Reviewer's report

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

Version: 0 Date: 03 Jul 2019

Reviewer: Martyn Lewis

Reviewer's report:

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?

[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)

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?

[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.

[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."

&gt; Firstly, only 6 month outcome results are presented descriptively in this paper

&gt; Secondly, the information on health resource use and travel costs relating to the health economics are not presented here.

Minor

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

[Lines 240-241, page 9] "… we recruited 14 GP practices to this study of which 13 practices 241 referred patients into the study. The 13 GP practices were spread across all deprivation scores."

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

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'

Figure 1: Lost to follow-up (give reasons) (n= 9) but no reasons are listed

[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).

&gt; 9/28 treatment dropouts was rather high for the intervention therapy - is this in itself unacceptable (perhaps the authors can comment)?
"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?!

"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?

"… 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’?

"…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.

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.

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