PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The Managed Activity Graded Exercise iN Teenagers and pre-Adolescents (MAGENTA) feasibility randomised controlled trial: Study Protocol.
AUTHORS	Brigden, Amberly; Beasant, Lucy; Hollingworth, William; Metcalfe, Chris; Gaunt, Daisy; Mills, Nicola; Jago, Russ; Crawley, Esther

VERSION 1 - REVIEW

REVIEWER	Dr Suzanne Broadbent Southern Cross University Lismore NSW Australia
REVIEW RETURNED	04-Feb-2016

GENERAL COMMENTS	GENERAL COMMENTS The manuscript is well written in most sections, and the aims of the project are consistent with similar studies involving adults with CFS. There is definitely a gap in the literature regarding management of CFS for children and adolescents, so this study proposal is timely and very worthwhile. However, some sections of the manuscript involving the description of the "treatment" or "intervention" and the GET program itself, lack clarity and are quite confusing. In particular, the description of the type of exercise, amount, duration, intensity and location of sessions is too brief and poorly written for a protocol paper. I would recommend publication if the authors can address the following points. ABSTRACT Line 4: Replace "no evidence" with "little evidence", because publications by Lim and Lubitz (2002), Gordon and Lubitz (2009) and Gordon et al (2010) already provide evidence of the effectiveness of GET for young adolescents with CFS. STRENGTHS & LIMITATIONS Dot point 1: Please remove or re-write this point as the study is not the first to investigate GET with young adolescents (see Gordon et al, Gordon & Lubitz publications). Dot point 5: Self-reporting presumably is a weakness? Will participants be supervised by parent or carer with reporting? INTRODUCTION Line 28: Replace "no evidence" with "little" or "some evidence" since there are already 3 studies of GET with young adolescents with

	CFS. Line 31: Replace “evidence on” with “evidence of”. Please reference this statement. Line 54: Please state what the “intervention” actually is i.e. a comparison of 2 interventions (GET versus AM), so the readers understand what you are comparing. Sections of the manuscript become unclear when you just refer to 1 intervention. AIMS AND OBJECTIVES One of the aims is to assess the effectiveness of GET compared to AM. You could include an aim that states exactly how you will assess “effectiveness” e.g. adherence, exercise compliance, evaluation of exercise performance. Point 6: GET and AM are the 2 interventions so make sure this is stated earlier in the Aims. METHODS P 6, Line 19 and Line 50: Your age group is earlier stated as 8 to 17 yr. Suggest you replace “child” with “child or adolescent” to accurately reflect the age group. Should be consistent throughout manuscript. Line 54: Possible participants will be excluded if they are “too severely affected”. Please state what this means (e.g. excessive fatigue, joint pain?) and who makes the decision (i.e. doctor, project clinician?). P 7, line 12: Use plural – “interventions”. Line 35-36: sample size for interventions – please provide the power calculation used, rather than “We believe that……”. Are there any references from previous studies regarding the sample size? P 8, Lines 4 and 29-30: A progression of 10-20% per week in physical activity is regarded as standard for healthy adults. Other CFS research suggests that progression for CFS patients should be a lot less or at least self-paced with periods of no progression if symptomatic. Can the authors explain why the 10-20% progression was chosen and support this with references from CFS literature? Lines 24 – 24: This section needs clarification, and extra information should also be included in Appendix 1. You state later in the manuscript that your interventions consist of 8 to 12 follow-up sessions per year delivered by a clinician, yet here the intervention is defined as weekly exercise measured by diary, app and accelerometer – presumably self-reported and not monitored by a parent/carer. Please clarify; also, is the exercise intervention is home-based, or are you including exercise at schools or other locations and how is that monitored? The other issue is that of monitoring exercise intensity, HR may be somewhat inaccurate; for CFS patients other research shows that rate of perceived exertion (RPE) used in conjunction with HR, is more useful for detecting fatigue and exercise limits, Can the authors please reference the sentence on target HR and explain

	why that is the most useful method for measuring intensity in children. Also can they actually state the target HR (e.g. between 60 – 80% max HR?) and why these limits were chosen (possibly referring to clinical exercise guidelines). P8, Line 39 Treatment Delivery: This is confusing as you have already partly discussed both GET and AM interventions. What is the "treatment" if not the intervention? Would be better to remove this word and use "Follow Up Sessions" as the heading. What treatment is the clinician providing, and what is involved in the follow-up sessions? This is not stated and confuses the reader. Where are these sessions being held (home? clinic? school?). Are the follow-up sessions interviews to assess how either GET or AM are going, or are they CBT sessions? Please re-write this paragraph making it very clear what the 8-12 sessions are, where they are and if any further exercise or AM occurs in these sessions. Line 53: also confusing as you state that participants can withdraw from "either treatment" or "treatment arm" – if you are talking about the GET or AM interventions then say so, otherwise describe what the "treatments' actually are. P 9, Line 53. Trial Interventions: This section needs better explanation. "Intervention sessions will be routinely recorded…". GET and AM interventions have previously been described as occurring at home or elsewhere (not really clear). Are the researchers going to audio-record the participants doing exercise or AM at home/school or wherever? Or is this going to occur during one of the 8-12 Follow Up sessions? Lines 15 – 25. "Treatments" again being used with no description of what is meant. Are you talking about the exercise or AM interventions or something else? Please clarify. Line 36: "Interviews" – are these with clinicians delivering GET/AM, or participants and parents/carers? Please state exactly who will be interviewed. Lines 46-56. Sample sizes. You have already written about sample sizes for GET/AM participants on Page 7. This is a separate sample size calculation for interviews only? If so, this section should be back on Page 7 under the Sample Size heading, in a separate paragraph explaining that the calculation will be for interviewees from the participants, parents and "practitioners" – what is meant by practitioners? Are these the clinicians who deliver the GET/AM or medical practitioners or other allied health professionals? How was the sample size of 45 "estimated"? Please explain if a power calculation was used and why a number of 45 was considered to be appropriate – a reference/references to the literature would be useful to support your estimation. P 11, Outcome Measures: The paragraph about Accelerometers and data should be in the Methods – Clinical Intervention section, with further clarification and detail. Please include – • Whether all participants in GET and AM will wear accelerometers • Will accelerometers be worn for each exercise session at

	home, school or elsewhere P 12, Line 35-36. Replace “treatments” with “interventions” for consistency, as you are referring to GET and AM. Lines 37-38. Confusing – you change from talking about interventions to follow-up sessions; are the sessions interviews or GET/AM – this needs to be clarified earlier in the manuscript. Line 44: remove “treatment” and replace with “intervention”. P 13, Line 10: as above Lines 11 and 14: What is DSMC? Please use full words in the first instance, then the anagram. Table 1: there is no exercise assessment or physiological data displayed. For clinical exercise professionals, it would be useful to see baseline exercise capacity and physiological measures (e.g. HR, BP, exercise assessment results) for comparison to later, post-training outcomes measures – after all, you are comparing GET to AM and intervention effectiveness was one of the project aims. P14, paragraph 2: All the accelerometer information should have been written in the Methods – Clinical Intervention section; please put it there with the relevant outcomes measures following (see my previous comment above). Line 49: please explain the “established methods” for calculating accelerometer data that you will use, with references. P 19, REFERENCES: suggest that the authors include publications by Lim and Lubitz (2002); Gordon and Lubitz (2009); Gordon et al (2010); van Cauwenbergh et al (2012); ACSM or similar guidelines for exercise prescription. Further references for power calculations and supporting documentation should be included. SUPPLEMENTARY FILES **AM,** P 1, Line 34. Please justify the use of 10-20% progression for use with children/adolescents with CFS. This group should have the same physical assessments as the GET group (for comparison), considering that both groups will be recording physical activity via app and accelerometer. Please add the use of accelerometers to record incidental exercise and physical activity. **GET**, This section is very poorly written and as a protocol paper, needs a lot more information. <u>Please add the following information</u> – • Will this group have the same cognitive assessments as the AM, as you will be comparing both groups (shouldn’t both groups will have exercise and cognitive assessments if you are comparing the effectiveness of both interventions). • Describe the physical/exercise assessments to be completed in Week 1. • Describe the types of exercise done in Week 1 (incidental, aerobic, anaerobic, strength or flexibility or mixed modes?)

	• State all the functional and aerobic tests used if more than 2 MWT and Sit to Stand (e.g. manual muscle tests, hand grip strength); you have written “included” so that suggests more than 2. Why did the AM group not do the same assessments? • Is the exercise only home-based or will it be done at school or other centres, and who is going to supervise or monitor it (parents, carers, or self-report only). • Please justify the use of 10-20% progression for use with children/adolescents with CFS. • Define “30 minutes of gentle exercise”. What exactly will they be doing? What are the intensities for “gentle”, since you are using HR as a measure of intensity? Would strongly recommend you also use RPE. • Please clarify the sentence “once children are doing 30 minutes of gentle exercise each day, the exercise will increase in intensity such that participants start doing aerobic exercise”. This makes no sense – aerobic exercise is sustainable exercise using the large muscle groups. If they are not starting with aerobic exercise such as walking, what are they doing? The usual progression for CFS patients is to gradually increase duration of exercise, before increasing intensity, otherwise you risk exacerbating symptoms. • “The aerobic component will then be slowly increased…..” What does this actually mean? What other exercise are they doing apart from aerobic (e.g. strength, flexibility, games?) and please state the components of the exercise program. • HR monitoring – how are children under 10 yr going to monitor intensity or effort? • Please reword sentence Line 36 to state that children will be using a HR monitor to prevent them doing too high an exercise intensity rather than “too much”. • How are target HR to be calculated? Please reference this section according to exercise guidelines for children. • Lines 47 – 52. Health Dept guidelines are for healthy children not those suffering from a fatiguing illness. Vigorous exercise is usually contraindicated for CFS patients due to the risk of symptom exacerbation. These guidelines mention a mixed-model approach to exercise programming (aerobic, strength and flexibility components) but the authors have not described the GET programs they will be using with the participants. For a protocol paper, this needs to be proposed in reasonable detail. • How is exercise participation to be managed in the event of increased symptoms? Will children be advised to rest and will their exercise program be scaled back to more manageable duration and intensity? • Flexible elements – it seems ROM is not a mandatory assessment but a flexibility (stretching) program can be given to participants and they can be “offered a strengthening program”…… If they are not doing strength and flexibility exercises in their program, are they only doing aerobic exercise? This is not clear in the first section of the GET appendix and should be.

	• When are you re-assessing exercise performance? Only pre- and post-trial or during the 12 months? In summary, the GET section needs to be re-written in more detail with regard to the GET exercises proposed for participants, and it should be referenced according to the available literature and guidelines. It is very concerning that participants may be pushed too hard to meet non-CFS exercise guidelines and with a high progression rate, poor management of intensity, and with unstructured programs.

REVIEWER	Lucy Clark QMUL, London
REVIEW RETURNED	10-Mar-2016

GENERAL COMMENTS	This study protocol investigating the feasibility of carrying out a RCT of GET for CFS/ME is written clearly and in enough detail for it to be repeated. It includes all the information it should regarding funding and ethics, and the references seem to be relevant to this population and up-to-date. The title and abstract are clear, and it describes an interesting study that, when completed, should add to the literature on GET for CFS/ME.

VERSION 1 – AUTHOR RESPONSE

I would recommend publication if the authors can address the following points.
Thank you for this feedback. We have responded the following points as detailed below:
ABSTRACT

Line 4: Replace “no evidence” with “little evidence”, because publications by Lim and Lubitz (2002), Gordon and Lubitz (2009) and Gordon et al (2010) already provide evidence of the effectiveness of GET for young adolescents with CFS.

We have changed “no evidence” to “little evidence” and the sentence now reads “but there is little evidence for the effectiveness”. We have now included references to Lim and Lubitz (2002), Gordon and Lubitz (2009) and Gordon et al (2010).

STRENGTHS & LIMITATIONS

Dot point 1: Please remove or re-write this point as the study is not the first to investigate GET with young adolescents (see Gordon et al, Gordon & Lubitz publications).

Thank you for raising this interesting point. We are very familiar with these papers. As the reviewer will be aware, these treatments are delivered in hospital which is different to MAGENTA, a large RCT testing treatment delivered in the outpatient setting. We therefore believe this is an important strength but have changed our sentence to reflect this. We have added “in the outpatient setting”. This now reads:
• “This feasibility study is the first trial to investigate Graded Exercise Therapy in children with CFS/ME in the outpatient setting”

Dot point 5: Self-reporting presumably is a weakness? Will participants be supervised by parent or carer with reporting?

We agree this is potentially a weakness (limitation) which is why we have raised it in the strengths and limitation section.

INTRODUCTION

Line 28: Replace “no evidence” with “little” or “some evidence” since there are already 3 studies of GET with young adolescents with CFS.

We have changed “no evidence” to “little evidence” and the sentence now reads “however there is little evidence for the effectiveness of GET in children although GET is moderately effective in adults”

Line 31: Replace “evidence on” with “evidence of”. Please reference this statement.

Thank you for pointing this out. We have replaced “evidence on” with “evidence of”.

Line 54: Please state what the “intervention” actually is i.e. a comparison of 2 interventions (GET versus AM), so the readers understand what you are comparing. Sections of the manuscript become unclear when you just refer to 1 intervention.

In the Introduction we state: “In this study we will determine whether it is acceptable and feasible to deliver GET compared with Activity Management in a multicentre randomised controlled trial (RCT)”, we believe that this provides the reader with a clear statement of the interventions being studied.
We agree that “intervention” may cause confusion and so we have been changed to “interventions” on pages: 2, 4, 7 and 11.

AIMS AND OBJECTIVES

One of the aims is to assess the effectiveness of GET compared to AM. You could include an aim that states exactly how you will assess “effectiveness” e.g. adherence, exercise compliance, evaluation of exercise performance.

Within the aims we state: “To ascertain the feasibility and acceptability of conducting an RCT to investigate the effectiveness and cost-effectiveness of GET compared to Activity Management for the treatment of CFS/ME in children. We will use the information to inform the design of a full-scale, adequately powered trial.”
If it is feasible to recruit into MAGENTA, we will detail how we will define effectiveness in the full trial, which will be to investigate the effectiveness of GET compared to AM.

Point 6: GET and AM are the 2 interventions so make sure this is stated earlier in the Aims.

In the first line of the AIMS AND OBJECTIVES we state: “To ascertain the feasibility and acceptability of conducting an RCT to investigate the effectiveness and cost-effectiveness of GET compared to Activity Management for the treatment of CFS/ME in children”. We believe this clearly outlines the two interventions that we are comparing.

METHODS

P 6, Line 19 and Line 50: Your age group is earlier stated as 8 to 17 yr. Suggest you replace “child” with “child or adolescent” to accurately reflect the age group. Should be consistent throughout manuscript.

Thank you. We agree that writing “child and adolescent” throughout will more accurately reflect our study population. We have changed all instances of “child” or “children” to “child and adolescent” or “children and adolescents”.

Line 54: Possible participants will be excluded if they are “too severely affected”. Please state what this means (e.g. excessive fatigue, joint pain?) and who makes the decision (i.e.doctor, project clinician?).

Thank you. We have expanded our definition and changed “Children will be excluded if they are too severely affected to attend hospital appointments (and require a domiciliary assessment)” to “Children and adolescents will be excluded if they are severely affected. NICE defines severe CFS/ME as individuals who are unable to do any activity for themselves, or can carry out minimal daily tasks only, they have severe cognitive difficulties and depend on a wheelchair for mobility1.”

We have added the following to clarify who carries out the eligibility assessment: “Eligibility assessment will be carried out by the clinician at assessment and confirmed by the recruiting researcher.”

P 7, line 12: Use plural – “interventions”.

“Intervention” has now been changed to “interventions”.

Line 35-36: sample size for interventions – please provide the power calculation used, rather than “We believe that……”. Are there any references from previous studies regarding the sample size?

We state: “Recruiting 100 children from 430 eligible children approached will give a 95% confidence interval of 20-28% for an estimated recruitment rate of 24% (0.6 eligible x 0.4 consenting), which is acceptably precise for planning the main study recruitment”. We have deleted the sentence starting “we believe…” because we had provided the power calculation in detail.

MAGENTA is a feasibility study focused on whether a trial comparing graded exercise versus activity management can be conducted in children and adolescents. Hence we show that the number of patients anticipated to be available at the feasibility study centres will estimate the proportion recruited with sufficient precision for it to be informative for the design of the future full trial. Power is not calculated; this will be appropriate when designing the future full trial, ensuring it is likely to detect a treatment effect of clinically important magnitude.

P 8, Lines 4 and 29-30: A progression of 10-20% per week in physical activity is regarded as standard for healthy adults. Other CFS research suggests that progression for CFS patients should be a lot less or at least self-paced with periods of no progression if symptomatic. Can the authors explain why the 10-20% progression was chosen and support this with references from CFS literature?

Thank you. We have clarified that this is following UK guidance. A progression of up to 20% is the guidance provided by the National Institute of Clinical Excellence1 and is standard practice in the UK. This is also consistent with the PACE trial, the largest trial done to date. We have now included a reference to NICE guidelines and the PACE trial, the protocol now reads: “The intervention will encourage children and adolescents to find a baseline level of exercise which will be increased slowly (by 10-20% a week, as per NICE guidance1 and the PACE trial2)”.

Our published systematic review on behavioural treatment approaches did not find evidence that a lower progression rate was preferable 3.

Lines 24 – 24: This section needs clarification, and extra information should also be included in Appendix 1. You state later in the manuscript that your interventions consist of 8 to 12 follow-up sessions per year delivered by a clinician, yet here the intervention is defined as weekly exercise measured by diary, app and accelerometer – presumably self-reported and not monitored by a parent/carer. Please clarify; also, is the exercise intervention is homebased, or are you including exercise at schools or other locations and how is that monitored?

Thank you. We have re-worded to clarify the treatment setting and the use of diary and apps as clinical tools rather than outcome measures. We have added the following to introduce the clinical intervention: “Both interventions are delivered in an outpatient setting. During intervention sessions clinicians and patients develop collaborative activity plans, which children and adolescents then implement in the community (including home and school environments). Children and adolescents will be advised to use paper diaries / Apps to assist with monitoring and recording of activity levels”.

Accelerometers are an outcome measure, they are not a clinical tool. As such, they are not described in the clinical interventions section. Instead they are detailed in the outcome measures section.

The other issue is that of monitoring exercise intensity, HR may be somewhat inaccurate; for CFS patients other research shows that rate of perceived exertion (RPE) used in conjunction with HR, is more useful for detecting fatigue and exercise limits, Can the authors please reference the sentence on target HR and explain why that is the most useful method for measuring intensity in children. Also can they actually state the target HR (e.g. between 60 – 80% max HR?) and why these limits were chosen (possibly referring to clinical exercise guidelines).

Thank you for pointing out that we have not referenced this. We have added references to PACE and NICE, this sentence now reads: “Participants will be advised to stay within the target heart rate zones of 60-80% of their maximum heart rate1 2”.
As feasibility study, we will be investigating the views of patients, parents and clinicians in terms of the appropriate levels to use. We therefore state: “We will interview parents and their children and adolescents about both interventions including … use of heart rate monitors” and “We will interview clinicians delivering both interventions in each centre to ascertain their views on … using heart rate monitors.”

P8, Line 39 Treatment Delivery: This is confusing as you have already partly discussed both GET and AM interventions. What is the “treatment” if not the intervention? Would be better to remove this word and use “Follow Up Sessions” as the heading. What treatment is the clinician providing, and what is involved in the follow-up sessions? This is not stated and confuses the reader. Where are these sessions being held (home? clinic? school?). Are the follow-up sessions interviews to assess how either GET or AM are going, or are they CBT sessions? Please re-write this paragraph making it very clear what the 8-12 sessions are, where they are and if any further exercise or AM occurs in these sessions.
Line 53: also confusing as you state that participants can withdraw from “either treatment” or “treatment arm” – if you are talking about the GET or AM interventions then say so, otherwise describe what the “treatments’ actually are.

To make this section clearer we firstly outline the context and delivery of both interventions, followed by a description of each individual treatment component. We have deleted the “treatment delivery” subheading that appeared after the description of GET and Activity management, incorporating this information in the introduction to the interventions. The entirety of the opening clinical intervention paragraph now reads: “Both interventions will be delivered in an outpatient setting. During clinical sessions clinicians and patients develop collaborative activity plans, which children and adolescents

then implement in the community (including home and school environments). Children and adolescents will be advised to use paper diaries / Apps to assist with monitoring and recording of activity levels. In both arms, children and adolescents, their parents and the clinician providing intervention will choose the number of clinical sessions (between 8 and 12) and the frequency of appointments (every 2-6 weeks) within a maximum length of treatment of one year.
In both arms clinicians will be encouraged to offer routine1 advice about sleep, medication use, symptom control and set backs at the assessment and during intervention sessions.
Participants who develop anxiety or depression that require treatment during the trial follow-up period will be offered up to 12 sessions of CBT delivered as individual sessions every two weeks by a CFS/ME specialist clinical psychologist.
Participants will be allowed to discontinue either intervention or withdraw from the trial at any time. If parents or clinicians request cross-over to the other intervention arm, we will encourage them to try the original allocation for 6 months (the primary outcome). Any cross-over will be recorded."
This is followed by a description of GET and Activity Management.
We have changed all instances of "treatment/s" to "intervention/s" for clarity.

P 9, Line 53. Trial Interventions: This section needs better explanation. "Intervention sessions will be routinely recorded…". GET and AM interventions have previously been described as occurring at home or elsewhere (not really clear). Are the researchers going to audio-record the participants doing exercise or AM at home/school or wherever? Or is this going to occur during one of the 8-12 Follow Up sessions?

Our re-worded introduction to the clinical intervention (stated above) now clarifies that patients have interventions sessions with a clinician and then implement the agreed activity plans in the community between sessions. "Intervention session will be routinely recorded" should now clearly refer to the clinical intervention session.

Lines 15 – 25. "Treatments" again being used with no description of what is meant. Are you talking about the exercise or AM interventions or something else? Please clarify.

As above our re-worded introduction to the clinical intervention should now clarify what is meant by "treatments". For consistency, where appropriate we have changed instances of "treatment/s" to intervention/s".

Line 36: "Interviews" – are these with clinicians delivering GET/AM, or participants and parents/carers? Please state exactly who will be interviewed.

We agree that it is important to be clear about who is being interviewed. We have therefore re-worded two sentences to provide further details about interviewees:

"Interviews will be semi-structured using a topic guide" has been changed to "Interviews with clinicians, participants and families will be semi-structured using a topic guide"
"a sample size of 45" has been changed to "up to 45 patient, parent and clinical staff interviews"

Lines 46-56. Sample sizes. You have already written about sample sizes for GET/AM participants on Page 7. This is a separate sample size calculation for interviews only? If so, this section should be back on Page 7 under the Sample Size heading, in a separate paragraph explaining that the calculation will be for interviewees from the participants, parents and "practitioners" – what is meant by practitioners? Are these the clinicians who deliver the GET/AM or medical practitioners or other allied health professionals? How was the sample size of 45 "estimated"? Please explain if a power calculation was used and why a number of 45 was considered to be appropriate – a

reference/references to the literature would be useful to support your estimation.

We felt it would be clearer to dedicate a section to the description of integrated qualitative methods, including a discussion of qualitative sample sizes. As the “sample size” section precedes the qualitative methods section, we felt presenting the qualitative sample size information in “sample size” section would be confusing to the reader; the reader would be presented with qualitative sample size without first being introduced to the qualitative element of the study.

Power calculations are not used in a qualitative context, instead we use the concept of data saturation to determine our sample size. We have now included a reference in our sentence describing data saturation. This sentence now reads; “Sample size will be determined by data saturation, i.e. when no new themes are being uncovered4.”

We have changed the following paragraph: “We estimate that a sample size of 45 will be sufficient to determine: feasibility, acceptability, the appropriate number of follow up sessions, paper/web based collection of outcome measures (or both) and to collect sufficient information to determine the sample size for a full, adequately powered study.” To “ “We estimate that up to 45 patient, parents and clinical staff interviews will be sufficient to determine whether it is feasible and acceptable to take the study to full trial, and to identify ways to improve study processes.” We feel this offers a more clear and concise description of the qualitative aims.

To clarify what was meant by practitioner we have re-worded this sentence from “10 practitioners will be interviewed at a location of their choice” to “10 clinicians involved in recruitment and/ or delivering the intervention will be interviewed at a location of their choice”. We have also changed “a sample size of 45” to “up to 45 patient, parent and clinical staff interviews”, in order to clarify exactly who we will be interviewing.

P 11, Outcome Measures: The paragraph about Accelerometers and data should be in the Methods – Clinical Intervention section, with further clarification and detail. Please include –
- Whether all participants in GET and AM will wear accelerometers
- Will accelerometers be worn for each exercise session at home, school or elsewhere

Accelerometers are not being used as part of the clinical intervention; neither participants nor clinicians see the data. The data from the accelerometer is being used purely as an outcomes measure. We therefore feel it is best placed in the outcome measure section rather than the clinical intervention section.

We state: “In addition to questionnaire measures, participants in both trial arms will be asked to wear an accelerometer (GT3X+) to measure physical activity”. We feel that this clearly indicates that both GET and AM participants will be asked to wear the accelerometer.

We agree that further clarification should be provided about where/when the accelerometers will be worn. We have therefore changed the current sentence: “participants in both trial arms will be asked to wear an accelerometer (GT3X+) to measure physical activity for seven days within one month of randomisation and at 3 and 6 months follow-up”. To: “participants in both trial arms will be asked to wear an accelerometer (GT3X+) to measure physical activity for seven days within one month of randomisation and at 3 and 6 months follow-up. During this seven day period, participants will be instructed to wear the device for the entirety of the day.”

P 12, Line 35-36. Replace “treatments” with “interventions” for consistency, as you are referring to GET and AM.

Thank you. Where appropriate we have changed instance of “treatment/s” to “intervention/s”

Lines 37-38. Confusing – you change from talking about interventions to follow-up sessions; are the sessions interviews or GET/AM – this needs to be clarified earlier in the manuscript.

Thank you. We agree that we have, rather confusingly, used the term “follow-up” for both research data collection follow-ups and clinical appointment follow-ups. We will therefore change all instances where we have described clinical follow-up to “clinical sessions”.

Line 44: remove “treatment” and replace with “intervention”.
P 13, Line 10: as above

This has been done, thank you.

Lines 11 and 14: What is DSMC? Please use full words in the first instance, then the anagram.

The first time we refer to the DSMC we state: is on page 13 and in this first instance we have written the full name “Data Safety Monitoring Committee”.

Table 1: there is no exercise assessment or physiological data displayed. For clinical exercise professionals, it would be useful to see baseline exercise capacity and physiological measures (e.g. HR, BP, exercise assessment results) for comparison to later, post-training outcomes measures – after all, you are comparing GET to AM and intervention effectiveness was one of the project aims.

The HR and exercise assessments are being used as a GET clinical tool to support clinical assessment and intervention. HR and exercise assessment only occur in the GET arm and therefore comparisons between the two arms would not be possible.
Accelerometer data is being used as our outcome measure for physical activity. This is detailed in the “outcome measures” section.

P14, paragraph 2: All the accelerometer information should have been written in the Methods – Clinical Intervention section; please put it there with the relevant outcomes measures following (see my previous comment above).

Thank you. We address this above.

Line 49: please explain the “established methods” for calculating accelerometer data that you will use, with references.

This feasibility study is determining whether the use of accelerometers is feasible and acceptable; analysis of the accelerometer data is beyond the scope of this feasibility study. The data will be analysed as an outcome measure should the study proceed to a full-scale trial. For the reporting of feasibility studies, detailed analysis plans of the full-scale trial outcomes measures is not necessary. We have now included references to our sentence about using established methods.

We will be guided by the editor as to whether full details of accelerometer data analysis should be included in this feasibility protocol.

P 19, REFERENCES: suggest that the authors include publications by Lim and Lubitz (2002); Gordon and Lubitz (2009); Gordon et al (2010); van Cauwenbergh et al (2012); ACSM or similar guidelines for exercise prescription. Further references for power calculations and supporting documentation should be included.

Thank you. References to these papers enhance our paper and have now been included in the introduction. Our sentence now reads: “GET stabilises physical activity levels, before gradually increasing at a manageable rate1 5 6 7 8 9”

SUPPLEMENTARY FILES

AM, P 1, Line 34. Please justify the use of 10-20% progression for use with children/adolescents with CFS.

Please see our previous response detailing NICE guidance on AM and GET delivery and reference to the PACE trial.

This group should have the same physical assessments as the GET group (for comparison), considering that both groups will be recording physical activity via app and accelerometer.
Please add the use of accelerometers to record incidental exercise and physical activity.

Physical assessments used in the GET arm are being used for clinical assessment and intervention purposes, they are not being used as comparative outcome measures. Therefore they are not detailed in AM.
The accelerometer is being used as the comparative outcome measures. As this is a research outcome measure and not part of clinical intervention, we do not feel it is appropriate to include this in a description of the clinical intervention.

GET, This section is very poorly written and as a protocol paper, needs a lot more information.
Please add the following information –

Will this group have the same cognitive assessments as the AM, as you will be comparing both groups (shouldn’t both groups will have exercise and cognitive assessments if you are comparing the effectiveness of both interventions).

Neither arms involves formal cognitive assessment, neither as a clinical tool nor as an outcome measure. In AM we state that “Participants will be taught how to find their baseline of cognitive activities”. We then explain that these include activities that young people spend most of their day doing and we explain that they include: “school, school work, reading, socialising, and screen time (phone, laptop, TV, games).”
We are not planning to do cognitive assessment in either arm and we cannot find reference to this in the paper.

Describe the physical/exercise assessments to be completed in Week 1.
Describe the types of exercise done in Week 1 (incidental, aerobic, anaerobic, strength or flexibility or mixed modes?). State all the functional and aerobic tests used if more than 2 MWT and Sit to Stand (e.g. manual muscle tests, hand grip strength); you have written “included” so that suggests more than 2. Why did the AM group not do the same assessments?

We appreciate that different clinicians may apply GET differently and different researchers may have different approaches to testing a very protocol driven or pragmatic trial. We believe that a pragmatic approach as opposed to a protocol or explanatory approach is helpful for research that will be delivered in the NHS10. This is because, we are interested in testing what therapists will ultimately deliver. Our initial qualitative work suggests that both children, and the clinicians involved in the study value this approach and we will be reporting on this later.
We have made this clearer by:

1. Adding the following to the introduction: “The trial is designed as a pragmatic trial as we are interested in the effectiveness of interventions delivered in routine practice10.”
2. The following to the description of AM: “Clinicians therefore have flexibility in delivering the intervention within their NHS setting.”
3. And the following to the description of GET “They will be encouraged to deliver GET as they would in their NHS setting”

We state: “Physical assessment, assessment of range and type of exercise used during the week at the first assessment. Functional muscle test at assessment and 6 months including: sit to stand and 2 minute walk test (distance covered)”. Physical assessments used in the GET arm are being used for clinical assessment and intervention purposes, they are not being used as comparative outcome measures. Therefore they are not detailed in AM.

Is the exercise only home-based or will it be done at school or other centres, and who is going to supervise or monitor it (parents, carers, or self-report only).

Thank you, we agree that further clarity about the setting is needed. We have now added in the following: “Both interventions are delivered in an outpatient setting. During intervention sessions clinicians and patients develop collaborative activity plans, which children and adolescents then implement in the community (including home and school environments).”

Please justify the use of 10-20% progression for use with children/adolescents with CFS.

Please see our previous response detailing NICE guidance on AM and GET delivery and reference to the PACE trial.

Define “30 minutes of gentle exercise”. What exactly will they be doing? What are the intensities for “gentle”, since you are using HR as a measure of intensity? Would strongly recommend you also use RPE. Please clarify the sentence “once children are doing 30 minutes of gentle exercise each day, the exercise will increase in intensity such that participants start doing aerobic exercise”. This makes no sense – aerobic exercise is sustainable exercise using the large muscle groups. If they are not starting with aerobic exercise such as walking, what are they doing?

GET is carried out as a person-centred treatment with exercise based on the child’s individual activities in their community (e.g. home and school environment), rather than a uniform exercise regime. We therefore state “Exercise targets will be negotiated with the child and parents/carer.”

We agree that gentle could be better defined and as such we have changed this sentence from “Once children are doing 30 minutes of gentle each day, the exercise will increase in intensity such that participants start doing aerobic exercise” to “Once participants are doing 30 minutes of daily exercise within the low intensity heart rate limits, the exercise will increase in intensity such that participants start doing aerobic exercise”.

The usual progression for CFS patients is to gradually increase duration of exercise, before increasing intensity, otherwise you risk exacerbating symptoms.
“The aerobic component will then be slowly increased…..” What does this actually mean? What other exercise are they doing apart from aerobic (e.g. strength, flexibility, games?) and please state the components of the exercise program.
We agree and we state:

The intervention will encourage children and adolescents to find a baseline level of exercise which will be increased slowly (by 10-20% a week). We have now referenced this increase (as discussed

above).

HR monitoring – how are children under 10 yr going to monitor intensity or effort?

We state: “Younger children or those who cannot measure their heart rate will learn how to monitor their heart rate with their parents”. This heart rate monitoring with parental supervision will allow participants to monitor intensity.

Please reword sentence Line 36 to state that children will be using a HR monitor to prevent them doing too high an exercise intensity rather than “too much”.

Thank you. We have changed the wording “too much” so this sentence now reads “Participants aged 10 and over will be taught how to monitor their heart rate using a heart rate monitor to prevent them doing too high an exercise intensity”.

How are target HR to be calculated? Please reference this section according to exercise guidelines for children.

We have now included references to NICE guidance and the PACE who both refer to calculating target heart rate zones for GET. This sentence now reads: “Participants aged 10 and over will be taught how to monitor their heart rate using a heart rate monitor to prevent them doing too high an exercise intensity. They will be set a target heart rate and asked not to exceed this1 2.”

Lines 47 – 52. Health Dept guidelines are for healthy children not those suffering from a fatiguing illness. Vigorous exercise is usually contraindicated for CFS patients due to the risk of symptom exacerbation. These guidelines mention a mixed-model approach to exercise programming (aerobic, strength and flexibility components) but the authors have not described the GET programs they will be using with the participants. For a protocol paper, this needs to be proposed in reasonable detail.

Please see our response above about pragmatic trials. We believe that given the high recovery rate in children, they have a right to aim for recovery and therefore to be as fit (ultimately) as healthy children. We therefore feel the DoH guidance for healthy children as an ultimate aim is appropriate. In addition, this is a feasibility study and our integrated qualitative methodology enables us to explore these issues.

How is exercise participation to be managed in the event of increased symptoms?
Will children be advised to rest and will their exercise program be scaled back to more manageable duration and intensity?

We will use our usual clinical approach (as recommended by NICE) to manage setbacks. We have added, “and setbacks” to the section describing general approaches applicable to both arms. This sentence now reads: “In both arms clinicians will be encouraged to offer routine1 advice about sleep, medication use, symptom control and set backs at the assessment and during intervention sessions.” We do not think it appropriate to detail all routine management in this protocol paper as it will add substantially to the length of the paper, but are happy to be guided by the Editor if they wish us to do this.

Flexible elements – it seems ROM is not a mandatory assessment but a flexibility (stretching) program can be given to participants and they can be “offered a strengthening program”…… If they are not doing strength and flexibility exercises in their program, are they only doing aerobic exercise? This is not clear in the first section of the GET appendix and should be.

We believe we have clarified this (see above)

When are you re-assessing exercise performance? Only pre- and post-trial or during the 12 months?

The assessment of exercise performance is for GET clinical assessment and intervention purposed not an outcome measures administered at pre and post time points. The assessment is therefore carried out at baseline and 6 months. We have indicated the time points for GET physical statement in our sentence: “Functional muscle test at assessment and 6 months”.

Thank you again for considering this protocol for publication
Yours

Dr Esther Crawley

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VERSION 2 – REVIEW

REVIEWER	Suzanne Broadbent Southern Cross University School of Health and Human Sciences Lismore NSW 2480 Australia
REVIEW RETURNED	03-May-2016

GENERAL COMMENTS	The authors have revised the manuscript once and it is much clearer. The section on Graded Exercise Therapy still needs minor revision, in my opinion, as it currently does not disclose the types of exercise participants will be engaged in, and a couple of the referenced guidelines from NICE are incorrect or not appropriate (see attached document for more detailed comments). If the authors can complete the minor revisions outlined, then the paper is ready for publication. **REVIEWER RESPONSES TO AUTHOR RESPONSES** Manuscript ID bmjopen-2016-011255.R1, entitled "The Managed Activity Graded Exercise iN Teenagers and pre-Adolescents (MAGENTA) feasibility randomised controlled trial: Study Protocol.." May 3rd 2016. Firstly, I thank the authors for their hard work on the manuscript, which reads much better and is certainly much clearer. I am happy with most of the amendments. The only issue I still have is with the lack of clarity and description of the graded exercise program itself, and some of my previous comments have not really been addressed. This is a protocol paper and as such needs to be clear enough to replicate – the current version still needs work. In particular, I highlight the author responses below and my concerns with those responses. 1) *"Once participants are doing 30 minutes of daily exercise within the low intensity heart rate limits, the exercise will increase in intensity such that participants start doing aerobic exercise".* This sentence still makes no sense. I think the authors are trying to say that participants will be doing up to 30 minutes of play and low intensity recreational physical activity (not planned exercise), and once this is established, participants may be able to move onto more structured aerobic exercise at a higher intensity. By definition, aerobic exercise is any exercise that noticeably increases heart rate, last for more than 10 minutes, and that uses the larger muscle groups (see Heyward and Gibson 2014 or ACSM guidelines), therefore relying on aerobic metabolism. So the authors need to be a lot clearer in their description of what the children will be doing BEFORE they incorporate aerobic activity and then what kind of aerobic exercise they may be doing (e.g. walking, sports involving running, swimming etc). The NICE definition is "any activity that increases pulse" which is not really correct as strength training also increases heart rate. The PACE trial results were very sketchy about what participants did and only mentioned walking as the most common example of aerobic activity undertaken (White et al, 2011) 2) *A progression of up to 20% is the guidance provided by the National Institute of Clinical Excellence1 and is standard practice in the UK. This is also consistent with the PACE trial, the largest trial done to date. We have now included a reference to NICE guidelines and the PACE trial, the protocol now reads: "The intervention will encourage children and adolescents to find a baseline level of exercise*

which will be increased slowly (by 10-20% a week, as per NICE guidance1 and the PACE trial2)".

The NICE guidelines state that a progression of up to 20% is deemed appropriate for CFS/ME clients. There is no reference in any of the published PACE articles, that I can find, that defines the actual progression. This was one of the many faults of the reporting of this trial. I suggest removing the reference to PACE and using the NICE guideline.

3) *Page 34, Line 24 – revised manuscript. Target heart rate of between 60 – 80% .*

The NICE guidelines state 50 – 70% of max HR. I used 60-80% as an example in my previous review. If the authors wish to follow NICE guidelines, I suggest they amend the HR zone to 50-70%. I also, again, strongly recommend that the authors include RPE (rate of perceived exertion) alongside HR to monitor intensity, as RPE is also recommended in the NICE guidelines.

4) *Revised Appendix – a mixed model (aerobic, strength and flexibility exercise) approach is mentioned as part of the Dept of Health Guidelines but the authors have not explained it clearly in their GET section. Gentle physical activity progressing to aerobic exercise is mentioned but nothing about how strength and stretching will be incorporated.*

For exercise clinicians/therapists, this really needs to be clear. An explanation such as "gradual addition of aerobic exercise, strength and stretching may be incorporated into the GET program as negotiated between participant, parents and therapists" could be included. The referencing of the PACE trial is not appropriate as nowhere in the PACE protocol paper (2007) or the main results paper (2011) can I find any description of what sort of graded exercise the participants actually did. Only the 2011 paper mentions that walking was the most popular choice.

In summary, the authors have made major amendments but the GET section still needs work, as it should be very clear to readers who are exercise therapists, physiologists and physiotherapists what sort of exercise programs/activities can be utilised as GET. Vague statements that therapists will administer GET as they would in the NHS settings means nothing to exercise professionals/allied health clinicians who are a) not working in NHS; and 2) work outside the UK but are interested in this project. The many references to the PACE trial may be inappropriate for this project, as the PACE trial has been highly criticised for fundamental flaws in its design and reporting of GET/APT and other outcomes.

VERSION 2 – AUTHOR RESPONSE

Please find below the reviewers comments in bold, with our responses.

1) **"*Once participants are doing 30 minutes of daily exercise within the low intensity heart rate limits, the exercise will increase in intensity such that participants start doing aerobic exercise*".**

   This sentence still makes no sense. I think the authors are trying to say that participants will be doing up to 30 minutes of play and low intensity recreational physical activity (not planned exercise), and once this is established, participants may be able to move onto more structured aerobic exercise at a higher intensity.

   By definition, aerobic exercise is any exercise that noticeably increases heart rate, last for more than 10 minutes, and that uses the larger muscle groups (see Heyward and Gibson 2014 or ACSM guidelines), therefore relying on aerobic metabolism. So the authors need to be a lot clearer in their description of what the children will be doing BEFORE they incorporate aerobic activity and then what kind of aerobic exercise they may be doing (e.g. walking, sports involving running, swimming etc). The NICE definition is "any activity that increases pulse" which is not really correct as strength training also increases heart rate. The PACE trial results were very sketchy about what participants did and only mentioned walking as the most common example of aerobic activity undertaken (White et al, 2011)

We state "During clinical sessions clinicians and patients develop collaborative activity plans, which children and adolescents then implement in the community (including home and school environments)." Low intensity activity is planned out by the therapist and participant in a structured way as part of the treatment plan. The types of planned low intensity exercise may include: low paced walking and low resistance cycling.

These types of activity meet the NICE definition for non-aerobic activity as they do not increase pulse rate. We have therefore clarified this sentence by making it clearer exercise is planned, providing examples, and changing the wording aerobic to exercise that increases heart rate. The sentence has been changed from "*Once participants are doing 30 minutes of daily exercise within the low intensity heart rate limits, the exercise will increase in intensity such that participants start doing aerobic exercise*" to "*Once participants are doing 30 minutes of planned exercise within the low intensity heart rate limits (such as slow paced walking), the exercise will increase in intensity such that participants start doing exercise that increases their heart rate (for example faster paced walking, cycling)*".

2) ***A progression of up to 20% is the guidance provided by the National Institute of Clinical Excellence[1] and is standard practice in the UK. This is also consistent with the PACE trial, the largest trial done to date. We have now included a reference to NICE guidelines and the PACE trial, the protocol now reads: "The intervention will encourage children and adolescents to find a baseline level of exercise which will be increased slowly (by 10-20% a week, as per NICE guidance[1] and the PACE trial[2])".***

   The NICE guidelines state that a progression of up to 20% is deemed appropriate for CFS/ME clients. There is no reference in any of the published PACE articles, that I can find, that defines the actual progression. This was one of the many faults of the reporting of this trial. I suggest removing the reference to PACE and using the NICE guideline.

The PACE trial provides the most detail to date in the largest trial ever conducted in CFS/ME. We therefore feel that referencing this important trial is valid. However, we have added further references to the trial manual which is publicly available and answers the reviewers questions as below. The PACE trial treatment manuals are available on the website, see "GET manual Version 7, ISRCTN54285094, MREC Version 2; 16/11/04" http://www.wolfson.qmul.ac.uk/images/pdfs/5.get-

therapist-manual.pdf Authored by Bavinton J, Darbishire L, White PD On behalf of the PACE trial management group. This manual states the following:

Page 38: “Negotiate and add baseline of exercise at low intensity” then “Add 20% duration, up to 30 minutes”

Page 49: “Once a baseline can be achieved comfortably, often leading to a reduction in Borg scale ratings, the participant should be encouraged to increase the duration of the exercise. The incremental increases should not be any more than around 20%. E.g. A 5-minute walk becomes 6 minutes; a 2-minute bounce on a rebounder might become at most 2.5 mins.”

We have updated the PACE reference to indicate that we are also referring to this treatment manual. Our sentence now reads: *“The intervention will encourage children and adolescents to find a baseline level of exercise which will be increased slowly (by 10-20% a week, as per NICE guidance[1] and the PACE trial [2 3])”.*

3) **Page 34, Line 24 – revised manuscript. Target heart rate of between 60 – 80% . The NICE guidelines state 50 – 70% of max HR. I used 60-80% as an example in my previous review. If the authors wish to follow NICE guidelines, I suggest they amend the HR zone to 50-70%. I also, again, strongly recommend that the authors include RPE (rate of perceived exertion) alongside HR to monitor intensity, as RPE is also recommended in the NICE guidelines.**

Thank you very much for highlighting this. We have revised the heart rate training zones from 60-80% to 50-70%. We have reworded the protocol from “Participants will be advised to stay within the target heart rate zones of 60-80% of their maximum heart rate[1 3”] to “Participants will be advised to stay within the target heart rate zones of 50-70% of their maximum heart rate[1 3”]

We have gathered extensive data from participants on questionnaire burden and do not intend to add this for children taking part in our trial.

4) **Revised Appendix – a mixed model (aerobic, strength and flexibility exercise) approach is mentioned as part of the Dept of Health Guidelines but the authors have not explained it clearly in their GET section. Gentle physical activity progressing to aerobic exercise is mentioned but nothing about how strength and stretching will be incorporated. For exercise clinicians/therapists, this really needs to be clear. An explanation such as “gradual addition of aerobic exercise, strength and stretching may be incorporated into the GET program as negotiated between participant, parents and therapists” could be included. The referencing of the PACE trial is not appropriate as nowhere in the PACE protocol paper (2007) or the main results paper (2011) can I find any description of what sort of graded exercise the participants actually did. Only the 2011 paper mentions that walking was the most popular choice.**

Thank you. Again, we have added the reference to the PACE trial manual which offers a detailed description of the GET programme delivered. We believe that providing examples of exercises (as outlined above) offers further clarity.

We state in the GET flexible component section: “Participants can be shown how to do stretches. They can also be offered a strengthening programme if this is one of their goals.” We feel this describes the strength and stretching components of our programme.