PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Dietary intervention in patients with age-related macular degeneration: protocol for a randomised controlled trial
AUTHORS	Tang, Diana; Mitchell, Paul; Flood, Victoria; Kifley, Annette; Hayes, Alison; Liew, Gerald; Gopinath, Bamini

VERSION 1 – REVIEW

REVIEWER	Jayne Woodside Queen's University Belfast, UK
REVIEW RETURNED	24-Jul-2018

GENERAL COMMENTS	The paper describes a protocol for an RCT of a dietary intervention in AMD, which is of interest and timely. I have a few queries which might help to make the manuscript more informative for researchers in this area: 1) I would like to see further detail added on the decision making process around the intervention, i.e. why these particular dietary factors were chosen, the strength of the evidence supporting their selection and that they play a causative role in AMD. MY reaction on reading the protocol was "is the evidence really strong enough to base this intervention on" so I would like that justified in some detail, particularly the different levels of intervention for the different stages of AMD. 2) Similarly it would be useful to see more detail on the intervention content and delivery - a theoretical basis is mentioned but not expanded upon, several behaviour change techniques appear to have been included, such as goal-setting, but this is not formally described. 3) Line 27 on page 7 describes "these patient-centred barriers" but these have not previously been discussed? Line 42 on the same page discusses a two pronged approach but the description of this is not clear to me - it it really two pronged - one is the delivery of the intervention and the second is the mode of delivery - these are not really prongs? On the same page on line 53 medium effect sizes are described - I don't find this description helpful and would like to see something more specific even at this stage in the manuscript. LAter the change is described as a 0.5 SD, but I would like to see this also presented as an idea of how many portions, even if this is approximate - is it half a portion, for example? 4) The study is powered for change in vegetable intake, but I don't think the authors pay enough attention to other aspects of the trial that will be important - the feasibility of recruitment, the fidelity of delivery of the intervention, likely drop-out rates, etc. and I would like to see more detail on some of the aspects being included as secondary outcomes. 5) the control group is a concern - it is described as a delayed

	control yet it then says the control will receive the intervention only if it is shown to work. Surely if participants are recruited saying they will get the intervention then they do need to receive it regardless? I would also like to see more details of what health tips and brochures they will receive, as distinction between intervention and control groups will be very important. 6) I don't think the distinction between the two forms of dietary assessment is well made. The FFQ is less likely to pick up change in dietary intake, and the authors say this, but then describe the nutrient analysis using the FFQ. This needs to be more clearly described, with a rationale. Did the authors consider using objective measures of nutritional status as well as self-report measures? 7) I also wondered whether some indication of eye health/AMD progression was to be included to power a future study looking at these outcomes? It would seem strange not to? In addition, even if the dietary changes do not ultimately affect AMD progression, they may improve other co-morbidities and it would be useful to acknowledge this somewhere in the manuscript.

REVIEWER	Paul S. Bernstein, MD, PhD Moran Eye Center University of Utah Salt Lake City, Utah 84132 USA
REVIEW RETURNED	03-Aug-2018

GENERAL COMMENTS	This is an interesting study protocol designed to assess whether a dietary intervention approach is feasible and effective in AMD patients. This is important because improved diet is a cost effective and rational approach to lower risk of future visual loss in patients diagnosed with AMD. Such behavioral studies are challenging to conduct in a rigorous manner, and the authors are commended for addressing this problem. My main critique lies in the proposed active intervention relative to the control "wait-list" group. The active intervention group has weekly phone calls with a dietician for four months. To me, this seems excessive and rather obtrusive. In the real world this degree of counseling would be difficult to implement and not sustainable. Monthly counseling would seem more reasonable. Conversely, the control group receives just a letter and then no further contact for four months. I would have liked to see at least monthly phone contact to discuss AMD without intensive nutritional counseling to remove the potential confound that frequent telephone contact as opposed to nutritional counseling is driving any detected effect. If telephone contact were conducted monthly in both groups, then they would be nicely matched.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment 1) I would like to see further detail added on the decision-making process around the intervention, i.e. why these particular dietary factors were chosen, the strength of the evidence supporting their selection and that they play a causative role in AMD. MY reaction on reading the protocol was "is the evidence really strong enough to base this intervention on" so I would like that justified in some detail, particularly the different levels of intervention for the different stages of AMD.

Response 1) Thank you for your feedback. We appreciate the effort you have taken to review our protocol and have endeavored to improve the paper accordingly. For this first comment, we have now

cited other population-based and clinic-based studies providing the evidence supporting the intervention as well as the specific dietary goals outlined in the introduction. The added detail also helps to justify the different levels of intervention for the different stages of AMD. Please see pg 6, para 2 and pg 7 para 2.

"Independent inverse associations between these dietary factors and risk of AMD development and progression have been observed. For example, the Coimbra Eye Study and Korea National Health and Nutrition Examination Survey found that higher intakes of vegetables, fruit and nuts related to a statistically significant reduction in the risk of AMD development[11] [12]. This relationship is likely due to fruits and vegetables, particularly the dark green leafy variety, being good sources of carotenoids (e.g. lutein and zeaxanthin), and nuts having a high fatty acid content.[5] Fish is also a good source of omega-3 fatty acids, and similarly, a reduced risk of AMD development was observed in the Age-Related Eye Disease Study (AREDS) and Nurses Health Study and Health Professionals Follow Up Study when at least one serving of fish was consumed.[13]/span>[14] The Blue Mountains Eye Study provided compelling data demonstrating that carriers of certain gene polymorphisms that increases AMD risk by 2- to 4-fold, substantially reduced their risk to close to their non-carrier counterparts by regular consumption of fish.[15] Dietary intake of wholegrains also shows a beneficial effect against risk of AMD in studies such as The Blue Mountains Eye Study and AREDS. Both studies found that reducing usual dietary GI by approximately 8-10 units was protective against AMD development.5 Moreover, the Melbourne Collaborative Cohort Study identified that higher intakes of wholegrains and fish was associated with a lower risk of late AMD, with 51% reduced odds in participants in upper quartile for intake versus the lowest quartile.[16] Another notable outcome from AREDS highlighted that strict adherence to a Mediterranean diet, which promotes an abundance of the above recommended dietary factors, showed a reduced risk of progression to late-stage AMD by 26%.[17] A similar inverse relationship between adherence to the Mediterranean diet and advanced AMD was also observed in the European Eye Study.[18]"

"Specific nutrients have been identified to have a protective effect on AMD. Landmark population studies – The Rotterdam Study, Blue Mountains Eye Study, and Beaver Dam Eye Study – support the inverse relationship between dietary zinc and risk of early and/or late AMD[5]… Based on this literature, patients most susceptible to AMD progression (i.e. have moderate AMD, or late AMD in one eye) are encouraged to take AREDS-based supplements. Preventative benefits of the supplements or use in mild AMD has not been adequately investigated, and therefore not recommended in routine practice.[5]

Comment 2) Similarly it would be useful to see more detail on the intervention content and delivery - a theoretical basis is mentioned but not expanded upon, several behaviour change techniques appear to have been included, such as goal-setting, but this is not formally described.

Response 2) Thank you for this suggestion. We have now provided a clearer and more detailed description of the intervention content and delivery, see the Methods section, pg 10, para 1. Further, the 4 A's approach has been expanded on to provide a better understanding of how the intervention calls will be structured and what is discussed, and as a result we have now expanded upon behavior change techniques such as goal setting (see pg 11, para 2).

"Intervention calls with follow the 4 A's approach[26]: 1) assessment (and feedback) – evaluation of participant stage of change as well as the adequacy of their diet. Follow up calls will re-assess these areas accordingly to capture any dietary behaviour changes. Stage of change is an important component of the dietary intervention and will help guide the focus of the phone calls (e.g. looking at diet-disease relationship, environmental factors or self-confidence). It is categorised as: pre-contemplation; contemplation; preparation; or action and maintenance (Figure 2).[27] [28] 2) Advice on optimal dietary behaviours – this will be tailored education according to the outcome of the assessment e.g. education on the diet-disease relationship in the pre-contemplative stage vs education on food preparation/ recipes in the action phase. Each monthly call will focus on one recommendation (i.e. vegetables; fruit; fish and nuts; or low GI), ordered from highest to lowest priority based on the participant's needs. 3) Assistance with collaborative goal setting and developing a personalised plan for modifying dietary behaviours – goal setting and empowerment will be important features of the telephone coaching.[25] The SMART principle – Specific, Measurable, Attainable, Realistic, and Timely – is an effective format for goal setting as it increases motivation through short-term achievements that build towards reaching a long-term goal.[29]"

Comment 3) Line 27 on page 7 describes "these patient-centred barriers" but these have not previously been discussed? Line 42 on the same page discusses a two-pronged approach but the description of this is not clear to me - it it really two pronged - one is the delivery of the intervention and the second is the mode of delivery - these are not really prongs? On the same page on line 53 medium effect sizes are described - I don't find this description helpful

and would like to see something more specific even at this stage in the manuscript. Later the change is described as a 0.5 SD, but I would like to see this also presented as an idea of how many portions, even if this is approximate - is it half a portion, for example?

Response 3) Apologies for the confusion and lack of clarity. Patient centered barriers were mentioned in the prior paragraph (pg 8, para 1) e.g. : *"..patients not having sufficient information and/or misconceptions regarding diet and AMD"* . We have now reworded the sentence: "*Telephone-delivered interventions involving regular coaching to support behavioural changes can help overcome some of the patient-centred barriers, address existing gaps in practice and facilitate adoption of complex dietary recommendations*."
The "*two pronged approach"* refers to the two levels of intervention – that being (1) the development and distribution of an evidence-based dietary resource and (2) the telephone counseling. And finally, our explanation of effect sizes was poorly described, we have revisited our power calculations and revised it accordingly to also present a servings per day outcome measure i.e. *"The primary outcome is a 0.5 serves per day change in total vegetable intake. This measure of change is informed by expected dietary improvement asserted by clinical expertise and data from an Australian population-based intervention which observed an increase in vegetable intake by roughly 0.5 serves per day from 2.6 serves to 3.2 serves.[31]"*

Comment 4) The study is powered for change in vegetable intake, but I don't think the authors pay enough attention to other aspects of the trial that will be important - the feasibility of recruitment, the fidelity of delivery of the intervention, likely drop-out rates, etc. and I would like to see more detail on some of the aspects being included as secondary outcomes.

Response 4) Thank you for your feedback. We agree that assessing other aspects of the trial will be important, hence, this is why we had already dedicated a section on 'Acceptability and Feasibility' (see Methods, pg 19, para 1): '*Practical implications of the intervention will be evaluated via systematically tracking all participant contacts. This includes reporting on: the number of call attempts, completed calls ('dose' of intervention received), number of calls completed at the scheduled time (versus via call back), reasons for missed calls, and call duration. The call content will be tracked via checklists completed after each call allowing for reporting on the extent to which the intervention content is delivered per protocol, and the percentage of participants setting goals for dietary behaviours. Treatment acceptability in the intervention arm will be assessed by questions via a post-intervention survey: (1) 'Overall, how satisfied were you with the program?' (2) 'How satisfied were you with the educational content?' (3) 'Would you feel confident in recommending this treatment to a friend? (4) 'Was it worth your time doing the program?' Participants will respond to the first 2 questions using a 5-point Likert scale, ranging from 'Very Satisfied' to 'Very Dissatisfied' and the second 2 questions with a simple 'yes/ no' response.' Further, we have revised our power calculations to reflect a serves per day change in vegetable intake instead of a standard deviation change."* Accordingly, the new recruitment target of 140 total participants has been determined using an online power calculator and was repeated using Altman's nomogram – yielding the same target, and takes into consideration a 10% drop-out rate. The new target is a more realistic and achievable figure. With the amendments, as per comment 6 below and to Reviewer 2's feedback regarding frequency of calls, the study will also be significantly less burdensome on participants so we are more confident in achieving low drop-out rates, and higher compliance. The reasoning behind the secondary outcomes has also been addressed through the inclusion of additional literature supporting these recommendations as suggested in this Reviewer's query 1.

Comment 5) the control group is a concern - it is described as a delayed control yet it then says the control will receive the intervention only if it is shown to work. Surely if participants are recruited saying they will get the intervention then they do need to receive it regardless? I would also like to see more details of what health tips and brochures they will receive, as distinction between intervention and control groups will be very important.

Response 5) This is a valid point made by the Reviewer. Therefore, we have now made changes in the protocol to allow all control participation in the intervention at the end of the study. We have also provided more detail on the brochures that control participants will receive e.g. 'Nutrition and Supplements' brochure from the Macular Disease Foundation Australia, and Eat for Health Australian dietary guidelines for adults" (see pg 13 'Control Group')

Comment 6) I don't think the distinction between the two forms of dietary assessment is well made. The FFQ is less likely to pick up change in dietary intake, and the authors say this, but then describe the nutrient analysis using the FFQ. This needs to be more clearly described, with a rationale. Did the authors consider using objective measures of nutritional status as well as self-report measures?

Response 6) Thank you for feedback. We agree that the distinction between the DBQ and the FFQ is not well explained and have modified this to describe the purpose of both (see pg 15, para 1).
"The DBQ aims to provide a comparison of recent dietary intake versus usual long-term intake to be indicated by FFQ responses. This questionnaire will also assess participant confidence in achieving key AMD-linked nutrition goals such as 'Eating 5 serves of vegetables a day'; and behaviours related to the consumption of nutrient-poor, discretionary food. Baseline understanding of participants' confidence will contribute to the dietitian's initial assessment during the intervention of participant stage of change, while the understanding of participant behaviour will assist with the development of strategies to achieve nutrition goals.... This data will be a usefulIndicator of the intervention's effectiveness in terms of short-term dietary improvements, and self-efficacy."
The DBQ will now be the only tool re-administered immediately post-intervention and 3-months post-intervention to short-term feedback about the participant's dietary behavior changes. As the FFQ's purpose is to provide long-term (12-month) dietary intake, we have realized repeating the FFQ immediately post-intervention and 3-months' post-intervention is not appropriate. Instead, we have revised our methodology to only administer the FFQ at baseline and 6-months' post-intervention, which theoretically will be 10 months from baseline, however realistically, considering likely delays in participant's response speed, will be closer to the 12-month timeframe. The DBQ will also be administered at the 6 month's post-intervention follow up to see if participants are maintaining or sustaining their dietary behavior change. We are very grateful to the reviewer for identifying this flaw, which in turn, will now be reducing participant burden as they will not need to complete the lengthy FFQ so frequently.
Regarding an objective measure, BMI and waist circumference are asked at baseline and 6-months post intervention questionnaire. These are however self-reported with the participant indicating whether the measurement has been estimated or measured.

Comment 7) I also wondered whether some indication of eye health/AMD progression was to be included to power a future study looking at these outcomes? It would seem strange not to? In addition, even if the dietary changes do not ultimately affect AMD progression, they may improve other co-morbidities and it would be useful to acknowledge this somewhere in the manuscript.

Response 7) This is a good point raised by the Reviewer. We agree with your feedback and have been considering investigating the effects of the dietary intervention on the participants' AMD progressionsince our submission in May. We have included a description on the collection of key diagnostic features (pg 16, para 2).
"AMD progression will be monitored through the collection of optical coherence tomography (e.g. central macula thickness, presence of fluid, pigment epithelial detachment) and additional information on visual acuity and number of injections received will be documented. All patients recruited from participating eye clinics will have this information collected at baseline and at the final follow up (6 months post-intervention). This data will be used in future investigations to evaluate the clinical outcomes of recommended dietary practices."
We have also acknowledged the general health benefits that may come from this intervention if not specifically for reducing the risk of AMD progression (pg 16, para 2).
"A reduced risk in AMD progression might not be observed in the short term i.e. at 6-month follow-up. However, reductions in the risk of other comorbidities such as obesity, and diabetes could be observed."

Reviewer 2

Comment 1) My main critique lies in the proposed active intervention relative to the control "wait-list" group. The active intervention group has weekly phone calls with a dietician for four months. To me, this seems excessive and rather obtrusive. In the real world this degree

of counseling would be difficult to implement and not sustainable. Monthly counseling would seem more reasonable. Conversely, the control group receives just a letter and then no further contact for four months. I would have liked to see at least monthly phone contact to discuss AMD without intensive nutritional counseling to remove the potential confound that frequent telephone contact as opposed to nutritional counseling is driving any detected effect. If telephone contact were conducted monthly in both groups, then they would be nicely matched.

Response 1) Thank you for your feedback regarding the practical application of our protocol, and fairness to both groups in the study. We agree that number of calls for the intervention group is quite excessive and not realistic and have now modified this (see pg 10, para 3)
"Scheduled phone calls with an accredited practising dietitian will also occur across a 4-month period. The dietitian will evaluate the frequency of calls based on individual needs, with all participants contacted at least monthly."
Similarly, we have increased the follow up contact with the control group to match with the intervention (monthly). Please see Methods section pg 13' Control Group'.
"Support staff will conduct monthly calls during the intervention, to help clarify any questions they have regarding the general dietary information they have received, discuss any general AMD queries…"

VERSION 2 – REVIEW

REVIEWER	Jayne Woodside Queen's University Belfast, UK
REVIEW RETURNED	25-Oct-2018

GENERAL COMMENTS	The authors have responded in detail to the suggestions - and I think this has helped the manuscript as a result. Now consider this to be acceptable for publication.