

BMJ - Decision on
Manuscript ID
BMJ.2018.046192

Body:

23-Aug-2018

Dear Dr. Ludwig,

I write with some good news about Manuscript ID BMJ.2018.046192 entitled "Effects of a Low-Carbohydrate Diet on Energy Expenditure During Weight Loss Maintenance: A Randomized Feeding Study"

We sent the paper for external peer review and discussed it at today's manuscript committee meeting with editors and our statistician in attendance. We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we can make a final decision about acceptance.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

Let me know if you have any questions about the revision process.

Thanks again for sending this to us.

Very truly yours,

Elizabeth Loder, MD, MPH
eloder@bmj.com

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****Report from The BMJ's manuscript committee meeting****

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Present: Wim Weber (chair); Tim Cole (statistician); Elizabeth Loder; Tiago Villanueva; Georg Roeggla; Jose Merino; Daoxin Yin

Decision: Put points. To be evaluated by statistician Dr. Tim Cole upon its return.

* We were pleased to see that the trial was prospectively registered. Thank you as well for submitting the study protocol. In your revision please be guided by the following: If there are any discrepancies between outcomes specified in the protocol and those specified in the trial registration, please default to the registry-specified entries. If there have been any changes to registry-specified outcomes during the course of the study, please explain the dates and reasons for the changes and as a general rule please report BOTH the originally specified and the changed outcomes so that readers can judge for themselves the effect of any changes.

* Please report prespecified outcomes in the paper in the order they are listed in the trial registry. Please make sure the paper (or the appendices) report all of the outcomes mentioned in the registry. If you plan to report some of these outcomes elsewhere in separate papers, please still list all of these outcomes and state that they will be published separately. Please make clear in any tables or figures whether the outcomes included are primary, secondary, or post-hoc outcomes.

* If you report any non-prespecified (post-hoc) outcomes, please clearly identify them as post-hoc and refrain from undue emphasis on them in drawing conclusions about the study.

* Many of the points that you make in your appeal letter to JAMA are persuasive. We thought that some of these explanations should be in the paper itself.

* Can you clarify why you were looking for a difference of 237 kcal/day in TEE? Is this a clinically meaningful difference? Can you justify this choice? We also think that general doctor readers might not be used to thinking about TEE and wonder if you can explain this in an easily understandable way. You might, for example, make it clearer than you do that the study question has to do with whether the overall composition of one's diet (balance of various types of nutrients) makes a difference in maintenance of weight loss.

* Figure 4 gives the data in kcal/kg/d, which is confusing. Looking at the CIs, there is not much difference between groups.

* As many reviewers have commented, it is also unclear how the trial was actually done. Were participants admitted to a ward and measured daily? If they were at home, how was compliance checked, etc? Did they use food diaries? It is difficult to find these details.

* The Abstract doesn't make clear that the results described are all prespecified, and hence more valid.

* The main results include lots of covariate adjustments that ought not to be necessary given the randomised design. Our statistician wants to see an unadjusted analysis presented first.

* Our statistician also notes that Table 3 should give the ITT results, not PP – as they stand the ITT results are relegated to supplementary Table e5. Also PP results are reported before ITT results in other places. Please be sure to present ITT results first, before the per protocol results. In interpreting the findings, you need to focus on the ITT results.

* The analysis should include a test for trend in the % carbohydrate content, not just HI vs LO.

* We acknowledge the concern of one of the reviewers that TEE was divided by weight but are not as worried about this, since you also did the alternative analysis of adjusting TEE for weight.

* The example weight and height on page 17 should be in metric not imperial units.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how and where (page number) you have dealt with them in the paper. Please return both a track changes and clean version of the manuscript.

Comments from Reviewers

Reviewer: 1

Comments:

Understanding why weight is frequently regained following weight loss is an important area of study. Although it is well known that energy expenditure declines with weight loss, facilitating weight regain, relatively less is understood about whether diet composition post weight loss is relevant.

The authors invoke the Carbohydrate-Insulin Model (CIM) which they have proposed is a mechanism which helps explain the burgeoning of obesity in the past decades. However, the approach taken is to test whether this theoretical model may alter energetics post weight loss rather than during weight gain. Hence, although the experimental work is interesting and valuable, the premise is not necessarily supported by this study design.

In my view, had there been less emphasis on the Model per se and perhaps a broader discourse on various models of obesity including the CIM, the paper would be more complete.

For example the authors dismiss discussion of other models (refs 8-12) except in the context that these dispute CIM due to lack of controlled feeding studies. A very recent review of body weight homeostasis <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6039924/> provides a comprehensive overview of this area and confirms that indeed energy expenditure is a critically important area of investigation in relation to obesity. In this regard, the study by Ebbeling and co-authors is important, notwithstanding divergent views on mechanisms of obesity. Indeed one of the strengths of this paper is the direct measurement of TEE using doubly labeled water methodology rather than indirect methods.

The paper provides valuable insights into post weight loss regain rather than the development of obesity per se. That regain is following what is a high protein energy restricted diet followed by one of three dietary patterns that vary carbohydrate and fat only with a stable protein composition. It is unclear why this particular pattern was selected.

My specific comments are as follows:

Abstract

I believe the abstract should describe the composition of the energy restricted diet as well as specify the timeline of the run in and intervention for greater clarity for the reader. Also important is to describe that TEE was measured by doubly labelled water.

For clarity suggest state: 164 were randomized to ONE OF THREE test diets.

It is not clear to me what "scaled to average post-weight loss body weight (82 kg) for reporting in kcal/d." actually means and why actual post-weight loss body weight wasn't used.

The conclusion in the abstract states: "Lowering dietary carbohydrate increased energy expenditure independently of body weight. This metabolic effect may facilitate weight-loss maintenance, especially among individuals with high insulin secretion."

I believe this is not entirely an accurate conclusion based on the study. My interpretation would be as follows: "Following a 12% weight loss on a higher protein energy restricted diet, lowering dietary carbohydrate/fat ratio increased energy

expenditure in energy balance. This metabolic effect may facilitate weight-loss maintenance especially among individuals with high insulin secretion.”

Introduction

Glycaemic load can be varied not only by exchanging carbohydrate for fat but also for protein. Is there a rationale for focusing specifically on fat/carbohydrate ratio alone?

Methodology

It would assist the reader in knowing this was a free living intervention or tightly controlled in a research institution. As such, no information is provided in the dietary methodology and how energy requirements were assessed. Assume it was based on the TEE data but this is not clear. It would also be useful to have TEE data prior to weight loss if this was performed as this would provide a useful reference point.

It would also very much assist the reader if the diagram that shows the study design also was annotated to show when and which measures were taken over the course of the study.

Why are not the actual diet compositions provided rather than a standard?

How was GL measured?

The change in TEE is adjusted for body weight but not adjusted for exercise? Would not that have been appropriate as there were subtle differences in exercise?

Results

Why is there no data on weight trajectory, and why adjustment per kg with a standard 82kg as per comment above?

Can the actual intervention diet compositions be provided rather than a standard?

Similarly, can the run in period diet information be provided as this is also part of the overall intervention?

Conclusion

The statement “In conclusion, dietary composition appears to affect energy expenditure independently of body weight. A low-glycemic load, high-fat diet may facilitate weight loss maintenance beyond the conventional focus on restricting calorie intake and encouraging physical activity.” Requires revision. In my view, a statement based on the methods and results should be the same as per the abstract : In conclusion, following a 12% weight loss on a higher protein energy restricted diet, lowering dietary carbohydrate/fat ratio increased energy expenditure in energy balance. This metabolic effect may facilitate weight-loss maintenance especially among individuals with high insulin secretion.”

Additional Questions:

Please enter your name: manny noakes

Job Title: senior principal research scientist

Institution: CSIRO

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: I have published in the field of the area of this manuscript.

I have co-authored a book in this field.

Reviewer: 2

Comments:

This is an important and excellently written MS indicating the potential benefits of restricting carb intake for weight maintenance after weight loss. The Authors thesis is that it is diet (lifestyle) not genetic change that is associated with the rise in body weight in Western populations. They demonstrate the value of lower carbohydrate diets at 20% and 40% versus 60% in maintaining weight lost.

1. The change from 60% to 40% carbohydrate diets would be unlikely to increase ketone body levels, probably the same applies for 20%. Did you contemplate 24h urine collections for β -OHB outputs? Even blood levels could have been useful if you have them. Possibly your spot urines might have been interesting if creatinine adjusted.

2. You may have published your methodology but it would be helpful to know more about the diets used. Was it weighed and eaten in a cafeteria. Were meals supervised (how many)? Were leftovers weighed and recorded? Were meals packed for weekends? etc

3. Do we have any idea if the participants preferred one carb level that might have influenced diet compliance

4. The SFA was fixed, what were the MUFA and PUFA intakes as a % of calories

5. The protein level was fixed. What was the nature of the protein foods? Were they the same across treatments? What was the % of animal, dairy and plant protein contribution to the total protein.

6. We have the glycemic load of the diets in Table 1, can we have the GI values also?

7. The ratio of carbohydrate/fiber differ between treatments. What was the nature of the carbohydrate foods used on the 3 treatments, did they differ?

8. Did you have a 3 or 7 day rotating menu? It would be helpful to see a day's menu plan for each treatment (2000 kcal)

Minor points

1. You need not qualify glycemic load with "carbohydrate" ("as in high glycemic load carbohydrate"). The carb is already implied. For GI, "high GI carbohydrates" would be correct.

2. With your detailed stratification did you have difficulty filling all your cells. Apart from center, some statisticians caution against too much stratification. Presumably in your case it worked?

3. Lines 31 to 50 I understand that you were using a repeated means ANOVA "spanning 3 time points" but you also state that for the change between PWL and weeks 10 & 20, the latter two (were) averaged. Am I missing something?

4. You log transformed hormones. Were they the only outcomes with a skewed distribution? Was this determination an iterative process (assessing outcomes) or was it determined on baseline values or predetermined?

5. You comment in Discussion on "consuming sugary beverages". Is the high glycemic load the problem or the inability to be satisfied by liquid calories?

6. Page 20 line 3 (your line 8) "opposite to what"

To Editor:

A good paper but it would be helpful to know considerably more about the diets used. Possibly the role of dietary glycemic index may be important. I have asked for these data.

Additional Questions:

Please enter your name: Dr. David Jenkins

Job Title: Professor/Director

Institution: University of Toronto/St. Michael's Hospital

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy)

please declare them here: I have worked with the food industry to produce more plant protein foods. I do not see this as a direct conflict with the MS.

Please see my COI for details.

Dr. Jenkins CONFLICTS OF INTEREST:

DJAJ has received research grants from Saskatchewan Pulse Growers, the Agricultural Bioproducts Innovation Program through the Pulse Research Network, the Advanced Foods and Material Network, Loblaw Companies Ltd., Unilever, Barilla, the Almond Board of California, Agriculture and Agri-food Canada, Pulse Canada, Kellogg's Company, Canada, Quaker Oats, Canada, Procter & Gamble Technical Centre Ltd., Bayer Consumer Care, Springfield, NJ, Pepsi/Quaker, International Nut & Dried Fruit (INC), Soy Foods Association of North America, the Coca-Cola Company (investigator initiated, unrestricted grant), Solae, Haine Celestial, the Sanitarium Company, Orafit, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, the Canola and Flax Councils of Canada, the Calorie Control Council (CCC), the CIHR, the Canada Foundation for Innovation and the Ontario Research Fund. He has received in-kind supplies for trials as a research support from the Almond board of California, Walnut Council of California, American Peanut Council, Barilla, Unilever, Unico, Primo, Loblaw Companies, Quaker (Pepsico), Pristine Gourmet, Bunge Limited, Kellogg Canada, WhiteWave Foods. He has been on the speaker's panel, served on the scientific advisory board and/or received travel support and/or honoraria from the Almond

Board of California, Canadian Agriculture Policy Institute, Loblaw Companies Ltd, the Griffin Hospital (for the development of the NuVal scoring system, the Coca-Cola Company, EPICURE, Danone, Diet Quality Photo Navigation (DQPN), Better Therapeutics (FareWell), Verywell, True Health Initiative, Institute of Food Technologists (IFT), Saskatchewan Pulse Growers, Sanitarium Company, Orafiti, the Almond Board of California, the American Peanut Council, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Herbalife International, Pacific Health Laboratories, Nutritional Fundamental for Health, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae, Kellogg, Quaker Oats, Procter & Gamble, the Coca-Cola Company, the Griffin Hospital, Abbott Laboratories, the Canola Council of Canada, Dean Foods, the California Strawberry Commission, Haine Celestial, PepsiCo, the Alpro Foundation, Pioneer Hi-Bred International, DuPont Nutrition and Health, Spherix Consulting and WhiteWave Foods, the Advanced Foods and Material Network, the Canola and Flax Councils of Canada, the Nutritional Fundamentals for Health, Agri-Culture and Agri-Food Canada, the Canadian Agri-Food Policy Institute, Pulse Canada, the Saskatchewan Pulse Growers, the Soy Foods Association of North America, the Nutrition Foundation of Italy (NFI), Nutra-Source Diagnostics, the McDougall Program, the Toronto Knowledge Translation Group (St. Michael's Hospital), the Canadian College of Naturopathic Medicine, The Hospital for Sick Children, the Canadian Nutrition Society (CNS), the American Society of Nutrition (ASN), Arizona State University, Paolo Sorbini Foundation and the Institute of Nutrition, Metabolism and Diabetes. He received an honorarium from the United States Department of Agriculture to present the 2013 W.O. Atwater Memorial Lecture. He received the 2013 Award for Excellence in Research from the International Nut and Dried Fruit Council. He received funding and travel support from the Canadian Society of Endocrinology and Metabolism to produce mini cases for the Canadian Diabetes Association (CDA). He is a member of the International Carbohydrate Quality Consortium (ICQC). His wife, ALJ, is a director and partner of Glycemic Index Laboratories, Inc., and his sister, CB, received funding through a grant from the St. Michael's Hospital Foundation to develop a cookbook for one of his studies.

Reviewer: 3

Comments:

Differences in total energy expenditure (TEE) estimated using an indirect technique were found during periods in which diets differing in macronutrient content were consumed. The authors conclusion was that a diet high in fat could translate into long-term weight loss.

The study protocol needs to be more fully detailed in the Methods section. It is not until the Discussion that we find out that participants were provided meals to take home. Was it the intention that participants only ate study-provided food? What about beverages?

Describe the strategies you used to promote dietary compliance.

I would have expected food records to be kept by the participants. If these were taken then the data need to be presented with statistical comparisons among diets. If not, then the lack of intake data should be discussed as a limitation.

Page 5 Line 22 and 33. Describe what you mean by high glycemic load carbohydrates. Any carbohydrate-containing food has variable glycemic load dependent on the amount eaten.

Note that the diets will differ in aspects other than glycemic load so it would not be appropriate to attribute differences to glycemic load alone as implied in various places.

Present the data for the number of people who required energy intake adjustment to keep within 2kg of the anchor weight. This is important data to present and to statistically compare among treatments.

Present the LDL, total and total/HDL ratio data with statistical comparisons among treatments as these have been found to be influenced by macronutrient composition.

In the discussion on translation to public health you mention poor long-term compliance, surely that would also apply to any diet that you might advocate?

There is a substantial body of literature in which it has been found that compliance to diet is the predominant predictor of weight loss/maintenance independent of macronutrient composition. Please discuss.

Using data from the NHANES survey, a positive relationship was found between the proportion of dietary fat and categories of body mass index (Yancy et al. Trends in energy and macronutrient intakes by weight status over four decades. Public Health Nutrition: 17(2), 256–265). Discuss in relation to your suggestion (page 17) that lowering the proportion of dietary energy intake from carbohydrates by increasing fat would result in weight loss.

Observationally, traditional Asian diets with carbohydrate contents providing up to 80% of dietary energy have been associated at a population level with normal weight, discuss how this aligns with the concept of encouraging more fat in the diet.

Comment on the male to female ratios among treatment groups and whether this could have had an influence on the outcomes.

Discuss whether there are specific limitations to the doubly labelled water technique when used in overweight humans and any implication of this to the present work (eg: Ravussin et al. Energy expenditure by doubly labeled water: validation in lean and obese subjects. Am J Physiol. 1991 Sep;261(3 Pt 1):E402-9).

Page 8, line 24. Randomization was done in an at Boston Children's Hospital

Additional Questions:

Please enter your name: Bernard Venn

Job Title: Senior Lecturer

Institution: University of Otago

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

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lists/declaration-competing-interests'target='_new'> (please see BMJ policy)
please declare them here:

Reviewer: 4

Comments:

Major comments

1. The authors have not complied with the BMJ requirement:

"The BMJ expects authors of clinical trials to report their findings in accordance with the outcomes listed in the trial registry. Outcomes that were not pre-specified in the registration should be identified as such in the text of the paper and in any tables. All registered outcomes should be described in the BMJ paper. If results for any outcomes will be or have been reported in another publication this should be made clear to readers. The timing and reasons for any changes in registered outcomes should also be disclosed."

<https://clinicaltrials.gov/ct2/show/NCT02068885> (registration document)

In the registration document there are multiple relevant secondary end-points that are not reported in the current paper, which indeed is required for the full analyses and interpretation of the findings. All these end-points can easily be reported in supplementary online material and the relevant results reported in the results section. If the discussion section is re-organized there will be plenty of space for a full discussion of the results.

2. The primary end-point TEE (Total Energy Expenditure) data is essentially not provided in the manuscript in a way that allows other scientist to re-calculate and understand the derived figures. This is particularly problematic because it is the primary end-point, so all the raw data and derived data needs to be given in a table. Currently, only mean baseline data for the three groups are given in Table 2 (TEE, mean (SD), kcal/kg/d), and then values adjusted for weight loss are given as changes (Table 3). Please provide unadjusted and adjusted values for all groups.

3. The primary end-point TEE (Total Energy Expenditure) is normalized for body weight simply by division of TEE by body weight. This is a serious flaw and can lead to artifacts, which have been shown very elegantly by Eric Ravussin and Clifton Bogardus in AJCN 2009 in their methods paper:

This analyses need to be done correctly by adjustments by linear regression ad modern Ravussin. The changes from baseline need to be analyzed with a transparent method that can be reproduced by other scientists. Please provide individual data before and after in a spaghetti-gram.

4. Insulin secretion based on insulin-30 is end-point number 52 in the protocol. It would be appropriate to conduct some sensitivity analyses by using other relevant biomarkers: fasting glucose, fasting insulin, AUC glucose based on OGGT, and the

two secondary protocol end-points 15 and 16 hepatic and systemic insulin sensitivity assessed by frequently-sampled oral glucose tolerance test.

5. According to the registration document the trial consists of 3 phases. Food is provided throughout the study to all 3 dietary arms, with the following phases: 1) Weight loss; 2) Weight maintenance; 3) Ad libitum. Please also report the "ad libitum" part of the trial in this paper.

6. Please present the adverse event by diet group in a table (could be supplementary material).

7. Please report ketone bodies as a biomarker of compliance.

8. Figures 3 and Figure 5 are missing from the manuscript.

9. The authors report that the mean difference in TEE between low- and high-carbohydrate diets among individuals in the highest tertile of insulin secretion (464 kcal/day) was triple the difference for those with lower insulin secretion. This is very interesting and an important finding. Please report the weight changes in these subgroups. If the difference in TEE is not translated into a weight loss the finding is less relevant. The data is available in the study, so please present them to the reader.

10. In the recent paper by Hjorth et al (Hjorth MF, Zohar Y, Hill JO, Astrup A. Personalized Dietary Management of Overweight and Obesity Based on Measures of Insulin and Glucose. Annu Rev Nutr. 2018 Jun 1. doi:) it is suggested that normoglycemic obese individuals and pre-diabetic obese respond very differently to high versus low GI diets. Please report the distribution of pre-diabetic status for the 3 groups, and if there is an effect-modification on the TEE outcome by glycemic status.

Additional Questions:

Please enter your name: Arne Astrup

Job Title: professor, MD, DMSc, head of department

Institution: University of Copenhagen

Reimbursement for attending a symposium?: Yes

A fee for speaking?: Yes

A fee for organising education?:

Funds for research?: Yes

Funds for a member of staff?: Yes

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy)

please declare them here: I don't have any that is relevant for this paper.

Reviewer: 5

Recommendation:

Comments:

General Comments:

This is a unique study with an exceptionally strong design evaluating the effects of a low carbohydrate diet on total energy expenditure during weight maintenance following a weight loss program. However, the paper is very difficult to read. The complex study design contributes to the poor readability, but it also is poorly written. The writing style suggests that different authors wrote various sections. One author needs to edit the entire manuscript for readability and clarity.

The abstract needs considerable editing. The rationale for the ITT and Per Protocol analysis needs to be included. How did the sample size vary for these two approaches? What was the sample size for the insulin secretion comparison? What was the p-value for the ghrelin outcome.

The final conclusion needs to be stated more clearly emphasizing that this was a post-weight loss study and that total energy expenditure was measured. Also, a rationale or mechanism for how low dietary carbohydrate increases TEE without altering body weight needs to be provided.

Methods:

Page 6, line 36. How many achieved targeted weight loss.

Page 6-7. Unclear if the description of participants is for the primary study or for those who participated in the maintenance phase.

Page 7-8. The randomization description is impossible to understand. Needs to be totally rewritten.

Page 9-10. Clarify when each set of measurements was made. Are there 4 or 3 timepoints? Baseline, PWL, MID and END.

Page 12, Line 5. What 4 comparisons were made. Not clear from the description.

Page 12, line 31. First sentence of this paragraph is not clear.

Results:

Page 15, line 20. Figure 3 is missing from the paper; there were two copies of figure 4.

Discussion:

In general, the authors do not adequately explain how a low carbohydrate diet increases TEE without any change in energy intake. This general finding is inadequately explained.

The discussion of the impact of a low carbohydrate diet on TEE on page 17, lines 24-54 is confusing and no potential mechanism is provided.

Page 16, lines 45-54. The primary outcome in this study was TEE. The link between the higher TEE on a low carbohydrate diet and the activation of brain areas is not clear.

The strengths and limitations of the study are adequately described. However, the discussion of the physiology and potential mechanisms is totally inadequate and confusing.

Additional Questions:

Please enter your name: Janet C. King

Job Title: Professor Emerita

Institution: University of California at Berkeley

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Fees for consulting?: No

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