PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	High-intensity Interval exercise Training before Abdominal Aortic Aneurysm repair (HIT-AAA): protocol for a randomised controlled feasibility trial
AUTHORS	Tew, Garry; Weston, Matthew; Kothmann, Elke; Batterham, Alan; Gray, Joanne; Kerr, Karen; Martin, Denis; Nawaz, Shah; Yates, David; Danjoux, Gerard

VERSION 1 - REVIEW

REVIEWER	Karin Valkenet University Medical Center Utrecht, The netherlands
REVIEW RETURNED	23-Oct-2013

GENERAL COMMENTS	Outstanding protocol with very detailed description of objectives and procedures. In the introduction the authors state that about half of all AAA surgery patients have decreased cardiopulmonary (CP) fitness which is a risk of impaired post-operative outcome. Therefore I expected that this protocol would only include the patients with decreased CP fitness. Since all patients will be included, I suggest that the authors provide their thoughts about applying their protocol on all patients without considering their preoperative CP fitness. The is no description of the used outcome measures (besides their name). The authors don't provide a discussion session in the protocol. I suggest they add that to discuss the benefits and limitations of their protocol more extensively in comparison of other trials on this subject. The discussion section can also be used to justify choices made in the protocol (e.g. including all patients).

REVIEWER	Dr Mathieu Gayda Cardiovascular Prevention and Rehabilitation Centre Montreal Heart Institute Canada No competing interest
REVIEW RETURNED	18-Nov-2013

GENERAL COMMENTS	**General Comments:** The study proposal is a very interesting research plan that aim to document the potential clinical benefits of HIIT (4 weeks) performed before AA repair. The authors, by this pilot

	study, wants to know if HIIT for 1 months before surgery would reduce pots surgery morbidity and mortality at 30 days after the surgery compared to a non-trained control group. They will also document the HIIT effects on physiological parameters (Fitness), co-morbidities, AA diameters, CV risk factors, QOL, adherence, enjoyement and safety of HIIT in those patients particularly at a higher CV risk during and after surgery. This study proposal is very original and of important clinical value, studying a new population with CV abnormality (AA). The protocol is well described and the main question I have is about the choice of the HIIT protocol (see specific comments). Do the authors have though to add another training group for example one trained with moderate intensity continuous exercise (MICET) ? May be in a future larger trials, after their pilot feasibility, this would help to document if HIIT is superior to MICET in regard to the recution of CV morbidity and mortality in those patients ….. **Specific comments:** **Abstract:** Pretty well described and clearly presented. The choice of the 2 or 4 min stage HIIT protocol has no real rational, and is mainly based on the Norwegian group studies (Wisloff et al. 2007). See later my comments on this topic. **Introduction:** The article review on the topic is very extensive, and the pervious studt of Arthur et al. 9 seems promising. P6: The clinical context is well exposed with this low fit population with an initial higher CV risk, that could be exacerbated by surgical procedure. L39-42: There is no outcomes reported in the ref. 19 and 20, we understand the need of those data in the future. L 53 : ref. 23. I would add a recent study of the Norwegian group demonstrating that HIIT is quite safe in term of events in CHD patients vs MICET. (ref 29) Rognmo Ø et al. Cardiovascular risk of high- versus moderate-intensity aerobic exercise in coronary heart disease patients.

	Circulation. 2012 Sep 18;126(12):1436-40. P7 : I agree with you. Due to its short time window (4-6 weeks), HIIT would appear to be the most efficient training strategy to improve fitness and CV risk. I was wondering also if a short component of resistance training could be added after HIIT to optimize exercise training. **Aims** **P7 L 26:** 30 day mortality: I do not see the details on the origin of the mortality ? It would be of great interest to have : - Total mortality (I suppose it would be done - CV mortality (detailed if possible) : ie- MI, sudden death… Same remark for morbidity : ie-MI, chest pain, stroke, rhythm disturbance…. **P7 L 38:** Did you though about potential non-ethical remarks regarding the non-exercise group? I am curious to see if you planned to have a comparative MICET group in the future …… **Sample size** Why did you choose exercise adherence as primary endpoint? Do you think that fitness (VO2max or VO2 at VT) would be a better choice, as it is related to prognosis ? I understand that due to the lack of previous studies with hard endpoint (mortality – morbidity…), this calculation is very theoretical. **P9 L 57 :** You have demonstrated the reproducibility (intra-observer) of VO2 at VT (ventilatory threshold) in AAA pts, not all CPET exercise variables. Please precise. I am curious to know the reproducibility of VO2peak in the same patients ? It is well known that VO2 at VT can have an important inter-observer variability …..How VT would be determined across all sites? Same observer or several ones ? **P 10 L 13:** Participant preferences: Not clear for me…Are you going

	to ask patient's preference prior to randomization? For what purpose? I would seem logical that patients would choose the training group? **P 10 L 35 :** Your are citing mainly the Norwegian HIIT protocol (ref 22, 29-31), those are important studies in the research domain. As you may know, there is an infinity of HIIT protocol were you can use different stage length, different nature of recovery (passive, active….). I have some major concerns about using the 4x3 min HIIT in AAA patients, as previously discussed for cardiac patients (Gayda M et al. 2012 - J Physiol Jul 15;590(Pt 14):3389, Meyer P et al. 2012, Am Heart J Mar;159(3):e21). 1) The scientific rational use of this HIIT has never been studied in cardiac patients: acute physiological responses during this HIIT vs. others protocols as well as patient's safety, tolerance and comfort has never been tested before its implementation. Moreover, the same authors demonstrated that the 4x3 min HIIT and the 15/15 sec HIIT protocols were **equivalent** in term of training responses in healthy subjects. Helgerud J et al. Aerobic high-intensity intervals improve VO2max more than moderate training. Med Sci Sports Exerc. 2007 Apr;39(4):665-71. 2) the use of target heart zones may not be the most optimal way to monitor exercise intensity in HIIT,3 particularly in patients with CAD or CHF, who require frequent titration of medications including β-blockers or calciumchannel blockers. **Monitoring cycling workload** at an intensity corresponding to a percentage of VO2max would represent a more reliable method. 3) We demonstrated in patients with CAD and CHF that **shorter intervals (15 to 30 sec. seconds)** at maximal aerobic workload interspersed with passive recovery periods provide a more optimal balance between patient comfort, safety, and maintenance of high % of VO2max compared to longer stage. See following ref.

	Normandin E et al. Acute responses to high intensity intermittent exercise versus moderate intensity continuous exercise in patients with heart failure. **Can J Cardiol. 2013 Apr;29(4):466-71.** Guiraud T et al. Acute responses to high-intensity intermittent exercise in CHD patients. **Med Sci Sports Exerc 2011 Feb; 43(2):211-7.** Meyer P et al. High intensity interval training in patients with chronic heart failure: acute cardiorespiratory responses and protocol optimization. **J Card Fail. 2012 Feb;18(2):126-33.** Guiraud T et al. Optimization of high intensity interval exercise in coronary heart disease. **Eur J Appl Physiol. 2010 Mar;108 (4):733-40.** Therefore, I would like to make some advice on your HIIT protocol (p 10 , L 45): 1) You don't need to use the VT intensity, to start your HIIT, rather use maximal power (or a given %) in parallel with the borg scale (example 5….), then gradually increase power and Borg scale …. 2) Your patient's will prefer passive recovery with shorter stages has we have previously demonstrated in CHD and CHF patient. I recommend to use shorter stage length (under 1 min) with passive recovery. Longer stage will potentially be perceived more tough, your patient will work at a lower power output, and exercise training adherence could be reduced. p 10 , L 50 : I think you mean : " does not exceed 180 mmHg " ? Once again, we demonstrated (with other works of Meyer K in the 1990's) that BP reponses during HIIT are very similar to that of MICET….. I do not think that such a high BP response would occur….once again, HR responses are not necessary….You will probably see near peak max. or even supra max HR peak reponses during HIIT (CV HR drift)…, with a mean HR responses 80 to 90 % Hrmax.. p 10 , L 52-54: There should be one HIIT protocol for the patients :

	the choice for a 2 min of 4 min stage could be a biais……I also recommend one HIIT protocol with shorter stage duration (15-30sec.). p 11, 32: definition for adverse events ? p 11, 37-45: I agree with you regarding safety. We are training 300 CHD patients per year since 2009 in our clinical program with HIIT, with no serious adverse reported. P 12 : 22-27: This is a major concern ….however, could a maximal test be considered more at risk than a HIIT session, that is probably true….but seems to be a rare event P 13, L 3: I don't see any rational for HR above 95 % of max…..I see one for excessive BP occurring during exercise…If patients are stable, with optimal medication, this would probably not occur in short stage HIIT …..

REVIEWER	Eivind Wang Norwegian University of Science and Technology
REVIEW RETURNED	25-Nov-2013

GENERAL COMMENTS	Although the general principle of improving aerobic capacity before an operation is very good, this paper is lacking data or a novel protocol. The HIT training protocol(s) have previously been tested in other studies, as well as the AAA procedure. Combining them in an intended protocol in the present paper does not represent anything novel. However, if you could present data that HIT training is beneficial before the AAA procedure, together with mechanisms explaining why, compared to a control group, this would have been interesting.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Karin Valkenet
Institution and Country University Medical Center Utrecht, The Netherlands
Please state any competing interests or state 'None declared': None declared

Outstanding protocol with very detailed description of objectives and procedures.

Thank you.

In the introduction the authors state that about half of all AAA surgery patients have decreased cardiopulmonary (CP) fitness which is a risk of impaired post-operative outcome. Therefore I expected that this protocol would only include the patients with decreased CP fitness. Since all patients will be included, I suggest that the authors provide their thoughts about applying their protocol on all patients without considering their preoperative CP fitness.

The research outlined in this protocol paper is of an exploratory nature and pivotal to informing subsequent definitive research. As such we have outlined a range of outcomes, which we expect will enable us to ultimately define the primary and secondary outcomes more robustly for subsequent research.
Outcomes explored for the current research include critical aspects such as safety, compliance and enjoyment of the exercise intervention in addition to surgical outcomes. Although the point is well made with regards to concentrating on patients with lower cardiopulmonary fitness, we believe that an overall representative sample of 'real life' fitness ranges to be essential at this stage to ensure our outcomes are subsequently generalizable and accurately inform future research.
Evolving evidence is very supportive of the concept that reduced fitness results in increased risk of postoperative complications, indeed this is the part of the underpinning theme for our research. However published fitness risk 'thresholds' specifically for AAA surgery have only recently been published and may be subject to geographical, even institutional variation.
For the above reasons we believe it more appropriate at this feasibility stage to concentrate our research on the broader spectrum of fitness levels in patients presenting for surgery. We do however acknowledge that ultimately this may become an important factor in defining future definitive research.

There is no description of the used outcome measures (besides their name).

Thank you for this comment. We believe we have provided sufficient detail for the reader to understand what we're doing and why. The manuscript is of significant length as it stands and we would be reluctant to add to this. For the exercise testing, we state that the protocol is available on request. Relevant references are provided for other outcomes and often there is a brief description of why an outcome has been selected. Other outcomes, such as mortality are more self-explanatory.

The authors don't provide a discussion session in the protocol. I suggest they add that to discuss the benefits and limitations of their protocol more extensively in comparison of other trials on this subject. The discussion section can also be used to justify choices made in the protocol (e.g. including all patients).

Thank you for this comment. We know of only one comparable trial, that of Arthur et al. (2000), and we make reference to this in the introduction section. Therefore, comparative discussions with previous perioperative research would add limited additional strength to the manuscript at this stage. Strengths and limitations of the study have been outlined (albeit briefly) in the "Article summary" part of the paper. In addition the emphasis of the current manuscript is on publication of the study protocol. We believe it will only be on completion of the research that we will be able to accurately demarcate strengths and weaknesses more robustly. These would of course be presented as part of the

discussion in our final study manuscript.
We have explained the choice of not limiting recruitment to unfit patients only above, and all of our responses will be published online next to the final article under “review history”. Unfortunately we believe providing this level of detail within the current manuscript will result in an unwieldy length publication for reasons outlined previously.

Reviewer Name Dr Mathieu Gayda
Institution and Country Cardiovascular Prevention and Rehabilitation Centre
Montreal Heart Institute
Canada
Please state any competing interests or state ‘None declared’: non competing interest

General Comments: The study proposal is a very interesting research plan that aim to document the potential clinical benefits of HIIT (4 weeks) performed before AA repair. The authors, by this pilot study, want to know if HIIT for 1 month before surgery would reduce post surgery morbidity and mortality at 30 days after the surgery compared to a non-trained control group. They will also document the HIIT effects on physiological parameters (fitness), co-morbidities, AA diameters, CV risk factors, QOL, adherence, enjoyment and safety of HIIT in those patients particularly at a higher CV risk during and after surgery. This study proposal is very original and of important clinical value, studying a new population with CV abnormality (AA). The protocol is well described and the main question I have is about the choice of the HIIT protocol (see specific comments). Do the authors have thought to add another training group for example one trained with moderate intensity continuous exercise (MICET)? May be in a future larger trial, after their pilot feasibility, this would help to document if HIIT is superior to MICET in regard to the reduction of CV morbidity and mortality in those patients …..

Thank you for your comments. The time between decision to proceed to elective AAA repair and the repair date itself is quite short; in the region of 6-8 weeks typically (driven by the National Abdominal Aortic Aneurysm Quality Improvement Programme). Therefore, we needed to select a training programme that was realistic, and effective in terms of evoking rapid increases in cardiopulmonary fitness. We believe that based on available published evidence that the HIIT protocol selected meets these requirements. We agree that it would be interesting to compare the relative effectiveness of HIIT and MICET in a subsequent definitive trial.

Specific comments:
Abstract: Pretty well described and clearly presented. The choice of the 2 or 4 min stage HIIT protocol has no real rational, and is mainly based on the Norwegian group studies (Wisloff et al. 2007). See later my comments on this topic.

We believe that there is good evidence to show that the “2-4 minute” HIIT regime can induce rapid improvements in cardiopulmonary fitness and other clinically relevant physiological variables in similar clinical populations to that of this study (patients awaiting elective AAA repair). Furthermore, given safety concerns about exercise-induced blood pressure “spikes” in patients with large AAAs, we thought it important to monitor BP responses during the harder exercise intervals and to reduce the intensity if systolic values >180 mmHg were noted. It usually takes around 30-45 s to take a manual BP reading during the work intervals; therefore, if we used shorter intervals of say 15-60 s, it would be difficult for us to accurately monitor BP responses.

Introduction:
The article review on the topic is very extensive, and the pervious study of Arthur et al. 9 seems promising.
P6: The clinical context is well exposed with this low fit population with an initial higher CV risk, that

could be exacerbated by surgical procedure.
L39-42: There is no outcomes reported in the ref. 19 and 20, we understand the need of those data in the future.

We are not sure what the reviewer is alluding to by this comment. These studies did report outcomes. The primary outcome for both studies was ventilatory (anaerobic) threshold. The study of Tew et al. (2012) also reported preliminary data on several other outcomes such as C-reactive protein, arterial blood pressure and AAA diameter. There has been (and perhaps still is) a school of thought that exercise training is not safe in AAA patients. These preliminary studies, and work of Jonathan Myers' group from California (e.g. Myers et al. in press, A Randomized Trial of Exercise Training in Abdominal Aortic Aneurysm Disease. MSSE), indicate that moderate intensity endurance exercise training is safe in patients with small AAAs (e.g. no evidence of exercise-related AAA expansion) and can lead to improvements in fitness and other surrogate health markers. In this regard, the pilot studies of Kothmann and Tew were important because they paved the way for the current study.

L 53 : ref. 23. I would add a recent study of the Norwegian group demonstrating that HIIT is quite safe in term of events in CHD patients vs MICET. (ref 29)
Rognmo Ø et al. Cardiovascular risk of high- versus moderate-intensity aerobic exercise in coronary heart disease patients. Circulation. 2012 Sep 18;126(12):1436-40.

Thank you for this suggestion. We do not think this change is necessary as the sentence is already supported by a good review paper and, as you have noticed, we do already make reference to the Rognmo paper elsewhere.

P7 : I agree with you. Due to its short time window (4-6 weeks), HIIT would appear to be the most efficient training strategy to improve fitness and CV risk. I was wondering also if a short component of resistance training could be added after HIIT to optimize exercise training.

Thank you we do acknowledge this as a potentially important area. However, one of the reasons we opted for cycle-based training only was that we needed to be realistic about what could be deliverable in most UK hospitals. The resistance training element is something we will consider as part of our future definitive research plan, especially if we find patient frailty to be a factor in conducting the current research.

Aims
P7 L 26: 30 day mortality: I do not see the details on the origin of the mortality? It would be of great interest to have:
- Total mortality (I suppose it would be done
- CV mortality (detailed if possible): ie- MI, sudden death…
Same remark for morbidity: ie-MI, chest pain, stroke, rhythm disturbance….

Thank you. We do plan to collect morbidity and mortality outcomes to the level of detail suggested. However we also plan to utilise the Postoperative Morbidity Survey (POMS) tool, which is validated to capture a range of magnitudes of relevant postoperative complications across 9 organ systems. We believe this provides a robust approach in capturing all relevant postoperative complications in addition to death.

P7 L 38: Did you think about potential non-ethical remarks regarding the non-exercise group? I am curious to see if you planned to have a comparative MICET group in the future ……

Thank you. As indicated above, we do not currently have any plans to include a MICET arm in the future. The ethics committee seemingly had no concerns with the use of a usual care (no supervised

exercise) control group.
At present there are no published studies showing exercise training prior to AAA surgery to be superior to usual care. This underpins our research plan and as such we do not believe represents an ethical dilemma. Building from this, it is our clinical (although anecdotal) experience that patients with AAA disease have a range of attitudes to undertaking exercise once they are aware of their diagnosis. Many believe they should not be undertaking any formal exercise for fear of precipitating rupture, whereas others embrace the concept of fitness benefits. Under 'Aims' point 3 in the manuscript we aim to explore this theme further as part of the outcomes for this research and therefore represents an area that we have previously given a significant amount of time and thought to.

Sample size
Why did you choose exercise adherence as primary endpoint?
Do you think that fitness (VO2max or VO2 at VT) would be a better choice, as it is related to prognosis? I understand that due to the lack of previous studies with hard endpoint (mortality – morbidity…), this calculation is very theoretical.

We chose exercise adherence as the primary endpoint given that this is a feasibility study. The acceptability of the protocol, manifested in the patient adherence to it, is critical to the success of any such intervention. The reviewer is, of course, correct that in a subsequent definitive trial adherence will not be the primary outcome. Rather, informed by the results of this feasibility study, the outcomes will likely be morbidity/ length of stay. The CPET variables that the reviewer mentions will be investigated as potential mediating variables – putative mechanisms explaining any benefit in reductions in morbidity and length of stay.

P9 L 57: You have demonstrated the reproducibility (intra-observer) of VO2 at VT (ventilatory threshold) in AAA pts, not all CPET exercise variables. Please precise. I am curious to know the reproducibility of VO2peak in the same patients?

Yes as part of our portfolio of research we have explored many themes with regards to CPET and exercise training in this patient population. The reproducibility of peak oxygen consumption is clearly a highly relevant area as part of this. During our original research (now several years ago) there was little published research into the safety of undertaking maximal exercise testing in patients with AAA disease during CPET. The evolving evidence base at that time was also around oxygen consumption at VT (clinically termed anaerobic threshold). As such all tests during this original study were conducted to a submaximal level and we are therefore unable to present robust research data as to the reproducibility of peak oxygen consumption for this study.

It is well known that VO2 at VT can have an important inter-observer variability …..How VT would be determined across all sites? Same observer or several ones?

All cardiopulmonary exercise tests will be read at the end of the study by two experienced readers who will be blinded to group allocation. This will be done to an agreed set of internationally recognised criteria.

P 10 L 13: Participant preferences: Not clear for me…Are you going to ask patient's preference prior to randomization? For what purpose? I would seem logical that patients would choose the training group?

Yes, we will ask for the patient's preference regarding group allocation prior to randomisation. The rationale for this is explained under aim 3 on page 7:
"In RCTs, patients might have strong treatment preferences resulting in a refusal to be randomised, affecting the generalisability of results. Or, they might agree to be randomised but suffer from

‘resentful demoralisation’ if they end up in the non-preferred arm of the trial, leading to poor adherence. This issue requires examination in a feasibility study, as the preference effects for exercise vs. control in this patient population are unknown. Theoretically, patients might have a preference for the exercise arm due to a belief in the benefits. Notwithstanding the patient information provided, others might be fearful of engaging in high-intensity exercise prior to surgery and therefore might exhibit a preference for the control arm. These issues could affect the success of a definitive trial.”
In summary, assessing group preference prior to randomisation will provide us with preliminary data about the impact of preference on the outcomes of this study and the feasibility of using the RCT design in a subsequent definitive study for answering our research question. We will also be assessing preference for group allocation following the 4-week exercise intervention, or control period, as a comparator. The full rationale for this based on our clinical experiences is outlined.

P 10 L 35: You are citing mainly the Norwegian HIIT protocol (ref 22, 29-31), those are important studies in the research domain. As you may know, there is an infinity of HIIT protocol were you can use different stage length, different nature of recovery (passive, active….). I have some major concerns about using the 4x3 min HIIT in AAA patients, as previously discussed for cardiac patients (Gayda M et al. 2012 - J Physiol Jul 15;590(Pt 14):3389, Meyer P et al. 2012, Am Heart J Mar;159(3):e21).
1) The scientific rational use of this HIIT has never been studied in cardiac patients: acute physiological responses during this HIIT vs. others protocols as well as patient’s safety, tolerance and comfort has never been tested before its implementation.
Moreover, the same authors demonstrated that the 4x3 min HIIT and the 15/15 sec HIIT protocols were equivalent in term of training responses in healthy subjects.
Helgerud J et al. Aerobic high-intensity intervals improve VO2max more than moderate training. Med Sci Sports Exerc. 2007 Apr;39(4):665-71.

We applaud the contributions to the literature you and your colleagues have made regarding work to identify an “optimal” HIIT protocol. There are multiple different protocol possibilities and we don’t think anyone truly knows which one is best yet. Each will have its merits and short-comings. Based on the available evidence, we think that the “2-4 minute” approach described should be a good choice for safely inducing meaningful improvements in cardiopulmonary fitness within 4 weeks. This approach also allows us to take manual BP measurements towards the end of each work interval, whereas this would be difficult to do this with shorter (e.g. 30 s) intervals. There’s also an issue about what protocol is easy to administer across a healthcare system. One could argue that a 15/15 s or 30/30 s protocol really requires an electronically-braked ergometer for it to be feasible. In contrast, you could probably easily run a 2/4 min protocol using a friction-braked cycle, which are much cheaper.

2) The use of target heart zones may not be the most optimal way to monitor exercise intensity in HIIT,3 particularly in patients with CAD or CHF, who require frequent titration of medications including β-blockers or calcium channel blockers. Monitoring cycling workload at an intensity corresponding to a percentage of VO2max would represent a more reliable method.

We agree. We use the power output at ventilatory threshold as a starting point and progress the intensity on an individual basis accordingly primarily to the participant’s ratings of perceived exertion, aiming to have them reporting “hard to very hard” exertion at the end of the work intervals. We suspect that most patients will end up exercising roughly in the middle of the power output at VT and the power output at peak VO2.

3) We demonstrated in patients with CAD and CHF that shorter intervals (15 to 30 sec. seconds) at maximal aerobic workload interspersed with passive recovery periods provide a more optimal balance between patient comfort, safety, and maintenance of high % of VO2max compared to longer stage.

See following ref.
Normandin E et al. Acute responses to high intensity intermittent exercise versus moderate intensity continuous exercise in patients with heart failure. Can J Cardiol. 2013 Apr;29(4):466-71.
Guiraud T et al. Acute responses to high-intensity intermittent exercise in CHD patients. Med Sci Sports Exerc 2011 Feb; 43(2):211-7.
Meyer P et al. High intensity interval training in patients with chronic heart failure: acute cardiorespiratory responses and protocol optimization. J Card Fail. 2012 Feb;18(2):126-33.
Guiraud T et al. Optimization of high intensity interval exercise in coronary heart disease. Eur J Appl Physiol. 2010 Mar;108 (4):733-40.
Therefore, I would like to make some advice on your HIIT protocol (p 10, L 45):
1) You don't need to use the VT intensity, to start your HIIT, rather use maximal power (or a given %) in parallel with the borg scale (example 5….), then gradually increase power and Borg scale ….

Many thanks for your constructive comments. We believe that both approaches to starting HIIT have their strengths and limitations. At the time of writing the approach we have chosen has been approved through the ethics process and our study has now commenced. To date this strategy appears to have been well received by recruited patients. As such we plan to continue as we have set out, but of course outcomes from this study will enable us to respond to your comments further on completion of this study.

2) Your patient's will prefer passive recovery with shorter stages has we have previously demonstrated in CHD and CHF patient. I recommend to use shorter stage length (under 1 min) with passive recovery. Longer stage will potentially be perceived more tough, your patient will work at a lower power output, and exercise training adherence could be reduced.

We have published two pilot studies of moderate continuous training of 30-45 min per session. Adherence to exercise sessions was excellent (>95%) in both studies. Therefore, we don't envisage adherence issues resulting from using the 2/4 interval approach, even with the intensity being higher. The first few patients have tolerated the sessions well, and no sessions have been missed to date. Participants have the option of active or passive recovery, as we believe this flexible approach to be participant focused.

p 10, L 50 : I think you mean : " does not exceed 180 mmHg " ? Once again, we demonstrated (with other works of Meyer K in the 1990's) that BP responses during HIIT are very similar to that of MICET…..

We are happy with the way the sentence currently reads.

I do not think that such a high BP response would occur….once again, HR responses are not necessary….You will probably see near peak max. or even supra max HR peak responses during HIIT (CV HR drift)…, with a mean HR responses 80 to 90 % Hrmax.

Hopefully you are correct regarding the BP responses, but many of our patients have a history of hypertension such that it is quite feasible that patients could approach or exceed 180 mmHg with hard exercise. We are using a high-intensity exercise protocol in a high-risk clinical population, hence, it was essential that we set safety criteria.

p 10, L 52-54: There should be one HIIT protocol for the patients: the choice for a 2 min of 4 min stage could be a bias……I also recommend one HIIT protocol with shorter stage duration (15-30sec.).

The exercise programmes used in different clinical trials of exercise training typically have some degree of flexibility in them. For example, in some studies patients are allowed to use different modes

of exercise with differing intensities and durations according to individual fitness levels and preferences. In this regard, our protocol isn't actually that flexible; patients always complete 16-min of higher-intensity exercise per session and the difference in absolute intensity isn't likely to vary that much between 2 and 4 minute bouts. That said the few people that we've trained so far have all stuck with the 2-minute bouts throughout the 4-week programme.
We justify the use of 2/4-minute intervals above and as this is an on-going trial we are reluctant to change anything now.

p 11, 32: definition for adverse events?

Serious adverse event – Any untoward medical occurrence to a participant deemed related to the exercise intervention that occurs during the participant's involvement in the study and results in one of the following criteria:
- Life threatening (i.e. event in which patient is at risk of death at the time of the event occurring)
- Requires unplanned or prolonged hospitalisation
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect.
- Any other medical condition not listed above, which may require medical or surgical intervention to prevent the above criteria occurring
OR:
- Death (regardless of whether or not the event has any relationship to the exercise intervention)

Non-serious adverse event – This is any untoward medical occurrence to the participant that is related to the exercise intervention but does not fulfil any of the serious adverse event criteria (e.g. muscle strain)

p 11, 37-45: I agree with you regarding safety. We are training 300 CHD patients per year since 2009 in our clinical program with HIIT, with no serious adverse reported.
P 12 : 22-27: This is a major concern ….however, could a maximal test be considered more at risk than a HIIT session, that is probably true….but seems to be a rare event

Yes, one might argue that a maximal test is more risky than a HIIT session. However, there might be something about repeated bouts of high intensity exercise in one discrete exercise session that makes a HIIT session at least of similar risk to a maximal test.

P 13, L 3: I don't see any rational for HR above 95 % of max…..I see one for excessive BP occurring during exercise…If patients are stable, with optimal medication, this would probably not occur in short stage HIIT …..

Thank you this again is a point well made. In previous published HIIT research in patients with underlying coronary disease/heart failure the investigators by definition will be aware of the severity of underling cardiac disease. Approximately 50-70% of patients with AAA disease have overt or covert cardiac disease, however the severity of this is not always available to investigators (hence our screening and baseline CPET). Given this state of play, and the lack of published literature currently available as to safety of HIIT in AAA patients, we have opted for a safety first approach for this feasibility study. As such we are using 95% of maximum heart rate achieved during the maximal baseline CPET as a one of our safety measures to guide exercise intensity. We accept that outcome from this research may subsequently enable us to 'relax' this approach during subsequent definitive research.

Reviewer Name Eivind Wang
Institution and Country NTNU, Norway

Please state any competing interests or state ‘None declared’: None declared

Although the general principle of improving aerobic capacity before an operation is very good, this paper is lacking data or a novel protocol. The HIT training protocol(s) have previously been tested in other studies, as well as the AAA procedure. Combining them in an intended protocol in the present paper does not represent anything novel. However, if you could present data that HIT training is beneficial before the AAA procedure, together with mechanisms explaining why, compared to a control group, this would have been interesting.

Many thanks for your comments, however we disagree otherwise we would not have set out on this planned research. There is very little empirical evidence (we are aware of) regarding the effects of pre-operative exercise training on post-surgical outcomes in patients undergoing major surgical procedures (e.g. see the review of Valkenet et al., Clin Rehabil 2011, 25:99-111). In fact, we are only aware of one published trial in this area – Arthur et al. (Ann Intern Med 2000, 133(4):253-262). As such we would be grateful if you would be able to forward our group details of other studies which you feel we have missed or should have taken into account during this study design.
We are also reassured that the other reviewers see the value in our study. Finally as part of the process of our grant award by the National Institute of Health Research (UK government’s main funding body for medical research) we received excellent peer review and feedback. Our study was highlighted as an example as to how exploratory research should be presented.
Finally, although it is fair to say that the subsequent paper that reports on the actual results of this trial will generally be of more interest, there is value in publishing a study protocol. Indeed, the following is taken from the “instruction for authors” section of BMJ Open’s website:
“Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.”