Author’s response to reviews

Title: The feasibility and acceptability of an early intervention in primary care to prevent Chronic Fatigue Syndrome (CFS) in adults: randomised controlled trial

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Author’s response to reviews:

Dear Sir,

RE: PAFS-D-19-00108

The feasibility and acceptability of an early intervention in primary care to prevent Chronic Fatigue Syndrome (CFS) in adults: randomised controlled trial

Thank you for the helpful reviewer’s comments which have improved the paper. We have addressed all the issues as detailed below.

Reviewer #1: Thank you for the opportunity to review this manuscript. This study describes an ambitious feasibility study to recruit patients with fatigue from GP and explore the feasibility and acceptability of offering usual care versus an early intervention. The study has several strengths including recruitment of 14 GP practices and cross-checking against medical record consultation codes etc. However, there are several aspects of the manuscript which need additional work and
revision. In particular, the recruitment and randomisation approach is not well described, it needs to be much more clearly and sequentially set out. In addition, the rationale and justification for the study needs to be strengthened, including the link between fatigue, chronic fatigue and CFS.

Please find below my specific comments and suggestions:

Abstract

Remove additional '.' Line 38
Thank you. This has been amended and the additional full stop within brackets removed

Should add detail about the participants- those with fatigue etc. Could also add something about the main outcome measures to the methods- eg % consent rate, GP and patient qualitative interviews about recruitment issues and acceptability of the intervention etc

Conclusion: Should fatigue be CFS?
Thank you. Details about participants are reported in Table 1 (Baseline characteristics). As this is a feasibility study, there were several aspects that we used to assess this which we discuss in “Data analysis”: “We estimated the number of eligible patients from routinely recorded data. We recorded the number of potentially eligible patients who consented to contact, the number who were eligible, and the number who consented to the study, were randomised and those who declined.”

Introduction

I was surprised at the high prevalence of chronic fatigue (10-24%)- what is the reference for this figure? This should be added. Also the study exploring progression from glandular fever to CFS is not referenced.
Thank you for spotting that we had not added references (now done). We have also made it clearer that we are referring to one month of fatigue only (and therefore possibly not chronic) by changing the sentence to read: “Fatigue lasting more than one month is reported by 10-24% of attendees in general practice (1-3).”

It's a little unclear whether the intervention is for 'disabling fatigue', for 'short or long term fatigue', or for CFS. In the introduction both CFS and disabling fatigue are mentioned, in the methods 'short or long term fatigue' is. The title implies it's about CFS, but really the study focuses on patients reporting short or long term fatigue. Presumably the full scale trial would look at whether patients with fatigue go on to develop CFS? This needs to be clarified throughout the paper. I think a better justification for intervening with fatigue is needed, including what proportion of patients with fatigue will go on to develop CFS.

Thank you. The aim of this study was to assess the feasibility of an intervention designed to try and stop patients with early fatigue that was disabling and lasted between 1-4 months to develop CFS/ME. We have tried to make this clearer by adding the following sentence to the first paragraph of the introduction: “however it is not known whether early identification and
treatment of disabling fatigue can prevent the onset of CFS/ME.” And then changing “an episode of chronic fatigue” to “a patient with disabling fatigue”. This sentence now reads: “Addressing these ‘predisposing’ factors using cognitive behavioural approaches could reduce the probability of a patient with disabling fatigue lasting 1-4 months becoming the debilitating long term condition that is CFS/ME.”

Was one of the study aims also to look at acceptability of recruitment/intervention to GPs? Not as a separate aim. We interviewed GPs because we couldn’t get recruitment to work.

It's not clear what is meant by 'the distribution of patient reported outcome measures'. Thank you. We have clarified this to “outcome measure results”.

Methods

Population: Deprivation scores- this is not clearly expressed. Do the authors mean that the patient sample aimed to be representative based on deprivation scores of the population of Bristol?
Add 'patients' after 'each had a list of 10,000'.

Thank you. We have clarified this (and included the comments from reviewer 4) so it now reads: “When a practice expressed an interest, their deprivation score was checked using the Public Health Observatories General Practice Profiles (8) to investigate how representative the sample of patients was. Practices across Bristol varied in their deprivation score which reflects population socioeconomic status.”

The calculation of 100 patients in 12 months is confusing. Wouldn't you need to also specify how many patients of the 10,000 visit the GP at least annually? See above the comments about 'short or long term fatigue' vs CFS.

We have added this to make it clearer that in each GP practice, we would expect 5000 appointments where fatigue is discussed. This paragraph now reads:

Add the reference for the 35% of patients reporting short or long term fatigue, and how is this consistent with 10% of GP consultations recording a complaint of fatigue?
We have deleted this sentence, even though this added weight to the fact that fatigue is common, because of reviewer 2 comments. This paragraph is now simplified and reads:

A target of 100 patients was set based on the fact that approximately a tenth of all GP consultations record a complaint of fatigue (1,3). Assuming each GP practices had a list of 10,000, this would suggest there would be 5000 appointments in each year where fatigue was discussed (10). We therefore assumed, it would be feasible to recruit 100 patients in 12 months. Sample size calculations are not always appropriate in feasibility studies (11), therefore this number was considered adequate to estimate the parameters required to design a larger trial.
The sentence 'usual medical management in primary care 70-75% patients report that their fatigue persists at a year' is unclear. Does this mean that of the 35% of patients reporting a primary complaint of fatigue, 70-75% of these will still report consistent fatigue one year later? Yes. Although this sentence has now been deleted.

Line 109: remove 'least' from 'reported fatigue for at least than a month but less than 4 months…' As noted above, this section needs more detail about the timing of recruitment. Eg a patient might see their GP for fatigue, but presumably the GP wouldn't have the blood test results available at this appointment- so did GPs recruit patients when they came back for their blood test results etc?
We have deleted “a” in this sentence. We are not certain that deleting “least” will clarify this sentence as this will lead to confusion over the timing. Patients needed to have had fatigue for at least one month and less than four months.

We think these problems were one of the main reasons why the study was not feasible and therefore we discuss this issue for GPs in the conclusions: “The majority (10/12) of GPs cited a general lack of patients fitting the study eligibility criteria as the main difficulty in referring the expected numbers of patients to the feasibility study for recruitment. The eligibility criteria were seen as limiting because the ‘window of opportunity’ that GPs had to identify and refer patients was too narrow (more than one, but less than four months of fatigue).

Patient recruitment:
Need comma after (patient information sheet); RCT should be spelt out for first time use; Remove additional '.' after consent forms.
We have added a comma after Patient Information sheet, changed RCT to study and removed the additional ‘.’ After consent forms.

Remove reference to randomisation in the patient section- since you have a section on this below.
We have carefully considered this, but this detail has been requested by the reviewer in the section on randomisation. We have therefore left this in the paper.

Add comma after (TATT)
A comma has been added.

Perhaps another subheading should be added in methods regarding extraction of consultation codes. It is not clear what the purpose of the patient consultation code extraction was? Was this to check how many of the potentially eligible patients were recruited? Or missed etc? Also, why is this reported under both patients and GP sections. Was this the same first 100 records, or was this done twice? You could add that this was to establish the prevalence of patients reporting fatigue or something like that, and to explore why patients were excluded.

This was to understand whether failure to recruit was because there weren’t any eligible patients. This is discussed in detail elsewhere in the paper. We would be happy to seek the editors’ advice on whether a further subheading is appropriate.
Randomisation- when did randomisation take place? What does 'allocation was minimised by gender and age' mean? It is not clear how patients were randomised- do you mean patients received an automated telephone call to be told their allocation? Was this after the home visit?

We describe when randomisation takes place in the first paragraph of patient recruitment. We state that this usually happened in the patient’s home.

Minimisation by gender and age is a standard term in trials. It is used to ensure an even balance between treatment arms.

It's not clear how allocation could be concealed when the intervention involved face to face treatment and phone calls- or was the therapist independent of the researchers i.e. the researchers conducting follow up did not know which patients were randomised to the intervention?

The statement about allocation concealment is about whether the recruiter could know about allocation prior to recruitment. It is not possible to conceal allocation during a behavioural intervention.

You should also add that patients could change their randomisation if they wished- is that correct?

Patients could not change their randomisation if they wished. Patients could opt out of treatment as we describe in this paper (most did not find treatment acceptable).

Results:

Numbers under ten should be spelled out. There are missing fullstops and incorrectly places commas through the results section-please revise.

This has been done however, we have not changed all the numbers as in some cases, this reduces readability. We would be happy to be guided by the editors if they wish us to do this.

Under methods you say that eligible patients were asked to consent to contact from the research team and a recruiter visited patients to provide and explain the PIS, but under results you say that patients did not respond "or were not given a PIS by the GP". This is unclear.

The methods state what should happen or the methods of recruitment. We are transparent in our reporting. And we are clear that in some cases, GPs did not provide potential participants with information about the study. In our experience, this is a normal part of recruiting into a study.

As above, the process of randomisation and whether patients could change/reject their allocation needs to be clarified. The results state that "all 28 participants accepted the allocation at the randomisation appointment", whereas the methods talk about: "whether or not the study participant accepted randomisation". This is unclear and confusing. What was the randomisation appointment? And why is this section labelled 'Lack of compliance with the treatment arm' when it talks about all patients accepting randomisation and describes the characteristics of the 2 groups (rather than anything about compliance with treatment)?

The methods are the protocol used in this study, and the results are what actually happened. This explains some of these differences. So, we would have been particularly interested in those that did not accept randomisation and this was in our matrix for recruiting to qualitative interview. However, they all accepted.
We could delete this information, but feel that full transparency is important.

Whether a patient accepts the allocation is different from whether they have treatment. In this study, patients accepted the allocation, but then didn’t actually like the intervention. This is why so many didn’t complete it.

The randomisation appointment is described in the Patient Recruitment section: “Patients were randomised to either usual care or usual care plus EI”

Under the patient note review, how can there be 100 records on EMIS sampled retrospectively, and 199 patients reported symptoms that matched the criteria?

We agree that this was confusing and unclear. It also did not provide the full picture of the data (additional file 1). In the methods we describe the two phases: “Data were requested from each practice on the consultation codes used during the period of the study. Consultations with the following codes on Egton Medical Information Systems (EMIS) were counted: Tired all the time (TATT), fatigue, exhausted, malaise, lethargy. EMIS records for a sample of the first 100 consultations from one practice from the date they entered the study were selected for more detailed analysis. The records were checked retrospectively, against the study eligibility criteria.”

We have made this clearer in the results section by adding changing the paragraph which now reads: “In the 14 recruiting practices, 1711 patients were recorded as being Tired All The Time (TATT) or presenting with fatigue, exhausted, malaise, lethargy between 1st of April 2012 and 30th of June 2013 (see additional file 1) In the more detailed review, of the 100 records on EMIS sampled retrospectively, 56 out of the 100 analysed, met criteria for eligibility, as they did not have any other exclusionary medical or psychological diagnosis to explain the fatigue which had lasted between one and four months, however only 2 patients were recruited into the study. Of the remaining 54 patients who appeared to be eligible but were not recruited, one later developed CFS and one developed post viral fatigue syndrome.

I'm not sure whether the results reported under 'Recruitment consultations' are necessary- you could just state that the recruiter was trained and provided with feedback.

This study was not feasible, and we believe it is important to demonstrate the likely areas that meant this study should NOT be repeated. We provided very detailed training for recruiters to try and improve recruitment which is unusual in RCTs and we do not believe this is why the study failed.

'Semi-structured, in-depth interviews were undertaken with patients and with the GPs'. This should be moved to the methods section.

We have deleted this sentence

Not sure that the quotes work well here- it might be better to group results under key themes raised?

We have presented a thematic analysis with quotes grouped under key themes raised (for example “interventions” and “study documentation”).
Conclusions

I was surprised that GPs did not mention time constraints as a barrier to recruitment of patients? This is why qualitative interviews with GPs are so important.

What are the implications of the findings of the feasibility study in terms of future research and the full scale trial? Will the authors still proceed with the larger trial? What will they modify in terms of recruitment approach and the intervention?

We do not believe this study is possible. We state: “Future studies should explore different recruitment mechanisms in GP surgeries including list searchers and using PCRN-funded staff to recruit patients as well as explore why GPs do not appear to feel that early intervention is helpful (and therefore refer into the study).”

Reviewer #2: Review

Abstract

Well written abstract with the appropriate components. Refreshing to note a transparent description of the outcomes and that many elements of the project were not feasible, thus resulting in a set of solid recommendations for the design of a future study. This is what a pilot or feasibility study is all about, so well done to the researchers for their transparency and honesty around outcomes. Although it is correct to explore recruitment and retention in a pilot study, this could be extended to cover the topics of randomisation, acceptability of treatment, research design and sample size calculations, although some of these outcomes are not that relevant in this particular study.

Thank you

Introduction

Good introduction and description of CFS related to glandular fever. A paragraph on additional factors or speculated causes of CFS could be added here to demonstrate the breadth of the problem.

We would be delighted to do this but given the multiple theories and lack of evidence on CFS/ME, this may take more than a paragraph and we are concerned this will extend the introduction by several paragraphs greatly extending the word count. We are not convinced this is helpful for this paper but will do this if the Editors think it will improve the paper.

Furthermore, the Introduction should include 2-3 paragraphs involving a critique of past research where design and confounding factors in the research are identified and discussed. This would support the need for a pilot or feasibility study to specifically investigate the design and implementation issues when investigating interventions for CFS.
We discuss the only relevant past research for this patient group (early disabling fatigue). The lack of papers discussed reflects a lack of evidence. We have improved these two paragraphs to be clearer and more critical. They now read:

“A study that explored the pathway from glandular fever to CFS/ME found that 9.4% of (N=234) participants were chronically fatigued at 3 months, and 7.8% of participants met the criteria for CFS/ME at 6 months (5). The conclusions indicated areas for early intervention based on addressing particular characteristics, including anxiety, depression, somatization and perfectionism (5). Addressing these ‘predisposing’ factors using cognitive behavioural approaches could reduce the probability of a patient with disabling fatigue lasting 1-4 months becoming the debilitating long term condition that is CFS/ME.

Evidence to support early intervention was provided by a small (N=69) randomised controlled trial based in primary care, which suggested there were fewer cases of fatigue (odds ratio 0.31, 95% Confidence interval 0.09-0.91) in patients randomised to a psycho-educational intervention compared to controls (6). The psycho-education was based on a behavioural model of fear-avoidance and suggests recovery may be delayed due to prolonged rest. This hypothesis is presented to the patient and a suggested activity plan is given to guide them on a graded reintroduction of physical activity. However, we do not know whether this approach translates to patients presenting with fatigue in general practice or whether it is only useful in those whose chronic fatigue has been triggered by glandular fever (or some other viral infection).”

There is not doubt that this study is needed since early intervention for a chronic problem like CFS is emerging as important in management.

The aim of this pilot feasibility study is clearly stated, but what are the objectives of the study that will address the aim or purpose of the study i.e. what will be done in the study to achieve the aim?

These are provided in the final paragraph of the introduction where we state: “The aim of the study is to estimate study parameters including: the feasibility of recruitment (including the number of eligible patients presenting to primary care); the acceptability of the intervention to patients and the distributions of patient-reported outcome measure results”

Methods

A sound rationale and argument are provided for the selection, population, and sample size for this pilot study, being reasonable and appropriate.
Patient recruitment was appropriate, with a good approach to selection and recruitment, which included information sharing and voluntary participation/consent.
GP recruitment was appropriate and a valuable contribution to the design and planning for the study. This approach described shows information sharing, planning and preparation of the GP practices, which is appropriate.
Randomisation is relevant and appropriate.
Thank you
Reasonable description of the interventions, although a bit more detail would be good regarding the usual interventions i.e. what medication is often prescribed, what are the common specialist services. The NICE guidelines are important, but do all GPs adhere to this? I am afraid this information is not available, although we provide some indicators from the qualitative interviews.

Satisfactory description of the experimental intervention, the early intervention. Qualitative analysis was appropriate and very done, demonstrating a good way of examining and evaluating patient and GP responses. Data management was good and considered anonymity and confidentiality. Thank you

Results

Good description of the patients, patient flow and CONSORT. Baseline and results data are appropriately described and presented. Good commentary on qualitative information/data with an effort to maintain equipoise. Good description and account of patient and GP interview, obtaining useful insights related to the research process and data collection. Good recommendations are offered to counter problems or unacceptable processes. Excellent that this study identified that recruitment of eligible patients was difficult, which would of course, have a major negative impact in a future definitive study. Thank you.

A paragraph on the funds and resources needed to recruit and treat patients in this pilot study would be useful, so to guide the costs/funding needs for future trials. Please can you clarify? We do not believe a future study using this methodology should be conducted.

Discussion

Good insights as to the problems encountered with the study and aspects that made the study design unacceptable to patients and GPs. A realistic outcome and transparent reporting on a very real problem within practice - recruitment and compliance.

A brief set or list of recommendation that may improve a future study and the research design would be good, to complete the paper.

Conclusion

Appropriate and good. Thank you
Reviewer #3: This is a reasonably written manuscript with most detail appropriately covered. However, I do have a number of issues that I would like addressing, which I have covered within major and minor issues (below):

Major

[Lines 102-106, page 4] Authors state: "A target of 100 patients was set based on the fact that approximately a tenth of all GP consultations record a primary complaint of fatigue (6). Either short or long term fatigue was reported in 35% of the population, with usual medical management in primary care 70-75% patients report that their fatigue persists at a year (1). Assuming ten GP practices each had a list of 10,000, it would be feasible to recruit 100 patients in 12 months."

The basis of the expected recruitment was not clear. Various statistics are presented but the extraction of 100 (100/10 per practice) given the reported prevalence figures is not clear. From these figures it would appear that (at least) 10% of all adults would be potentially eligible and hence based on an average adult practice size of around 7,000 that would be 700 potentially eligible per practice per year? That being the case, the requirement to identify 10 GP practices and a sample of 100 in total over 8 months is very unclear (and would represent a very small proportion of possible patients, which may question the representativeness of the sample). There was no clear rationale for this sample size or in turn what would reasonably represent "successful uptake" other than achieving the 100 total e.g. would 75% expected recruitment rate have been reasonable or was 100 an absolute minimum?

Thank you. We disagree that 10% of GP consultations mean that 10% of adults will be eligible. This is because not all adults with fatigue will consult a GP.

We have simplified this paragraph and removed the population level data which we had included to demonstrate that fatigue is common. The paragraph now reads:

"A target of 100 patients was set based on the fact that approximately a tenth of all GP consultations record a complaint of fatigue (1,3). Assuming each GP practices had a list of 10,000, this would suggest there would be 5000 appointments in each year where fatigue was discussed (10). We therefore assumed, it would be feasible to recruit 100 patients in 12 months. Sample size calculations are not always appropriate in feasibility studies (11), therefore this number was considered adequate to estimate the parameters required to design a larger trial."

[Lines 243-244] "... there were 1711 consultations which included the codes: TATT, fatigue/malaise/lethargy (see additional file 1). From these, 90 referrals were made and 44 patients recruited."

Figure 1 is, as would be expected, not an additional file (but part of the main paper)

The additional file is not the same as Figure 1 but is a table of the consultation codes. For ease of reference, this has been reproduced below:
We asked practices for data on the number of consultations with patients that were recorded as ‘tired all the time’ TATT or a simile. The details are presented below.

Patients coded TATT between 1st April 2012 - 30th June 2013

<table>
<thead>
<tr>
<th>GP practice</th>
<th>TATT consultations N= 1711</th>
<th>total number referred</th>
<th>total number recruited</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>382</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>139</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>248</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
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<td>5</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>105</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>277</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
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<td>11</td>
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<td>42</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>14</td>
<td>203</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>1711</td>
<td>90</td>
<td>44</td>
</tr>
</tbody>
</table>

&gt; Figure 1 starts from the 90 'potential recruits who may or may not be eligible' but the problem with the recruitment process stems higher, which is missed in the flowchart - and hence I feel is somewhat misleading. The above point leads to the major problem with the recruitment process and that is regarding the loss of potential patients from the 1711 figure to the 90 that were actually referred. Is there any information available to ascertain why this dramatic loss has occurred? Could any data (e.g. age / gender / index of multiple deprivation) be compared between the 90 referred and 1621 non-referred, albeit possibly at the level of aggregated data?

We have no information on patients that were not recruited to the study. Our paper points out that few of them were recruited, and then discusses the reasons why from the qualitative work.

[Lines 513-519, page 21]: Related to the above point, only a very small proportion of patients were expected in the first place to be referred (why might this be the case?) and even less were actually recruited (i.e. probably around 1-2% of total numbers that have a relevant code). Since it is the shortfall relating to lack of referral where the recruitment problem lies this should be emphasised strongly within the Discussion section - and a key way forward is to address ways of improving on this but also to be able to assess the reasons why this is the case. It seems like this study was not able to address the reasons why except to postulate; this issue needs highlighted more fully as a key limitation in the discussion section.
We agree. Our opening sentence in the discussion states: “Despite fatigue being one of the most common complaints in general practice, this study shows that a trial designed to identify patients with fatigue and offer early treatment to prevent the development of CFS/ME is not feasible or acceptable in primary care. “

We then say:” GPs found it hard to recruit to the study because of difficulties identifying patients with fatigue between 1 and 4 months onset, and difficulties with obtaining the correct screening blood test results.”

We then go on to discuss the different reasons, but we have limited information on why this happened. Our reason for writing this paper is that we believe it is very important that others don’t try and recruit patients using this method:

“The level of fatigue documented by EMIS (1711 consultations within the study period) is consistent with previous studies (1,2,20,21) which have suggested that 10-24% of patients attend their GP with fatigue as their primary symptom. In our study, only 90 patients were referred as potential participants. This could be for a variety of reasons including the fact that the majority of patients may have had fatigue for longer than 6 months (or less than 1 month), the difficulties GPs faced in identifying patients or a reluctance of patients to take part in the study. This is not consistent with one study (6) which successfully recruited patients after an episode of EBV and provided self-help advice on implementing a graded approach to exercise.”

[Lines 173-179, page 7]: "The following inventories were completed by participants at their assessment with the researcher (baseline) and then at 12-week and 6-month follow-up... and a health resource-use questionnaire, developed for this study which asked questions about health service use and travel costs most relevant to the CFS/ME population.”

Firstly, only 6 month outcome results are presented descriptively in this paper. Secondly, the information on health resource use and travel costs relating to the health economics are not presented here.

Thank you. Given the sample size, we did not feel it was appropriate to do any form of statistical analyses as this would be likely to lead to erroneous conclusions. As this was a feasibility study, the outcomes of interest are feasibility. Given the small sample size, we couldn’t perform any type of analysis. However, in the methods, we described all the outcomes collected for transparency.

Minor

Grammatical issues
[Line 109, page 5]: "fatigue for at least than a month"

One

We have corrected this to read:
Adults were eligible for this study if they were aged over 18, reported fatigue for at least one month
… we recruited 14 GP practices to this study of which 13 practices referred patients into the study. The 13 GP practices were spread across all deprivation scores.

I believe the last sentence should have included the non-recruiting practice too.

We have corrected this to read:
The 14 GP practices were spread across all deprivation scores.

Figure 1: make clear that individual exclusion numbers are not mutually exclusive (i.e. numbers do not tally to 35 under 'Not meeting inclusion criteria’

The numbers are correct and do add up to 35, however, there are sub-categories that may have made this confusing. These are “Total Fatigue Exclusion = 18” and “Total blood screening exclusions = 18.” We have deleted these sub-categories but the Editors may feel they are better kept in the figure.

Figure 1: Lost to follow-up (give reasons) (n= 9) but no reasons are listed
We have deleted “give reasons”

[Lines 259-260, page 10] Of those patients allocated to EI, 19/28 attended 4 sessions, and 9 were lost to follow up (2 at session 1, 2 at session 2, 3 at session 3, 2 at session 4).

9/28 treatment dropouts was rather high for the intervention therapy - is this in itself unacceptable (perhaps the authors can comment)?
We agree. We comment on this in the paper in the results (see the qualitative feedback on the intervention), and in the discussion. In the discussion we state: “Not all the participants found the intervention acceptable. This is not consistent with previous trials in CFS/ME which have shown a high level of patient satisfaction and low dropout rates with similar treatment approaches (23). This may be because the treatment sessions were much shorter (20 minutes) than the treatment sessions provided in specialist services (and trials testing effectiveness) which are normally 60 minutes long (24). We noted that most of the participants were still in employment and that this is a different group of patients to those attending a specialist service where studies indicate over 50% of patients are unemployed (25).
Some patients found attending the sessions difficult as they required appointments outside of work time and did not want follow-up phone calls. This may be because the early intervention needs to be adapted more for patients who are still working unlike those with CFS where many patients are no longer in work.”
We also discuss this as a problem for future studies and a reason why this study was not feasible.

[Lines 294-296, page 13] "Of the 100 records on EMIS sampled retrospectively, 56 out of the 100 analysed, met criteria for eligibility, and 2 had been referred to the study. One-hundred and ninety patients reported symptoms that matched the criteria."
This is not clear - 196 patients from 100?!

As we state in the methods there were two phases: “Data were requested from each practice on the consultation codes used during the period of the study. Consultations with the following codes on Egton Medical Information Systems (EMIS) were counted: Tired all the time
fatigue, exhausted, malaise, lethargy. EMIS records for a sample of the first 100 consultations from one practice from the date they entered the study were selected for more detailed analysis. The records were checked retrospectively, against the study eligibility criteria.” We have made this clearer in the results section by adding “data from each practice using EMIS suggested that” and giving these results, and then adding “in the more detailed review” and giving these results. This paragraph now reads: “Data from each practice using EMIS suggested that one-hundred and ninety patients reported symptoms that matched the criteria. Sixty-one were male and 129 were female. In the more detailed review, of the 100 records on EMIS sampled retrospectively, 56 out of the 100 analysed, met criteria for eligibility, and 2 had been referred to the study. Of the first 100 patients in one randomly selected

Lines 310-313, page 14] "Instead of using statements such as;
Recruiter: "when people come into the study and they either get the therapy or they just see the doctor for their usual care"
Is there something missing here?

Thank you for pointing this out, we had removed a quotation, this section now goes on to state:

Information about the usual care arm was provided, in addition to information about the early intervention;
Recruiter: “Already GPs are able to do quite a lot of things to help, they can run blood tests and exclude other medical problems, they can refer onto other specialists, they can help people with ways of managing day-to-day”

Lines 172-173, page 19] "… few of the GPs involved routinely carried out the full range of screening needed for the early intervention study."
Does this imply that 'Usual care' in this context is more than that i.e. 'Best standard care’?

The bloods are recommended by NICE and are routine screening blood tests that all GPs should carry out.

Lines 500-502, page 20] "…this study shows that a trial designed to identify patients with fatigue and offer early treatment to prevent the development of CFS/ME is not feasible or acceptable in primary care." Is this a blanket statement or is it that is not feasible/acceptable using the methodology adopted in this study (as detailed in the Abstract conclusion)? Indeed, the conclusion hints at further exploration of recruitment methodology and intervention development.
Thank you. We have added “using this methodology”.

My understanding upon reading was there was no treatment crossover (in the first 4 months) in the usual care arm but that a few people did receive the CBT/intervention later on. How many (what proportion) was this - and is there any case in thinking that this may be an issue for any main trial and a possible requirement for a design-change to avoid contamination e.g. to cluster randomisation? Perhaps this could be discussed.
Contamination is interesting but is unlikely to apply for this particular methodology as it is for patients very early on in the course of their fatigue. During this time, patients didn’t receive other treatments. The addition of CBT later would suggest that this would need to be taken into account at the analyses stage for secondary outcomes (it was after 6 months) when we usually measure the primary outcomes. We have tried to keep our recommendations succinct in this paper.

Reviewer #4: Thank you for the opportunity to read your manuscript, which I believe tries to tackle an important problem for patients, clinicians, and the health service.

I have the following observations to make, in a spirit of constructive engagement.

Major

The Consort statement refers to Additional files 1-5. I can only trace Additional file 1. Can you clarify whether the other such files exist or amend please.

Thank you. Additional files do not exist (the relevant data was included in the paper or additional file 1). We have amended the Consort Statement and rechecked and amended all the other statements on the Consort statement as the page numbers in the main paper have changed with the corrections.

Introduction

- the first two sentences of the introduction seem not to provide a reference for the assertions. I have looked at reference 1 and cannot readily find the details contained within it, so maybe I have either missed it or there are other supporting sources?
Thank you. We have added the missing references.

- line 79, consider giving the odds ratio (with 95% confidence interval) rather than the percentages of people fatigued in each arm at control. Also (line 80) the secondary outcomes seem not to have reached statistical significance (or even close to it), so I have reservations about your argument that "outcomes favoured the intervention" - a signal is the best that can be taken from those secondary measures.
Thank you. This comment is referring to a paper in the introduction. We have used the Odds ratios and removed the secondary outcomes. This paragraph now reads:

Evidence to support early intervention was provided by a small (N=69) randomised controlled trial based in primary care, which suggested there were fewer cases of fatigue (odds ratio 0.31, 95% Confidence interval 0.09-0.91) in patients randomised to a psycho-educational intervention compared to controls (6). The psycho-education was based on a behavioural model of fear-avoidance and suggests recovery may be delayed due to prolonged rest. This hypothesis is presented to the patient and a suggested activity plan is given to guide them on a graded re-
introduction of physical activity. However, we do not know whether this approach translates to patients presenting with fatigue in general practice or whether it is only useful in those whose chronic fatigue has been triggered by glandular fever (or some other viral infection).”

Methods

- line 99; the fact that you have chosen different sampling frames with a spread of aggregated population socioeconomic scores does not "[ensure] a representative sample of patients” and so this needs to be reworded
Thank you. We have changed this to “investigate how representative”……

- line 102; your cited reference does not seem to argue that a tenth of GP consultations record a primary complaint of fatigue. The opening sentence of that reference actually references another article from 1990 when it states that "Over 10% of patients attending primary care clinics describe at least one month of substantial fatigue" but the nature of the complaint (as primary or other) is not stated.

- line 104; "Either short or long term fatigue was reported in 35% of the population, with usual medical management in primary care 70-75% patients report that their fatigue persists at a year (1)" - I suspect that there is a punctuation mark missing between "care” and "70" but also I have not found this information in the NICE guideline - again, I may simply have missed it but would be grateful if you would check.

- line 105; your statement that "it would be feasible to recruit 100 patients in 12 months” based on the list size assumption given is not self evident to me - you have gone on to demonstrate problems with recruitment and so I think this needs rephrasing (also, what was the pooled list size of the practices recruited?)
This paragraph was trying to demonstrate how common fatigue is in those presenting to primary care. And therefore why we thought 100 participants would be a reasonable number to recruit.
We have tried to clarify this paragraph (in line with the other reviewers) and it now reads:
“A target of 100 patients was set based on the fact that approximately a tenth of all GP consultations record a complaint of fatigue (1,3). Assuming each GP practices had a list of 10,000, this would suggest there would be 5000 appointments in each year where fatigue was discussed (10). We therefore assumed, it would be feasible to recruit 100 patients in 12 months. Sample size calculations are not always appropriate in feasibility studies (11), therefore this number was considered adequate to estimate the parameters required to design a larger trial.”

- line 112; do you mean ≥4 on the Chalder scale?
Yes, this has been corrected. Thank you.

- line 124; the exact Read codes and terms specified should be given
These are no longer available

- line 126 and 136; there seem to be two paragraphs in which a sample of 100 patients is referred to. Do both paragraphs refer to the same sample? Also, (line 138) a consecutive sample of 100
patients does not seem to me to fulfil the criteria for random selection. The fact that you have used a sample from only one practice makes conclusions hard to generalise since coding practices differ between organisations. Was the practice chosen at random or purposively? Yes, and the second paragraph is confusing and has therefore been deleted. The first paragraph makes it clear that the selection was a sample to enable us to look more clearly at the results from the EMIS data collection and was not random.

- line 157; the EI group may have continued to receive all the component of usual care as well as EI but it seems inappropriate to argue that the intervention group "continued to receive usual care". We have clarified this to show that they continued to receive their usual care from their GP. This now reads: “Participants in the EI arm continued to receive their usual care from their GP.”

- line 160; your intervention comprised a book, a single face-to-face treatment session, and three follow up sessions yet you say the "intervention was given...within two weeks of randomisation" - do you mean the first two elements only? We state the follow up sessions were provided at 2, 6 and 10 weeks. Thank you for spotting this error in the next sentence. We have changed this to “started”.

- line 162; when you say that the Bristol service "follows NICE guidelines", so you mean the assessment and treatment is guided by and often consistent with the guidelines? As phrased, it could create the impression of an inflexible service delivering only what guidelines recommend (which is of course not the purpose of guidelines).

This particular guidance on treatment is sufficiently flexible and individualised that this statement is correct.

Results

The number of instances of patients consulting with a relevant fatigue code recorded is specified but the denominator is not so clear. This impacts on your conclusion that the 1711 consultations in the study period is consistent with other studies. Can more information be provided? This is a good point but I am afraid no further information is available.

- lines 283-289 and Table 3; as you highlight in the abstract, this study was not powered to support statistical analysis of differences in outcomes. It therefore seems incongruous to use descriptive epidemiology to show comparisons between groups in outcomes. I consider this should be removed and numerical results focus on study and recruitment processes rather than outcomes.

We agree however, there is considerable interest in theseis data (even though the sample size is small) and previous reviewers have asked us to include this. The text focusses on the study and recruitment outcomes which are the point of the paper. If the Editors would like us to remove these tables, we will be happy to oblige.
In the 14 recruiting practices, 1711 patients were recorded as being Tired All The Time (TATT) or presenting with fatigue, exhausted, malaise, lethargy between 1st of April 2012 and 30th of June 2013.. In the more detailed review, of the 100 records on EMIS sampled retrospectively, 56 out of the 100 analysed, met criteria for eligibility, as they did not have any other exclusionary medical or psychological diagnosis to explain the fatigue which had lasted between one and four months, however only 2 patients were recruited into the study. Of the remaining 54 patients who appeared to be eligible but were not recruited, one later developed CFS and one developed post viral fatigue syndrome.

- line 302 and subsequent; reporting of qualitative findings. This reporting style does not seem to me explicitly to follow a clear thematic analysis approach (see line 212 "systematically assigned codes and analysed thematically to identify themes..." Would it be possible to clarify the reporting? We used a thematic analyses approach (as detailed in the methods) and present the themes as they arose. The detail of our methods is in the methods section.

Conclusions

- line 551; I do not believe that the entirety of the first sentence is justified by your results. If these are conclusions that others have drawn, this should be clearly stated and referenced. Otherwise, the conclusions should tie in directly to the results.
We have added two references to the first sentence of the conclusion.

Minor

General issues

- there is inconsistent use of capitalisation for terms that are not proper nouns nor typically, in non-abbreviated form at least, subject to capitalisation.
We have corrected this.

- punctuation in lists is inconsistent with missing commas, as well as more than one item connected to its predecessor by "and".
We have corrected these

- there seems to be at least one occurrence of a Harvard style reference (NICE 2007) in a manuscript that otherwise uses Vancouver style. A critical proofread would help.
- similarly, the plural form of GP occurs both as GP's and GPs. I think the latter is correct but a form should be adhered to throughout.
We have checked all 61 referencees to GPs and found and corrected the one reference which had an inappropriate “‘”, thank you.

Methods

- line 96; I think the CRN has changed its name again so this should be updated and any abbreviations given in full
  Thank you. This has now been corrected to NIHR Clinical Research Network West of England.

- line 118; I think there is a missing punctuation mark between ..."sheet)" and ..&gt;"the"...
  This is now correct.

- line 190; "principals" should in this case be "principles", I think.
  Thank you. This has been changed.

Results

- Table 2; the final 2 rows presumably refer to the number of days in which productivity was affected but this requires inference and should be clarified
  This is Median Health Problems not days. However, it is confusing and does not add any further information so we have deleted this.

- line 496; you report one intervention and one comparator arm so this should I think be rephrased.
  We are unable to find this have searched near line 496 and searched on comparator so assume this has already been corrected.