PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A pilot randomised controlled trial of a structured, home-based exercise program on cardiovascular structure and function in kidney transplant recipients: The ECSERT study design and methods
AUTHORS	Billany, Roseanne; Vadaszy, Noemi; Bishop, Nicolette; Wilkinson, Thomas; Adenwalla, Sherna; Robinson, Katherine; Croker, Kathryn; Brady, Emer; Wormleighton, Joanne; Parke, Kelly; Cooper, Nicola; Webster, Angela; Barratt, Jonathan; McCann, Gerry; Burton, James; Smith, Alice; Graham-Brown, Matthew

VERSION 1 – REVIEW

REVIEWER	Rolid, Katrine Oslo University Hospital, Dep of Cardiology
REVIEW RETURNED	08-Jan-2021

GENERAL COMMENTS	Thank you for the opportunity to review the paper entitled:"A pilot randomised controlled trial of a structured, home-based exercise program on cardiovascular structure and function in kidney transplant recipients: The ECSERT study design and methods by the authors Billany et al. This is a very interesting pilot study. The paper is well written. I have a few comments: The primary objective of this study is to asses: "1.The deliverability and feasibility of the home-based exercise intervention in KTRs, defining recruitment, retention, and compliance (line 140-141)." In the method and analysis section of the abstract (lines 48-57) it is however not clear that this is the primary aim. I suggest to rewrite the following sentence (lines 55-57) "The study will also evaluate the feasibility of recruitment, randomisation, retention, assessment procedures, and the intervention implementation". such as it is clear that this is the main objective of the study, and how this will be assessed (outcomes). In addition, I suggest to move the sentence up (before the other outcomes reported). Background: :The authors might include an updated systematic review in exercise training after kidney transplantation.E.g three reviews have been published during 2018-2019. Oguchi, H., Tsujita, M., Yazawa, M. et al. The efficacy of exercise training in kidney transplant recipients: a meta-analysis and systematic review. Clin Exp Nephrol 23, 275–284 (2019). https://doi.org/10.1007/s10157-018-1633-8 ,

	Gang Chen, Liu Gao & Xuemei Li (2019) Effects of exercise training on cardiovascular risk factors in kidney transplant recipients: a systematic review and meta-analysis, Renal Failure, 41:1, 408-418, DOI: 10.1080/0886022X.2019.1611602 and Calella, P., Hernández-Sánchez, S., Garofalo, C. et al. Exercise training in kidney transplant recipients: a systematic review. J Nephrol 32, 567–579 (2019). https://doi.org/10.1007/s40620-019-00583-5. The authors should include a reference to the last sentence/statement "Many KTRs have had enforced sedentary lifestyles prior to transplantation as dialysis patients and their goals for rehabilitation as well as the disease processes at work may be different " (lines 134-136). Methods and analysis: Aerobic component (lines 182-183). Have the authors considered to objectively measure the exercise intensity? E.g by % of maximal heart rate and use a heart rate monitor to monitor the exercise intensity in addition to RPE in the aerobic exercise sessions? Cardiopulmonary exercise test (lines 250-260): I suggest to add some more information about the CPET test. E.g that the test is symptom-limited and information about criterias for an "acceptable" VO2peak test, e.g measured by RPE and/ or respiratory exchange ratio (RER). The authors should also add information about ECG and blood-pressure measurement before and during the test. Survey pack (lines 296-322).:Have the authors suggested to include a kidney transplant specific health-related quality of life questionnaire? A disease specific questionnaire might be more sensitive to changes in health related quality of life than the generic (SF-12). The dates of the study (start and completion) should be included in the manuscript.

REVIEWER	Tierney, Seda Stanford University
REVIEW RETURNED	25-Jan-2021

GENERAL COMMENTS	This is a design paper on a randomized clinical intervention on kidney transplant patients, a patient population with a high cardiovascular risk profile. The investigators will test the feasibility of delivering a structured, home based exercise intervention and evaluated the adherence and the impact on cardiovascular health, quality of life, and health care utilization. Patients will be randomized to a 12-week home- based combined resistance and aerobic exercise intervention or usual care. Intervention participants will have an introductory session for instruction and practice of the recommended exercises prior to receiving an exercise diary, dumbbells, resistance bands, and access to instructional videos.

	Outcomes will include cardiac structure and function with stress-perfusion cardiac magnetic resonance imaging, cardiorespiratory fitness, physical function, blood biomarkers of cardiometabolic health, quality of life, and patient activation. The study will also evaluate the feasibility of recruitment, randomization, retention, assessment procedures, and the intervention implementation. These data will be used to inform the power calculations for future definitive trials. This is a very well-designed protocol. The investigators plan to perform a comprehensive assessment. The only comment I have is that they need to make their check-in protocol much more robust than described. The patients might need daily check-ins via text and weekly check-ins via phone call or videoconferencing for adequate adherence. Often, these patients are not familiar with exercise in any shape or form and need a lot motivation to overcome the inertia.

REVIEWER	Totti, Valentina University of Bologna, Department of Biomedical and Neuromotor Sciences
REVIEW RETURNED	01-Feb-2021

GENERAL COMMENTS	Dear author Thank you for an interesting study. The aims of the study are absolutely relevant. However, this reviewer suggests some major changes before it may be published. The text is very confusing, please divide better between chapters and sub chapters and specify the methods well. A certified native English language review is required. There are many mistakes. 1. The language needs a better flow, and a revision of it is needed ABSTRACT - line 38: specify which CVD risk score is being discussed - line 45: explane what you mean with "patient activation" In general methods have to be explain better, specify the tools for detecting the variables that will be collected. ARTICLE SUMMARY Before the study are baseline physical activity levels assessed in the two groups? Even if the two groups are randommized, there is no test that evaluates the aptitude or in any case the starting physical activity level of the patients. Please add or justifies. - line 82: you write "musclular effects" but you never say before in the abstract. With which tests or blood parameters are muscular effects evaluated? Please add and explain better. BACKGROUND - line 87 I suggest to change "modality", please rephrase the sentence. - line 89 Add the reference about the significant survival advantage over remaining on dialysis. - line 91-93, to much repetions about "which drive" anche the sentence is redundant. Please make the sentence more fluid by also connecting the next part (line 95-97) relating to traditional and non-traditional risk factors. - line 114 Add more recent references releted to 24-26

	- line 115-119 there are redundant concepts, making sentences more fluid and connected. You name a "meeting national", which countries are you referring to? Is it a study on the national trend? Please quote the correct references and explain. Add the WHO reference. - line 120-125 please add more recent references releted to 34-40. The same for 46-47. - line 131-132 "but the effectiveness and deliverability of home-based exercise interv are untested in KTRs". This statement is incorrect. Please read the article of Painter P. et al. "A randomized trial of exercise training after renal transplantation" - line 140-141, please consider also the adverse events as you mention after in the manuscript - line 140-147 please add for each variables the assessment tools that will be used, for example which biochemical markers of cardiometabolic health will be used? - line 151, what do you mean by "healthy controls"? General population or other? With what characteristics? Please specify. METHODS AND ANALYSIS - line 159-160 unnecessary information - line 161 please add the inclusion and exclusion criteria in the text. - line 177 please indicate the precise number of sessions in total per week and also add the total number of training hours per week - line 182 please indicate the precise number of aerobic sessions per week - line 197 you say "at 60% 1 repetion maximum (RM)" first of all, an "of" is missing and also how and when will it be evaluated in the patient? Indicate scientific evidence of why 60% of 1 RM was chosen. As for the "control group" I would put a sub-chapter for the intervention group for greater clarity. - line 210-211 "continue to attend any clinic schedule ...." please also specify for the intervention group. - line 220 Please insert the study timeline in the text for clarity. - add capter related to the tests. The capter "study timeline" it is not explanatory in relation to the content of the text. - line 249 add specific parameters of muscle quality and size. It is also not described previously at any point in the manuscript. - line 273 "4 m", put "m" in full. Please specify that an initial test will be made to practice the patient and then two official tests. - line 281 "previosly reported method" it does not appear anywhere in the text. Please add the parameters/variables that the device measures. - quote 54 "as previously described" it does not appear before in the text. - line 295 "is validated for CKD...." redundant, the correct reference is sufficient. - line 310-311 redundant, the correct references are sufficient. - line 325 when will it be delivered? To both groups? - line 329-334, specify the markers (IL-6, IL-8, etc.) eGFR or creatinine? Justify the reason for choosing urinary protein: creatinine ratio. For each test insert the references if not included. - line 336 write the follow up visits in the text.

	- line 346 what do you mean by "pragmatic development"? Please specify - line 353 "healthy control" Do you mean not transplanted or what? With what characteristics? - line 459 frequency, intensity and duration of the exercises are not specified first in the methods then correct. - line 459-460 Discuss the statement "This is often a limitation of unsupervised interventions". Expanding the discussion regarding the benefits of this type of exercise linked to cardiovascular, renal parameters and all the variables that are considered in the methods (strength, aerobic capacity, gait speed, mobility, etc.) also for the future studies/developments. Finally, update the References with more recent papers on the most relevant issues.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

We thank reviewer 1 for their kind comments.

The primary objective of this study is to asses: "1.The deliverability and feasibility of the home-based exercise intervention in KTRs, defining recruitment, retention, and compliance (line 140-141)." In the method and analysis section of the abstract (lines 48-57) it is however not clear that this is the primary aim. I suggest to rewrite the following sentence (lines 55-57) "The study will also evaluate the feasibility of recruitment, randomisation, retention, assessment procedures, and the intervention implementation". such as it is clear that this is the main objective of the study, and how this will be assessed (outcomes). In addition, I suggest to move the sentence up (before the other outcomes reported).
We agree that this is not clear. We have moved and amended this sentence within the abstract.

Background: :The authors might include an updated systematic review in exercise training after kidney transplantation.
We agree and have replaced reference 34 with this up to date review.

The authors should include a reference to the last sentence/statement "Many KTRs have had enforced sedentary lifestyles prior to transplantation as dialysis patients and their goals for rehabilitation as well as the disease processes at work may be different " (lines 134-136).
Thank you, we have included 2 references. One showing the impact of dialysis days on physical activity levels and one showing the difference in physical activity between patients on dialysis and transplant recipients which represents the potential for different goals and requirements between the populations.

Methods and analysis: Aerobic component (lines 182-183). Have the authors considered to objectively measure the exercise intensity? E.g by % of maximal heart rate and use a heart rate monitor to monitor the exercise intensity in addition to RPE in the aerobic exercise sessions?
There was considerable discussion around this topic during the set-up stage of the trial. We chose not to include heart rate monitoring for two reasons: (1) many patients are on medication which impacts heart rate (e.g beta-blockers). We therefore cannot ascertain a true maximal heart rate from the exercise test in order for them to safely (and reliably) monitor intensity this way without supervision. (2) This is also a pragmatic decision based on the potenial for translation

into future studies and then clinical practice. The use of RPE to guide exercise intensity requires no additional costs, whereas heart rate monitors would. Should participants in the trial already own a smart watch or heart rate monitor however, we would not discourage them from using it if they wish to. We have added details around this discussion within the manuscript.

Cardiopulmonary exercise test (lines 250-260): I suggest to add some more information about the CPET test. E.g that the test is symptom-limited and information about criterias for an "acceptable" VO2peak test, e.g measured by RPE and/ or respiratory exchange ratio (RER). The authors should also add information about ECG and blood-pressure measurement before and during the test.
Thank you, we have added details around ECG and blood pressure and agree that these are needed. We agree and have also added 2 criteria for the usability of the VO2peak tests: RER ≥1.00 and RPE ≥18. RER is perhaps lower than we would use in a 'healthy' population but this cut-off has previously been utilised in patient populations based on the fact that they are likely to have symptoms before reaching maximum. We would not include criteria based on a plateau in VO2 because this would be unlikely in an untrained population. As per the comment above, we would also not add a criteria based on heart rate given the wide variety and quantities of medications taken by these participants that directly influence heart rate.

b>Survey pack (lines 296-322).:Have the authors suggested to include a kidney transplant specific health-related quality of life questionnaire? A disease specific questionnaire might be more sensitive to changes in health related quality of life than the generic (SF-12).
Thank you, this is a valid point. Unfortunately, we are not in a position to change this now as the trial is well underway and this outcome measure has been included. We are grateful for this comment though and we will include this in future studies. It is encouraging to see that the SF-36 has been deemed valid and reliable in the kidney population (https://pubmed.ncbi.nlm.nih.gov/15205553/). The SF-12 has been compared to the SF-36 and deemed valid in the dialysis population which is somewhat reassuring (https://cjasn.asnjournals.org/content/5/2/252).

The dates of the study (start and completion) should be included in the manuscript.
Many thanks, we have added the date of the first participant recruited and the expected study completion date to the ethical issues section.

Reviewer 2

We would like to thank reviewer 2 for their kind comments. Thanks for the comments around check-ins, we have clarified the regularity of check-ins within the text and the changes that have been necessarily made due to COVID. To be clear, we plan to have telephone calls/video calls every 2 weeks, but study participants are able to contact the study team at any time. Daily calls are not feasible to deliver and, moreover, would not be translatable into a clinical setting.

Reviewer 3

Thank you. We were surprised by the comments about the language and that a native English review is required given that all the authors are native English speakers. We have reviewed the manuscript and disagree that there are ‘many mistakes’ in the language. Equally, the paper is structured in the format outlined by BMJ Open Guidelines for authors and in keeping with the CONSORT statement on reporting for clinical trials. As per reviewers 1 and 2, we believe the manuscript is clearly laid out and we have not made changes to the language or formatting. Additionally, the paper is presented as per the SPIRIT checklist which is uploaded as part of the submission.

line 38: specify which CVD risk score is being discussed

Thank you, unfortunately we are unable to include references in the abstract. The risk scores we refer to are referenced in the introduction.

line 45: explane what you mean with "patient activation"

Unfortunately we do not have the space to explain this within the abstract. We have however, defined patient activation within the background.

Before the study are baseline physical activity levels assessed in the two groups? Even if the two groups are randommized, there is no test that evaluates the aptitude or in any case the starting physical activity level of the patients. Please add or justifies.

Many thanks, for clarification, baseline physical activity is assessed directly with 7-day accelerometer reading as defined in the methods. Additionally we are capturing self-reported physical activity with a questionnaire (GPAQ).

line 82: you write "musclular effects" but you never say before in the abstract. With which tests or blood parameters are muscular effects evaluated? Please add and explain better.

Thank you, it would be nice to include all outcome measures in the abstract, but due to limitations in space this is not possible. The rationale for assessing muscular function is justified within the manuscript and we do not feel the addition of specific detail on these assessments are needed as a priority in the abstract.

line 87 I suggest to change "modality", please rephrase the sentence.
Thank you, modality is a commonly used word to describe the mode of renal replacement therapy patients undertake and is accepted language for clinicians, patients and researchers.

line 89 Add the reference about the significant survival advantage over remaining on dialysis.
Many thanks, this has been added.

line 91-93, to much repetions about "which drive" anche the sentence is redundant. Please make the sentence more fluid by also connecting the next part (line 95-97) relating to traditional and non-traditional risk factors.
Many thanks, we have adjusted these sentences.

line 114 Add more recent references releted to 24-26
Thank you, we have amended these references.

line 115-119 there are redundant concepts, making sentences more fluid and connected. You name a "meeting national", which countries are you referring to? Is it a study on the national trend? Please quote the correct references and explain. Add the WHO reference.
Thank you, we are not sure what is meant by redundant concepts, but agree adding which National standards we are referring to is helpful and have added this.

line 120-125 please add more recent references releted to 34-40. The same for 46-47.

Thanks, reference 40 is the most up to date systematic review on this topic. For the factors mentioned in references 36-46, there are very limited newer studies in this population.
We have added some references in relation to 47 and replaced 46 with a newer review. Please note that reference numbers may have now changed.

line 131-132 "but the effectiveness and deliverability of home-based exercise interv are untested in KTRs". This statement is incorrect. Please read the article of Painter P. et al. "A randomized trial of exercise training after renal transplantation"

Thank you, this should have read ‘largely untested’ and we have amended this.

line 140-141, please consider also the adverse events as you mention after in the manuscript

Thank you, this has now been amended.

- line 140-147 please add for each variables the assessment tools that will be used, for example which biochemical markers of cardiometabolic health will be used?

Thanks, this section is an overview of the objectives. Detailed information is within the method section including specific markers so we have not amended this section here.

line 151, what do you mean by "healthy controls"? General population or other? With what characteristics? Please specify.

Thank you, healthy controls are defined by the inclusion/exclusion which are now included in Table 1.

line 159-160 unnecessary information

Thanks, for the purpose of feasibility it is important to understand the pool of participants who are potentially eligible to take part in the study so as future estimates of recruitment rates can be made. This is a fundamentally important criterion to include for the feasibility aspects of this study and suggest this information remains.

line 161 please add the inclusion and exclusion criteria in the text.
Thank you, the manuscript is over the word limit (we have explained to the editor that this is because we have added details of how the protocol was amended due to COVID-19). In line with standard practices it is also inadvisable to duplicate information within the text that exists in a table. We feel the inclusion/exclusion criteria sit well in the table and addition to the text is unwarranted.

line 177 please indicate the precise number of sessions in total per week and also add the total number of training hours per week
Thank you, these details are included in subsequent sections for each type of exercise that participants are undertaking. We do not have a specific number of training hours as participants may choose their duration (20-30 min for aerobic). Participants can also choose the number of resistance exercises (6-8) and the number of sets they perform. We therefore cannot put a number of minutes/hours. All of this information will be reported as part of the feasibility.

line 182 please indicate the precise number of aerobic sessions per week
Thank you, 2-3 session is the number of sessions; this provides the participants with a choice. Less active participants may start at 2 which is more manageable and then progress to 3.

line 197 you say "at 60% 1 repetion maximum (RM)" first of all, an "of" is missing and also how and when will it be evaluated in the patient? Indicate scientific evidence of why 60% of 1 RM was chosen
Thanks, we have added further clarity to this section with regards to equipment limitations. We have added a reference of the method that will be used to estimate 1RM. Regarding why we have used 60% of 1RM, it is important to find a weight that is effective at making physiological changes but also that does not put off participants (particularly as many are untrained and/or inexperienced). In the review by Schoenfeld et al., they analysed the impact of light (<60% of 1RM) and heavy (>60% of 1RM) loads. Whilst the analysis did favour heavier loads for increasing strength, the effect size was still large for lighter loads. And in terms of muscle size, both light and heavy loads were effective. As the results did not show a clear advantage of higher loads, we chose the higher end of the lighter loads/lower end of the heavier loads. This justification is added to the text.

line 210-211 "continue to attend any clinic schedule ...." please also specify for the intervention group.
Thank you, we have added a sentence on this to the intervention section.

line 220 Please insert the study timeline in the text for clarity.
Thank you, this will be included within the text upon publication.

line 249 add specific parameters of muscle quality and size. It is also not described previously at any point in the manuscript.
Thanks, as previously described is referring to the reference (64) of which is a publication by our group showing the method of assessment. We have added details on the parameters.

line 273 "4 m", put "m" in full. Please specify that an initial test will be made to practice the patient and then two official tests.
Thank you, m is a standard unit and therefore should be acceptable. We have left this unchanged.

line 281 "previosly reported method" it does not appear anywhere in the text. Please add the parameters/variables that the device measures
“Previously reported method” refers to the reference at the end of the sentence. Full details are reported within this paper by our group. The parameter has been added.

line 295 "is validated for CKD...." redundant, the correct reference is sufficient.
Thank you, this has been removed.

line 310-311 redundant, the correct references are sufficient.
Thank you, this has been amended.

line 325 when will it be delivered? To both groups?
Thank you, details have been added.

line 329-334, specify the markers (IL-6, IL-8, etc.) eGFR or creatinine? Justify the reason for choosing urinary protein: creatinine ratio.
Thank you, the biomarker panels are extensive and there is not room for a comprehensive list. These will be detailed and justified in results manuscripts. Urine PCR is a standard clinical measure of renal disease and is routinely acquired as part of clinical visits. Its prognostic value is unquestioned. Researchers in the field and clinicians have absolute understanding of the importance of this measure. eGFR is included within the ‘renal profile’.

line 336 write the follow up visits in the text.
The text following this sentence describes the visits.

line 346 what do you mean by "pragmatic development"? Please specify
Thanks, by pragmatic development we mean that we will use the written patient feedback to adjust the intervention for future studies rather than just base adjustments on our own thoughts as researchers.

line 353 "healthy control" Do you mean not transplanted or what? With what characteristics?
Than you, please see reply to previous comment on ‘healthy controls’.

line 459 frequency, intensity and duration of the exercises are not specified first in the methods then correct.
Thank you, we are allowing flexibility in how much participants do. We have specified ranges within the method (for example aerobic exercise of 20-30 mins). We will ask participants to report exact values within their diaries.

line 459-460 Discuss the statement "This is often a limitation of unsupervised interventions"
Thank you, we have made this sentence clearer as it is linked to the previous sentence.

Expanding the discussion regarding the benefits of this type of exercise linked to cardiovascular, renal parameters and all the variables that are considered in the methods (strength, aerobic capacity, gait speed, mobility, etc.) also for the future studies/developments.
Thank you, whilst we agree discussion of this kind is interesting, this is a protocol paper not a review article and the literature presented adequately explains the rationale for the study. A detailed review of the literature is beyond the scope of this particular work.

Finally, update the References with more recent papers on the most relevant issues.
Thank you we have updated some of the references throughout where appropriate.

VERSION 2 – REVIEW

REVIEWER	Totti, Valentina University of Bologna, Department of Biomedical and Neuromotor Sciences
REVIEW RETURNED	04-May-2021

GENERAL COMMENTS	Thank you for this valuable contribution on a topic that is now so important as exercise and lifestyle changes to increase post-transplant longevity. I report my review below: - Pag 4, line 116, I suggest to add recent reference like Masiero et al. Physical activity and renal function in the Italian kidney transplant population

	- pag 5 line 151, Please specify what you mean with 'healthy controls'. Will they be not transplant? Please add this information. - pag 6 line 155, your writed "blinded" and after (line 175) you writed that "given the nature of the intervention, it is not possible for the partecipants to be blinded to their allocation. Please correct line 155. - pag 6 line 160-161 Please add the specification that the inclusion and exclusion criteria will apply to all participants (all KTRs and the healthy controls enrolled for the substudy). - pag 7 line 202 Add references, if any - pag 7 line 204, please specify by whom and when the submaximal strength test will be performed for the calculation of 1RM - pag 8 the title "study timeline" I would not put it in bold and the title "baseline assessments" I would put it in bold as the main title above "collection of routine information ..." - pg 9 line 282, add reference about these tests - page 10 line 283-284, explain why the sit to stand 60 test is also performed, what do you evaluate specifically - page 10, line 287 add reference related - page 10 line 291, add reference related -page 10, line 300 add reference - pag 12, before "follow up assessments" I suggest to insert the part that goes from pag 13 line 400 to pag 14 line 413 - about the sub-studies, do you think 10 healthy controls are enough to assess the differences? please comments -pag 13 line 378, add reference, if any -pag 16 line 479, add reference, if any I suggest that you also consider this recent article https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7230877/ and add it in the references chapter. - pag 25 table 1 please fix the exclusion criteria which appear the same for both groups. You can simply insert a dividing line.

VERSION 2 – AUTHOR RESPONSE

Reviewer 3

We would like to thank the reviewer for their kind comments.

Pag 4, line 116, I suggest to add recent reference like Masiero et al. Physical activity and renal function in the Italian kidney transplant population
Thank you, we have added the suggested reference.

pag 5 line 151, Please specify what you mean with 'healthy controls'. Will they be not transplant? Please add this information.
Thank you, we have added detail to this.

pag 6 line 155, your writed "blinded" and after (line 175) you writed that "given the nature of the intervention, it is not possible for the partecipants to be blinded to their allocation. Please correct line 155.
Thank you for your comment. A PROBE study is an alternative to the double-blind, prospective study design. In this type of study, patients are allocated randomly different treatment regimens but unlike double-blind studies, the regimens are obvious to both researchers and patients and it is the endpoints that are blinded to an independent committee who are unaware of treatment allocation. Therefore the information in the text is still correct.

pag 6 line 160-161 Please add the specification that the inclusion and exclusion criteria will apply to all participants (all KTRs and the healthy controls enrolled for the substudy)
Thank you, healthy control inclusion/exclusion criteria are introduced in lines 168-169.

pag 7 line 202 Add references, if any
Thank you for your suggestion. There are no specific references for these exercise modifications. However, they were designed by a suitably qualified member of the team.

pag 7 line 204, please specify by whom and when the submaximal strength test will be performed for the calculation of 1RM
Thank you, the details have been added.

pag 8 the title "study timeline" I would not put it in bold and the title "baseline assessments" I would put it in bold as the main title above "collection of routine information ..."

Thank you, we have amended this.

pg 9 line 282, add reference about these tests
Thank you, we have added a reference.

page 10 line 283-284, explain why the sit to stand 60 test is also performed, what do you evaluate specifically
Thank you, details have been added.

page 10, line 287 add reference related
Thank you, we have added a reference.

page 10 line 291, add reference related -page 10, line 300 add reference
Thank you, these references have been added.

pag 12, before "follow up assessments" I suggest to insert the part that goes from pag 13 line 400 to pag 14 line 413
Thank you for your suggestion. We feel that the section regarding feasibility analysis falls better within ‘data analysis’ rather than under the ‘baseline assessments’ heading as suggested.

about the sub-studies, do you think 10 healthy controls are enough to assess the differences? please comments
This sub-study is the first to explore this relationship and is designed only as an exploratory analysis which can be expanded on in future studies with larger sample sizes.

pag 13 line 378, add reference, if any -pag 16 line 479, add reference, if any I suggest that you also consider this recent article https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.ncbi.nlm.nih.gov%2Fpmc%2Farticles%2FPMC7230877%2F&data=04%7C01%7Cr.billany%40leicester.ac.uk%7Cc8e57491dd2c4924600308d9566d3a21%7Caebecd6a31d44b0195ce8274afe853d9%7C0%7C0%7C637635849401462292%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=rxbYYjjgzYUxNkT%2BGV4IdlHFerU8G7uM6eSZwhp8AOo%3D&reserved=0 and add it in the references chapter.
Thank you. There are no references for line 378 and we have added a relevant reference to 478/479.

pag 25 table 1 please fix the exclusion criteria which appear the same for both groups. You can simply insert a dividing line.
Thank you, we have made this clearer.