PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Healthy Ageing Through Internet Counselling in the Elderly – the HATICE randomised controlled trial for the prevention of cardiovascular disease and cognitive impairment
AUTHORS	Richard, Edo; Jongstra, Susan; Soininen, Hilkka; Brayne, Carol; Moll van Charante, Eric; Meiller, Yannick; Groep, Bram; Beishuizen, Cathrien; Mangialasche, Francesca; Barbera, Mariagnese; Ngandu, Tiia; Coley, Nicola; Guillemont, Juliette; Savy, Stephanie; Dijkgraaf, Marcel; Peters, Ron; van Gool, Willem; Kivipelto, Miia; Andrieu, Sandrine

VERSION 1 - REVIEW

REVIEWER	Richard McManus University of Oxford, UK Nil declared for this review.
REVIEW RETURNED	22-Dec-2015

GENERAL COMMENTS	This is a protocol for an EU funded study that will have previously undergone extensive peer review and has already started with ethics committee approved protocols. There is therefore little that can be changed. The trial was registered in 2014 and appears to have been sensibly designed. Given the fact that the study takes place in three countries, it would be worth the authors stating how they will ensure that the interventions are as similar as possible in each country and centre and what efforts they will make to record precisely how the interventions -albeit triggered by the same internet based coaching system - are actually delivered. It might be worthwhile including a process evaluation section to this end. The primary composite outcome is rather unusual and difficult to understand from a clinical stand point however the individual end points that are included as secondaries should allow interpretation. My other concern is that although a statistical analysis plan will no doubt be produced prior to analysis, this should be specifically stated. In addition, whilst a secondary analysis will take into account baseline differences, I would have thought (and indeed the authors state) that country and centre effects may be great and these should be taken into account in the analysis. It would be sensible - if the authors agree - to state this prospectively.

REVIEWER	Thomas C. keyserling, MD, MPH Professor of Medicine University of North Carolina at Chapel Hill USA
REVIEW RETURNED	04-Jan-2016

GENERAL COMMENTS	--I note that the methods are not described sufficiently for this study to be repeated. This was marked because the details of the content of the intervention are not given. I do not think it needs to be given for this paper. It should be included as a supplement when results are published. --regarding statistics, see comments below about sample size. --concerning standard of written English, I think the text is reasonable, but with some wording that is not clear or could be improved. I address this in the comments for the authors. ABSTRACT --page 3, line 7. Change “great opportunities” to “increasing opportunities” or something like that. --page 3, line 27. Should “mood” be “quality of life?” --page 3, line 38. I think “easy implementable” should be “easily implementable” --page 3. Line 44. “Limitations include the relatively short follow-up and the impossibility to operate double blind.” “Impossibility to operate double blind.” This refers to the fact that the intervention cannot be blinded. This in inherent in lifestyle studies. I am OK dropping this. The study will utilize a blinded research assistant for assessment of 18 month outcomes and a blinded adjudication committee for clinical outcomes. These approaches address “blinding” issues for this trial in an appropriate fashion. INTRODUCTION (all page 4) --line 27. This sentence starting with, “In spite of clear…” is not clear and I don’t think entirely accurate, as there are clinical guideline for management of some CVD risk factors among the elderly; specifically, hypertension. --line 33. Patient self-management is a potentially powerful strategy to improve adherence to therapy in CVD [19, 20] risk reduction. --line 46. The internet has become a major source of information for people of all ages, and its use among older people throughout Europe has increased dramatically, making it a potentially suitable medium for the delivery of widely implementable health care interventions [24]. METHODS --page 5, line 20. Table. Please provided more information on history of cardiovascular disease and diabetes. Are these health care

	provider diagnoses? Is diabetes defined by A1c or fasting blood glucose levels? --page 6, starting line 36. Due to the heterogeneous population in this trial, which includes participants with elevated cardiovascular risk with or without established CVD, primary as well as secondary prevention guidelines will be applied --page 7, line 32. I don't think there should be a comma after aging. Also, I think the ASCVD pooled risk factor equation (2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. doi: 10.1161/01.cir.0000437741.48606.98) may be superior to the Framingham Risk Score and recently seems to be well supported by the literature. --page 8 line 7. Consider alternative wording to "stimulate," possible "facilitate." --page 8, line 12. The participants from the intervention group will have an additional interview with a strong focus "on motivation talk with their own coach." "On motivation talk with their own coach" is not clear. Please improve this wording. --page 8, line 19. "All data with be anonymized." I don't think data with be anonymous, but more likely, coded with a number, to insure confidentially. --page 8, line 46. "(myocardial infarction, stroke, transient ischemic attack/angina pectoris/peripheral arterial disease/diabetes mellitus)." Suggest using all commas instead of commas and back slashes. --in the methods sections, please add paragraph on what type of data with be used to adjudicate clinical outcomes and who will do so. This is address in figure 3, but I think a bit of detail in the text would be helpful. STATISTICAL ANALYSIS --sample size, starting bottom of page 8. This section seems long and is not clear to me. The primary outcome is stated to be "composite score based on the average z-score of the difference between baseline and 18 months follow-up values of systolic blood pressure, low-density-lipoprotein (LDL) and body mass index (BMI)," yet the sample size section starts with "based on a proportion." I don't think this is consistent. --page 10, line 13. "Depending on the outcomes of the CEA and CUA it will be assessed whether a modelling scenario of internet counselling with a lifetime horizon is opportune and if so, how it should be elaborated." Not sure use of wording "opportune" and "elaborated" is appropriate. I think a bit more detail would be useful. DISCUSSION --page 10, line 32. s[47](C.R.L. Beishuizen et al., 2015), Include the Beishuizen reference as a number.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Richard McManus

University of Oxford, UK

Please leave your comments for the authors below This is a protocol for an EU funded study that will have previously undergone extensive peer review and has already started with ethics committee approved protocols. There is therefore little that can be changed. The trial was registered in 2014 and appears to have been sensibly designed. Given the fact that the study takes place in three countries, it would be worth the authors stating how they will ensure that the interventions are as similar as possible in each country and centre and what efforts they will make to record precisely how the interventions -albeit triggered by the same internet based coaching system - are actually delivered. It might be worthwhile including a process evaluation section to this end. The primary composite outcome is rather unusual and difficult to understand from a clinical stand point however the individual end points that are included as secondaries should allow interpretation. My other concern is that although a statistical analysis plan will no doubt be produced prior to analysis, this should be specifically stated. In addition, whilst a secondary analysis will take into account baseline differences, I would have thought (and indeed the authors state) that country and centre effects may be great and these should be taken into account in the analysis. It would be sensible - if the authors agree - to state this prospectively.

Thank you for your comments; we would like to address them all. It is indeed a challenge to assure the similarity of the intervention between countries and coaches. Strict guidelines for all coaches are captured in a coach protocol, set up by the research team, and translated in the three languages. We have added a section to make this more explicit in the manuscript (page 5, paragraph 'Intervention'). We also organise regular meetings with the coaches nationally and internationally to discuss challenges and tips and tricks in order to strive for a uniform approach. Although we aim to have a uniform intervention in every country, there is indeed a risk of differences between countries, centres or coaches. We have now explicitly stated this point in the manuscript, we will correct for country, centre and coach differences. (data analysis section on page 8).
We have adapted the text and have now specifically stated that the analysis plan will be finalized prior to the data analysis. We agree with the reviewer that although this might be obvious, it is best to clarify this in the manuscript. (page 9, paragraph 'Data analysis')

Reviewer: 2

Thomas C. keyserling, MD, MPH

Professor of Medicine
University of North Carolina at Chapel Hill

Please leave your comments for the authors below Comment for author are below with additional comments for author and editors.

--I note that the methods are not described sufficiently for this study to be repeated. This was marked because the details of the content of the intervention are not given. I do not think it needs to be given for this paper. It should be included as a supplement when results are published.

We thank the reviewer for this comment. We agree that the full study protocol of an RCT should be included as an online supplement when RCT-data are published.

--regarding statistics, see comments below about sample size.

--concerning standard of written English, I think the text is reasonable, but with some wording that is not clear or could be improved. I address this in the comments for the authors.

We thank the reviewer for these comments. We have addressed most of them and if not, we explained the reason why.

ABSTRACT

--page 3, line 7. Change “great opportunities” to “increasing opportunities” or something like that.

We have changed the word ‘great’ into ‘increasing’.

--page 3, line 27. Should “mood” be “quality of life?”

We understand the confusion about the stated secondary outcome ‘mood’, but we do intend to assess mood. Depressive symptoms and depression have repeatedly been related to cardiovascular disease and its risk factors. Therefore we include this as a secondary outcome. We do assess ‘quality of life’ with the EQ5D EuroQol to transpose into quality adjusted life years (QALY) for the cost utility analyses, but QOL is not one of the clinical secondary outcomes.

--page 3, line 38. I think “easy implementable” should be “easily implementable”

We changed this.

--page 3. Line 44. “Limitations include the relatively short follow-up and the impossibility to operate double blind.” “Impossibility to operate double blind.” This refers to the fact that the intervention cannot be blinded. This in inherent in lifestyle studies. I am OK dropping this. The study will utilize a blinded research assistant for assessment of 18 month outcomes and a blinded adjudication committee for clinical outcomes. These approaches address “blinding” issues for this trial in an appropriate fashion.

We understand the point of the reviewer. We have dropped this limitation. The 18-months blinded outcome assessment is clearly described.

INTRODUCTION (all page 4)

--line 27. This sentence starting with, “In spite of clear…” is not clear and I don’t think entirely accurate, as there are clinical guideline for management of some CVD risk factors among the elderly; specifically, hypertension.

We have changed ‘only for younger adults’ into ‘mainly for younger adults’. There are indeed guidelines for hypertension management in older adults, but not for the oldest old and the scientific underpinning is less robust than for younger age groups. In spite of guidelines, including target values for the specific risk factors, targets are often not met. This leads to a large window of opportunity for improvement of the cardiovascular risk profile.

--line 33. Patient self-management is a potentially powerful strategy to improve adherence to therapy in CVD [19, 20] risk reduction.

We have added the words ‘risk reduction’ as the reviewer suggested, since that is indeed what we meant.

--line 46. The internet has become a major source of information for people of all ages, and its use among older people throughout Europe has increased dramatically, making it a potentially suitable medium for the delivery of widely implementable health care interventions [24].

We have added the word ‘interventions’ as the reviewer suggested.

METHODS

--page 5, line 20. Table. Please provided more information on history of cardiovascular disease and

diabetes. Are these health care provider diagnoses? Is diabetes defined by A1c or fasting blood glucose levels?

We have added the sentence ‘diagnosis by specialist or GP’ in the table for these diagnoses. This was indeed inconsistent and unclear, since this was explicitly stated for other inclusion criteria (hypertension and dyslipidaemia). History of diabetes is defined as previously diagnosed by a GP or specialist; it is not defined by blood glucose or HbA1C levels.

--page 6, starting line 36. Due to the heterogeneous population in this trial, which includes participants with elevated cardiovascular risk with or without established CVD, primary as well as secondary prevention guidelines will be applied

We have added the word ‘guidelines’ as the reviewer suggested.

--page 7, line 32. I don’t think there should be a comma after aging. Also, I think the ASCVD pooled risk factor equation (2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. doi: 10.1161/01.cir.0000437741.48606.98) may be superior to the Framingham Risk Score and recently seems to be well supported by the literature.

We removed the comma.
We agree with the reviewer that the ASCVD pooled risk factor equation seems to be a more valid measure than the Framingham risk score, although both measures are not entirely appropriate for our study. Both equations are validated for secondary prevention and our population is mixed secondary and primary prevention. We decided to use a well-known risk measurement as secondary outcome. In fact the mixed population of primary and secondary prevention is the reason we have constructed our primary outcome the way we have, instead of using either the Framingham risk score or the ASCVD risk equation as primary outcome. We think changing into the ASCVD will not make a substantial difference, because similar to the Framingham risk score it is not validated in a mixed population like ours. We therefore choose not to change this secondary outcome.

--page 8 line 7. Consider alternative wording to “stimulate,” possible “facilitate.”

We have changed stimulate into facilitate.

--page 8, line 12. The participants from the intervention group will have an additional interview with a strong focus “on motivation talk with their own coach.” “On motivation talk with their own coach” is not clear. Please improve this wording.

We have improved the wording by removing the word ‘talk’.

--page 8, line 19. “All data with be anonymized.” I don’t think data with be anonymous, but more likely, coded with a number, to insure confidentially.

We agree with the reviewer. We have changed this into coded and clarified that this is done to assure confidentially.

--page 8, line 46. “(myocardial infarction, stroke, transient ischemic attack/angina pectoris/peripheral arterial disease/diabetes mellitus).” Suggest using all commas instead of commas and back slashes.

We have changed the back slash into commas.

--in the methods sections, please add paragraph on what type of data with be used to adjudicate clinical outcomes and who will do so. This is address in figure 3, but I think a bit of detail in the text would be helpful.

Since this is only explained in figure 3, this may need some additional textual explanation indeed. We have summed the clinical diagnoses in the secondary outcome paragraph that will be judged by the independent outcome committee. We will collect correspondence about the new diagnoses from hospitals and specialists/GPs. Every country (Finland, France and the Netherlands) will have its own

committee, since all the correspondence about these diagnoses will be in the language of the participant that it concerns. Each committee will consist of doctors who can adequately judge these diagnoses and who are not involved in the trial otherwise.

STATISTICAL ANALYSIS

--sample size, starting bottom of page 8. This section seems long and is not clear to me. The primary outcome is stated to be “composite score based on the average z-score of the difference between baseline and 18 months follow-up values of systolic blood pressure, low-density-lipoprotein (LDL) and body mass index (BMI),” yet the sample size section starts with “based on a proportion.” I don’t think this is consistent.

We understand this paragraph was a bit confusing. We have shortened it and adapted the text on the sample size calculation based on proportions and a continuous primary outcome, in order to clarify this (paragraph statistical analysis – sample size, page 8)

--page 10, line 13. “Depending on the outcomes of the CEA and CUA it will be assessed whether a modelling scenario of internet counselling with a lifetime horizon is opportune and if so, how it should be elaborated.” Not sure use of wording “opportune” and “elaborated” is appropriate. I think a bit more detail would be useful.

We think these words are appropriate, although this was indeed not well explained. We have tried to explain these two words in the following sentences in the manuscript.

DISCUSSION

--page 10, line 32. s[47](C.R.L. Beishuizen et al., 2015), Include the Beishuizen reference as a number.

This reference is recently accepted for publication. We have incorporated the reference in the manuscript now. In the regulations of the BMJ Open it is stated that; “Only papers published or in press should be included in the reference list. Personal communications or unpublished data must be cited in parentheses in the text with the name(s) of the source(s) and the year.” Since the reference is now in press, the reference is included in the reference list.

VERSION 2 – REVIEW

REVIEWER	Richard McManus University of Oxford UK I have received BP monitoring equipment for research from Omron and Lloyds pharmacies and travel expenses and honoraria from JSH and ASN to speak at conferences.
REVIEW RETURNED	09-Feb-2016

GENERAL COMMENTS	I think that this is now fine and do not require any further revisions

REVIEWER	Thomas C. Keyserling, MD, MPH University of North Carolina at Chapel Hill
REVIEW RETURNED	19-Feb-2016

GENERAL COMMENTS	Regarding no responses above, #4 I addressed in my initial review. I think the authors did an excellent job with revisions. I accept their

	rationale for not making some of the changes I suggested. My only additional suggestion is below. --first sentence under sample size: “Although the primary outcome is a continuous measure, the sample size calculation was based on proportion of participants successfully improving on the composite score. The threshold defining ‘improvement’ will be based on the effect-sizes observed in the datasets of the three previous RCTs[14, 27, 28], all applying similar types of interventions in comparable populations.” I think “will be” should be “was,” as sample size was set prior to beginning the trial.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Richard McManus
University of Oxford UK

Please leave your comments for the authors below I think that this is now fine and do not require any further revisions.

Thank you very much.

Reviewer: 2
Thomas C. Keyserling, MD, MPH
University of North Carolina at Chapel Hill

Please leave your comments for the authors below Regarding no responses above, #4 I addressed in my initial review.

I think the authors did an excellent job with revisions. I accept their rationale for not making some of the changes I suggested. My only additional suggestion is below.

--first sentence under sample size: “Although the primary outcome is a continuous measure, the sample size calculation was based on proportion of participants successfully improving on the composite score. The threshold defining ‘improvement’ will be based on the effect-sizes observed in the datasets of the three previous RCTs[14, 27, 28], all applying similar types of interventions in comparable populations.” I think “will be” should be “was,” as sample size was set prior to beginning the trial.

Thank you very much for this last comment. We tried to clarify it. Until now, defining this threshold was not possible, because data on which it will be based have not been published yet. The moment this is possible, we will define the threshold, since this will allow for a translation of our expected treatment effect on our intermediate primary outcome into clinical relevance. We have changed the first words of the sentence.

“Although the primary outcome is a continuous measure, the sample size calculation was based on proportion of participants successfully improving on the composite score. The A new threshold defining ‘improvement’ will be based on the effect-sizes observed in the datasets of the three previous RCTs[14, 27, 28], all applying similar types of interventions in comparable populations.”