants will receive a repeated dietary intervention at months 3, 6, 12 and 18.

2.4.6. Sample size

As there are no similar studies to date, we will employ a two-stage trial design – we estimated a likely accurate participant number of 384 accounting for drop-outs, equally allocated (192–192) to both intervention groups which we will refine according to the results of an interim analysis performed at the time of reaching 50% (n = 192) of the planned participant number. We based this preliminary estimate on (1) recurrence rates among patients with at least 2 episodes of AP within 2 years from the Hungarian Pancreatic Study Group's (HPSG) AP registry and (2) an RCT conducted by Nordback et al. [17] examining the effect of two types of alcohol-intervention on pancreatitis recurrence.

2.4.7. Recruitment

Recruitment will be performed in 2 distinct ways: (1) patients can be asked to participate during their pancreatitis-associated hospital stay, or (2) eligible patients identified through medical database search can be contacted with a proposal of participation. The planned start of recruitment is 2021.07.01. with a proposed end of 2026.07.01.

Table 2
SPIRIT schedule outlining timing of interventions and assessments.

STUDY PERIOD	Screening	Allocation	Visit 2	Visit 3	Visit 4	Visit 5	Close-out
	–4 – 0 weeks	0 week	3 months	6 months	12 months	18 months	24 months
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS (dietary consultation)							
Reduced-fat group		X	X	X	X	X	
WHO-diet group		X	X	X	X	X	
ASSESSMENTS:							
Physical examination	X	X	X	X	X	X	X
BP, HR measurement		X	X	X	X	X	X
BMI measurement	X	X	X	X	X	X	X
Laboratory testing	X	X	X	X	X	X	X
Handgrip test		X	X	X	X	X	X
Food Frequency Questionnaire		X	X	X	X	X	X
Quality of life		X	X	X	X	X	X
Comorbidities, socioeconomic status, pancreatic history		X					

WHO: World Health Organization; BP: blood pressure; HR: heart rate; BMI: body mass index.

2.5. Assignment of interventions

2.5.1. Sequence generation and allocation concealment mechanism

Central randomization will be used with randomly permuted block size and allocation ratio of 1:1 using a computer-generated random sequence. Participants will be stratified based on (1) the presence of CP and (2) the presence of DM. Inclusion criteria and exclusion criteria will be checked prior to computer-aided randomization via an online platform to ensure that only eligible patients are included in the trial. The platform generates a PIN. The computer-aided randomization ensures allocation concealment. The randomization procedure will be performed by the same person who screened and consented the patient.

2.5.2. Blinding

Due to their role in delivering the individualized dietary intervention, study dieticians cannot be blinded to the group of the participants. Since they complete the FFQs with the participants, the assessment of dietary habits will not be blinded. Doctors caring for the participants and assessors of all other outcomes (laboratory parameters, BMI, blood pressure, adverse events) as well as statisticians handling the data will be blinded to the participants' allocated group. Participants will also be blinded – they will be informed of the trial structure and that they will be randomized to one of two diets with different dietary fat contents but they will be warned in advance that dieticians will not reveal to them whether they are in the 'reduced fat diet' arm or the 'standard healthy diet' arm. Naturally, they will be informed and allowed to ask in detail regarding the composition of these two diets, but it is our firm belief, that based only on this information and the meal-plan that the dietician will give to the participants, the vast majority will not know which arm they are on.

2.6. Data management, analysis and monitoring

2.6.1. Data management and monitoring

Investigators will be responsible for the accuracy, reliability and quality of the collected data. Detailed data flow will be described in a Data Management Plan. Data from completed electronic case report forms (eCRFs) will be validated under the direction of the Data Manager on the DMC according to a Data Cleaning Plan. Any missing, implausible, or inconsistent recordings in the eCRFs will be referred back to the Investigator using a data query form and will be

documented for each subject before clean file status is declared. All changes to eCRFs will be recorded.

The DMC will perform an independent assessment of trial-related documents and activities to ensure respect for subjects' rights, safety and well-being and to guarantee the plausibility of clinical data. The similarity of groups at baseline will also be checked.

After written consent of the subjects, data will be recorded by the investigators. Clinical research data will be processed separately from participants' personal data. Data may only be accessed by persons acting under the authority of the controller and in accordance with the authorization system established within the controller's organizational structure, only to the extent and in the manner necessary for the performance of tasks. Personal data will not be made accessible to third parties.

2.6.2. Statistical analysis plan

In the final analysis, the intention-to-treat analysis will be favored over per-protocol (or "as-treated") analysis. We expect there will be no missing data for the primary outcome. In case there is, we will use available case analysis. The "last observation carried forward" strategy will be followed to impute missing data for other outcomes measured during the study, including data from the National Health Insurance Fund (or similar organizations in case of foreign centers).

In descriptive statistics, the count and percentage will be provided for each treatment arm for binary outcomes. For continuous outcomes, *n*, mean, median, interquartile (Q3–Q1), standard deviation, minimum, and maximum values will be provided for each treatment arm. In a univariate comparative analysis, we will calculate relative risk with 95% confidence interval (CI) when comparing the primary endpoint between two groups ($\alpha = 5\%$) with a reference arm using non-repeated intervention complemented with chi-square or Fisher's exact test (the same strategy will be followed for binary secondary outcomes). For continuous variables, we will use *t*-test assuming unequal variances or the Mann-Whitney test. We will perform univariate (Kaplan-Meier and Cox-regression) and multivariate (Cox-regression) survival analysis for binary outcomes. An adjustment will be carried out at least for age, sex, BMI, smoking and education.

Results derived from the FFQs of the patients will give ground for subgroup analyses based on dietary factors. Pre-planned subgroup analyses will be based on: dietary adherence, alcohol consumption, daily calorie intake, true fat consumption, unsaturated and saturated fat consumption, *trans*-fat consumption and processed food consumption. We are also planning to conduct subgroup analyses based on the presence of known genetic variants in AP.

All analyses will be carried out with SPSS version 26 and Stata version 15.

2.6.3. Trial organization, committees and boards

The corresponding center of the EFFORT study is the Center for Translational Medicine at the University of Pécs Medical School (www.tm-centre.org), whereas the coordinator and designer research team is the HPSG (<https://tm-centre.org/en/study-groups/hungarian-pancreatic-study-group/>). The Centre for Translational Medicine and the HPSG have been running high-quality international, multicentre clinical trials together since 2014 [18–21] and have published relevant guidelines for pancreatic diseases with the aim of improving patient care [22–24].

The Steering Committee (SC) will be led by PH (principal investigator, gastroenterologist, specialist in internal medicine and clinical pharmacology). SC members will be MFJ (study coordinator), NF (biostatistician); ZsV (dietician coordinator); FI, LCza, MP,

AP (center representatives). There will be independent members as well, and the SC will include a patient representative. The SC will supervise the trial primarily and will make decisions regarding all critical questions (e.g., premature termination of the study, drop-outs, etc.).

All data gathered for research purposes will be handled confidentially and anonymously, which will be ensured by the Data Monitoring Committee (DMC). For each participant, a PIN will be generated that will be present on all forms and documents of each individual.

The International Advisory Board (ITAB) will include MW, SJP, FJ and GC.

The study was designed by the SC and was supported by the University of Pécs, Medical School. The sponsor had no role in the design of the trial and will have no access to the randomization codes or the data.

Five eligible patients were invited to review the protocol and to discuss any concerns or doubts that emerged. Remarks made during this meeting were incorporated into the final version of the protocol. The participant prospects positively responded to the concept of the study and highlighted its importance, agreed that the primary outcome was crucial. They deemed the forms and questionnaires understandable and appropriate. We originally planned only 2 follow-ups at months 12 and 24, but upon discussing it with the participant prospects they highlighted the importance of frequent controls in supporting dietary adherence, thus we modified the study schedule to include more visits. We also added the option of calling for dietary advice and for relatives to attend the dietary consultation to augment adherence, as described in the 'Adherence' and 'Description of interventions' sections of the protocol. The participant prospects described no negative feelings or ethical concerns regarding blood sample tests and the two interventions used in the study.

The independent Safety Monitor will be LCzo. The monitor will ensure the safety of the patients.

2.6.4. Interim analyses

- (1) Upon reaching 10% of the target sample size an interim safety analysis will be performed wherein the Safety Monitoring Board will review data of the patients and determine whether the occurrence of any negative effects can be linked to any of the interventions and if needed the given intervention or the trial will be terminated for the safety of the patients.

At the point of the safety analysis, patient data will only be made available to the Safety Monitoring Board and they will make the final decision whether or not to terminate the trial.

- (2) Upon reaching 50% of the target sample size an interim analysis will be performed in order to refine the number of participants necessary to complete the trial (see 'Sample size').

2.6.5. Safety

As our primary interest was the safety of participants, we did not overstep the WHO recommended maximum 30% fat intake (which already qualifies as a low-fat diet) just to better observe differences in AP recurrence. Maintaining such a balanced diet or a diet with an added reduction in fat content similar to what we aim to assess poses no health risks whatsoever. Adverse events in these cases might be due to a formerly excessive eater attempting controlled intake, such as irritation, fatigue, maybe headache. Other

minor and moderate events may occur, but we expect no serious side effects with either of the interventions. In case a potentially serious health problem is detected by the investigators related to the intervention, the Safety Monitoring Board will be notified. To avoid detection bias in assessing adverse events doctors conducting patient examination will be advised to ask all patients about the presence of nausea, abdominal pain and changes in stool.

The frequent dietary monitoring will also allow for the prompt recognition and treatment of malnourished participants.

Upon reaching 10% of the target sample size an interim safety analysis will be performed wherein the Safety Monitoring Board will review data of the patients and determine whether the occurrence of any negative effects can be linked to any of the interventions and if needed the given intervention or the trial will be terminated for the safety of the patients.

2.6.6. Ethics, dissemination

This trial is registered on clinicaltrials.gov (NCT04761523).

This study was approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (40304-11/2020/EÜIG), on 2020.08.17.

Planned start of patient recruitment: 2021.07.01.

Anticipated study duration: 5–6 years.

Study results will be published in an international scientific journal. Study sponsors have no role in writing the publication, deciding to publish and choosing the target journal.

2.6.7. Protocol amendments

In case of any changes and deviations from the original protocol, investigators and past participants will be contacted via email, letter, or phone; future participants will be notified in person during inclusion; deviations from the original protocol will be indicated on clinicaltrials.gov and in any and all publications originating from the acquired data.

Consent

Informed consent for participation in the study and providing biological samples will be collected by medical doctors. For a model adult consent form see our supplementary material. Consent forms are tailored to the age of the participant, each having received ethical approval.

3. Discussion

It has been a long-standing conviction that dietary fat content, even in the absence of immoderate calorie intake and putting biliary factors aside, can influence pancreatic pathogenesis. This study is the first to test this hypothesis in a randomized, controlled setting.

The results of our study will determine the effect of modifying the dietary fat content on AP recurrence, mortality, serum lipids and weight loss in idiopathic ARP cases ie. the patient group in which there is a dire need for interventions to positively influence the course and progression of the disease.

4. Strengths and limitations

The main strength of this study is that it is the first RCT to test the effect of dietary fat content on pancreatitis recurrence, thus providing high quality evidence for one of the central questions of pancreatology.

4.1. Limitations

As we tried to counteract the expected low event rate and finer

differences between interventions with a select population of frequent relapsers and a larger estimated sample size it is likely that enrolment will be slow. This could be ameliorated by multiple centers joining and supplying eligible participants already in their care. While it will provide insight on the effect of dietary fat content on recurrence, this comparison in itself is unsuitable to determine the effect of a low-fat diet compared to not dieting/excessive eating. We did not include such an arm as we found it unethical to not provide an individual with dietary recommendations after AP. However, we plan to estimate this effect, by comparing the groups with the best and worst dietary adherence based on the result of FFQs.

5. Implication for research: ketogenic diet

Originally, we planned to include a 3rd arm in our trial: a ketogenic diet arm. Several meta-analyses of RCTs compare such a diet to a low-fat diet in healthy individuals, or patients with malignancies, observing a favorable effect on diastolic blood pressure (DBP), serum TG and HDL-cholesterol levels [25–28]. However, issues regarding feasibility emerged. A ketogenic diet arm would have significantly raised the required patient number while introducing additional exclusion criteria to an already select patient population. Interview of participant prospects (see 'Roles and responsibilities') also revealed a low willingness to adhere with this diet. However, we encourage fellow researchers to pursue the possibility of the beneficial effect of ketosis on disorders of the pancreas.

Declaration of competing interest

Authors declare no conflicts of interest.

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None

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pan.2021.10.002>.

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There are no financial or other competing interests among the principal investigator, the included participants or any member of the trial.

Authors' contributions

Authorship was determined according to International Committee of Medical Journal Editors (ICMJE) recommendations. All authors participated in either drafting the study or providing critical revisions; all authors have read and approved the final manuscript version and are in agreement to be accountable for all aspects of the work.

Apart from above mentioned responsibilities, MFJ, KO, LS, NF, ZS, NZ, AP and PH made substantial contributions to the concept and design of the trial. Data collection was carried out by MFJ. NF performed the sample size estimation, based on data provided by MFJ and AP. MFJ wrote the majority of the manuscript. LCzo will also act as an independent Safety Monitor for the study. MW, SJP, FJ, GC, PGA, FI, LCza, MP, AP and PH will play a key role in participant enrolment and data acquisition. Every involved center can name coauthors for later publications for every 15 enrolled participant. Further roles are detailed in the 'Trial organization, committees and boards' section of the protocol.

Role of study sponsor in study

Study sponsors have no role in the planning, executing, analyzing and interpreting results of the study, nor in the decision to write and submit the report.

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