PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Mental health and functional impairment outcomes following a six week intensive treatment programme for UK military veterans with post traumatic stress disorder (PTSD): a naturalistic study to explore dropout and health outcomes at follow up.
AUTHORS	Murphy, Dominic; Hodgman, Georgina; Carson, Carron; Spencer-Harper, Lucy; Hinton, Mark; Wessely, Simon; Busuttil, Walter

VERSION 1 - REVIEW

REVIEWER	Don Richardson Parkwood Operational Stress Injury Clinic, Western University, London Ontario I personally know one of the authors:Busuttil, Walter
REVIEW RETURNED	23-Jan-2015

GENERAL COMMENTS	This is an important study examining a population of veterans that is often treatment resistant. Also, since it is a clinical research manuscript, it would be helpful to have more information on variables better known to clinicians such as rates of PTSD and comorbidity (major depression) and what percentage of the sample recovered with treatment. SPECIFIC inquiries: 1. In the abstract, under conclusions, you indicate that your results "suggest that treatment programs for veterans with PTSD need to combine both individual TF-CBT and group sessions." Did you have a control group? How do you know that combining treatment is needed? If not, I would suggest that your findings only demonstrate that "individual TF-CBT and group sessions" are helpful in treating PTSD. 2. In introduction, first paragraph, page 5, you indicate "there have been no studies to our knowledge of treatment outcomes in this ex-military population with most of the evidence coming from the USA and to a lesser extent Australia." I would suggest a more comprehensive review of the literature examining treatment outcomes in veterans. There has been two Canadian studies examining treatment outcomes in outpatient settings and several recent American studies examining treatment outcomes including cognitive processing therapy. 3. In methods, under Settings: Does your program provide ongoing psychiatric services? Specifically, is pharmacotherapy incorporated in the treatment? 4. On page 11, in Results: you indicate that 72% of the sample described how this was the first time they had received

	psychological treatment for PTSD. Is there any data in the UK to assess whether this is consistent with your veteran population? 72% seems to be high. How does this compare and other populations such as Canada, US, Australia? 5. In results, I think it would be helpful to have in text or as a table the mean scores at intake, discharge, six weeks and at six month follow-up of your outcome variables of PTSD, PHQ-9 and GAD-7. Also, what percentage no longer met the criteria for probable PTSD and probable major depression at the follow-up time points? 6. In Discussions, Page 13, Line 54: You indicate that "anecdotally, this is supported clinically at follow-up where veterans often describe improvements in their daily functioning and how improvements are more meaningful to them in many ways than the reduction in their PTSD symptoms." Did the veterans complete a qualitative evaluation? I think it would be helpful to have a reference for this statement. 7. In Discussions, Page 14, Line 5-12: You state "in view of these findings we conclude that offering individuals a mix of group sessions aimed at emotional regulation and individual TF-CBT appears to be an effective intervention for presentations of complex trauma within a veteran population." Research has demonstrated that chronic PTSD presents with a fluctuating course with symptom exacerbations and even spontaneous remissions. Also, peer support and the act of seeking treatment or being in a supportive environment might also have contributed to the observed symptom improvement. Perhaps, you might want to consider indicating, if it is known, the length of time the majority of your sample were suffering from PTSD as it might make the notion of spontaneous recovery less likely. Also, please define "complex trauma." Furthermore, were patient's offered pharmacotherapy? If they were on medication at intake, did they have to remain on the same medication throughout the treatment? What percentage were on medication and if it is known, what were they prescribed? If they were stable on medication could your treatment be considered psychotherapy augmentation; especially since 72% indicated that they had not previously received psychological treatment? 8. In Discussion, in Strengths and Weaknesses, Page 17, Line 6-10: You state "our findings need to be interpreted cautiously because we were unable to use randomization to deal with confounding." Is there something missing with the sentence? 9. In Conclusions, Page 17, Line 17-23: You state that your study demonstrate that your program is "effective at treating veterans presenting with PTSD, comorbid mental health difficulties and severe functional impairment." However, you then state that a Randomized Controlled Study is recommended to formally "test the efficacy." Perhaps, modifying the word "effective" in order to better reflect your results. 10. Finally, a line with regards to Ethics Review.

REVIEWER	Jonathan Davidson Department of Psychiatry and Behavioral Sciences Duke University Medical Center USA

	In the past 12 months: 1. Royalties derived from sales of: Connor-Davidson Resilience Scale, Davidson Trauma Scale, Social Phobia Inventory (SPIN) and MINI-SPIN. Authored books or chapters published by McFarland (Downing Street Blues), Guilford (Pharmacotherapy of PTSD) and Springer (A Century of Homeopaths). 2. Honoraria for consultation with Edgemont, Tonix and Lundbeck pharmaceutical companies. 3. Fees for service on INTRuST Consortium Data Safety and Monitoring Board, University of California San Diego. 4. Honorarium for speaking at University of Tennessee, Departments of Internal Medicine and Psychiatry.
REVIEW RETURNED	29-Jan-2015

GENERAL COMMENTS	The authors have conducted the first study of its type in UK veterans, the majority with PTSD of many years duration. By intent, this is an open label trial without a control group and the authors are appropriately circumspect in how far one can take such results. The measures are broad in what they capture, as is desirable for such a study, and assess the domains of chief interest. This group is to be commended for retaining so many of those assigned to treatment. Other strengths include an inpatient sample and the provision of group therapy. Most comments and suggestions are of a minor nature but the two most substantial will be addressed first. 1. For the practicing clinician it is difficult to know what to take away from the results beyond the fact that symptom severity gets less over time. The report would make more impact if it contained baseline scores and scores at subsequent points either instead of, or in addition to, change scores, and more interpretation of the scores. Many readers will want to know the meaning of a PSSI score of 36 for example. I could not find how "response" was defined. It is recommended that rates of response and remission both be given. As I understand the PSSI, a baseline score of 36 corresponds to very severe PTSD, 23 (the week 6 score) to moderate PTSD and 12 (6 months) to mild. On the IES-R, a score of 33 is taken to be a threshold for PTSD probability, so if subjects had a mean post-treatment score of 30 at week 12, then many would still meet full diagnostic criteria for PTSD, despite an intensive treatment program. The same comments apply to measures of depression and GAD if those scales have diagnostic cut-off points, and to the functional scales too. 2. The fundamental question concerns outcome of ITP for the entire group. For that reason, it is suggested that presentation of results starts out at that point, analyzing the outcome for the full group (n=246), and then detailing the subgroups of responders/non-responders, completer/dropouts etc. As it is, the main emphasis seems to be the subgroups. I do not worry too much about responder bias here and consider it receives too much emphasis. 3. The paper can be condensed. Much of the discussion adds little in

	that it contains a number of impressionistic statements that are not backed by data or statistical analysis. Phrases like "anecdotally, this is supported...." (page 13), "these were more modest than..." (page 13), "reductions appeared greater than..." (page 12) are some examples. Tables 2 and 3 could be dropped, to be replaced with a table that provides total scores at each assessment, rates of response and remission. Subsidiary comments: 1. Page 5, line 23. To the countries mentioned, the authors could add Israel and Canada. 2. Page 7, para 1. It would help to picture a typical day (or week) by describing patient activity schedule, and how much time was spent in structured activity and how much in other activities. Despite later stating that the sole focus of treatment was PTSD (page 13, lines 46-47), the impression given in this paragraph suggests otherwise, with the acquisition of skills like mindfulness, relaxation, goal-planning, building resilience, that go beyond PTSD. Were patients given post-discharge homework or instructions for self-directed use of their newly acquired skills? Were any complementary treatments such as acupuncture and herbal remedies/dietary supplements like chromium, vitamins used or self-administered? Was yoga offered? 3. Page 7, lines 48-56. Quite reasonable exclusion criteria, but the authors could state more emphatically that already the sample was selected for being treatment resistant (please provide mean duration of PTSD in years), yet the most resistant of all were excluded and that is likely to be a large percent of the PTSD population. If the ITP offered here achieved modest results, then there's a real challenge in finding effective treatments for that large and even more complicated PTSD subgroup. 4. Page 8, line 1. How many were screened and rejected for the study, and why? How were potential subjects initially recruited/selected? 5. Page 8, line 28. I believe that 75% is the relevant proportion followed at 6 months, using 246 as the denominator in an intent-to-treat evaluation. 6. Page 9, line 25. Anger, depression and worry are really intrinsic parts of how PTSD is defined - it wouldn't be PTSD without them. Therefore "comorbidity" may not be the most felicitous term. 7. Page 10, lines 34-52. As noted above, more emphasis needs to be placed on the entire group outcome and less on the completer/dropout division. For an ITT, one is interested in the full group first, going by the "all randomized all analysed" principle.. 8. Page 12, lines 41-48. A quick hand-calculation suggests that the drop in score on the PSSI is greater than the IES-R (e.g. 36% vs 28% at six weeks). (This was based on rough averaging of the baseline score for the 2 groups since it was not presented as a whole). Regardless, I do not think the material in this paragraph adds to the manuscript. While it is true that greatest speed and quantity of improvement is seen in the first few weeks, this is seen with placebo and in open-label reports of drug treatment, and is unlikely to reflect some unique property of ITP.

	9. Page 13, line 3: Although the mean scores at 6 months reflect overall group improvement, the question arises as to whether any subjects experienced a relapse. 10. Page 13, line 30. Is the word "significant" referring to clinical or statistical significance? 11. Page 14, line 10: In what way was trauma "complex"? 12. Page 15. Much of this can be condensed into a few lines. 13. Page 16, line 3. To underscore the problems of treating PTSD in military veterans, it may be worth adding that meta-analyses of pharmacotherapy also show poor response for drugs - it's not confined to psychotherapy. 14. Page 17, line 21. How effective do the authors judge ITP to have been in this sample? My own take is that gains were modest to fair. A drop of 58% on the PSSI from base to last visit is decent, but if there remained a substantial proportion who still have PTSD (e.g. by IES-R), that is not so good. Was response bi-modal, i.e. if you respond, you respond really well? How were subjects functioning at follow up? Given the extensive investment of staff and patient time, and health resources, it would be useful to hear more about when and for whom ITP might be recommened, and whether it delivers value for money. 15. The overall abstract is representative of the full paper. However, in the abstract conclusions, my own opinion is that the results do not yet suggest that treatment programs for veterans should routinely incorporate group and TF-CBT as packaged here. Maybe for a select subgroup or in a watered-down form for many others. It is hard to tell from this study design if group treatment is even necessary at all. 16. I concur with the summarized strengths and limitations. The authors may wish to consider adding the following - (strength) broad-based assessments, and (limitations which were unavoidable) - lack of women subjects and exclusion of more complicated PTSD such as those with TBI, psychosis, alcohol etc, which leaves open the question of ITP for these individuals. 17. How many subjects were receiving psychotropic medications for PTSD?

VERSION 1 – AUTHOR RESPONSE

Reviewer one's comments

Comment 1
We would like to thank the reviewer for drawing our attention to where we had over-concluded based on our study and we have amended the conclusions in our abstract to reflect the reviewer's comments.

Comment 2
We have updated the introduction to take into account the reviwer's comments by adding references to Canadian, CPT and Israeli studies.

Comment 3
Pharmacotherapy was not included as part of the ITP. However, when participants were taking medication, this needed to be stable prior to them enrolling on the ITP. We have updated the inclusion criteria of the methods section to reflect this. In addition, we have added several of sentences to our limitation section to state that we did not record psychiatric medication.

Comment 4
Whilst we stated this figure, we have also stated that it is reliant on self-report and could not be validated. We have added an additional sentence referencing work done by UK and US researchers that reported that only between 20/25% of military personnel with mental health difficulties had been able to access treatment. We have expanded the first paragraph of the results to reflect this.

Comment 5
As suggested we have added mean scores into table four. Because of space constraints we have limited this to baseline and 6 month scores. We have not presented cut-offs because the IES-R and PSS-I have not been validated for use within this population. For example, when looking at the IES-R a cut-off of 33 and above has been suggested for Australian Vietnam War veterans. However, upon further reading this was validated for use within a community sample rather than help-seekers and the authors of this study questioned the use of the IES-R to detect probable PTSD1. Within the discussion section we have added a discussion of these scores and made comparison to other studies. We have explicitly stated that we have evidence for a reduction in PTSD severity rather than remission.

Comment 6
We have removed the sentence making reference to anecdotal evidence about improvements in daily functioning. This is because this was a clinical observation, rather than deriving from qualitative analysis.

Comment 7 – Part A
This comment appeared to have two parts. The first connected to length of time with PTSD and the second about psychiatric medication. We would like to thank the reviewer again for their constructive feedback about including information about the length of time the majority of participants had experienced PTSD. Whilst we do not know this information directly, we do know the length of time since participants left the military. Given that their traumas were connected to military service we have used this as a proxy measure for time since trauma. This should be a conservative estimate of the time since trauma because an individual's index trauma may have occurred at any point during their military service, rather than at the end. We have updated the results to include the mean number of years since leaving the military (14.6 yrs: 95% CI 13.2-16.0) and updated the discussion at the end of page 14 to discuss this. In addition, we have removed reference to 'complex trauma' throughout the paper to improve clarity.

Comment 7 – Part B
As indicated above, we have updated the inclusion criteria within our methods to state that prior to enrolling on the ITP participants had to be stable on any medication and that they had to remain on the same medication throughout the ITP. Unfortunately, we did not record whether participants were receiving medication. We have updated our limitation section to reflect this.

Comment 8
We have updated this sentence to read "we have taken this opportunity to evaluate the ITP. However, our findings need to be interpreted cautiously because we were unable to use randomisation to deal with confounding from unmeasured variables".

Comment 9
We have changed the word ‘effective’ to ‘reduce the burden of symptoms in’.

Comment 10
We have added a sentence at the end of the manuscript to mention ethical approval for the study. This was granted by the Combat Stress ethics committee.

Reviewer two’s Comments

Main Comments
Comment 1
As suggested we have added mean scores into table four. Because of space constraints we have limited this to baseline and 6 month scores. We have not presented cut-offs because the IES-R and PSS-I have not been validated for use within this population. For example, when looking at the IES-R a cut-off of 33 and above has been suggested for Australian Vietnam War veterans. However, upon further reading this was validated for use within a community sample rather than help-seekers and the authors of this study questioned the use of the IES-R to detect probable PTSD1. Within the discussion we have added in a discussion of these scores and made comparison to other studies.

Comment 2
We welcome the reviewer’s comments about whether an intention to treat (ITT) analysis would have been more appropriate. Whilst we can see the benefits of using an ITT approach, when we planned out the analytic strategy for this paper we took statistical advice that recommended the use of random slope nonlinear growth models as the most appropriate for our dataset. We were advised that an ITT analysis would not be suitable for our study design because we employed a within subject design rather than a between subject RCT design. In addition, we have missing data at different time points which would mean an ITT strategy could not be adopted (for example the 45 individuals whose 6 month follow up data we did not have) 2. Given this advice we have opted to continue to use the current analytic strategy.

One of our a priori hypotheses was that there would be differences in the health profiles between both completers of the programme and non-responders. For this reason we feel it is important to keep these analyses in. We understand the reviewers concerns that there is a lot of emphasis on these subgroups in the results and we have attempted to write our discussion in such a way as to put the main emphasis on the analysis of outcomes post treatment rather on these subgroups (completer/non-completers etc). In addition, we have attempted to condense sections within the results to reduce the emphasis given the subgroup analyses.

Comment 3
We have made efforts to condense the paper throughout based upon the two reviewers’ comments. However, as mention above we feel it is important to keep tables two and three because we were concerned about the possibility of bias in our sample and had made a priori decisions to explore these.

Subsidiary Comments
Comment 1
As indicated by the reviewer we have added Canada and Israel to the list of countries.

Comment 2
As suggested by the reviewer a sentence has been added to page 7, para 1 to describe the amount of structured activity each day during the ITP. The later reference on page 13 noted by the reviewer

has been removed. The reviewer asked whether complementary treatments were offered during the ITP and we can confirm that no complementary treatments were offered.

Comment 3
Based upon the reviewer's suggestion we have added a sentence to the introduction to more clearly state that the sample for the ITP was selected for being treatment resistant. We have also updated the exclusion criteria section within the methods to state how if veterans failed to meet criteria support was provided to them and they were re-assessed. Further, we have updated our limitations section to take into account the reviewer's comment in relation to the PTSD subgroups that were excluded from the study. We clarified that individuals with brain injuries were not excluded. Only individuals with more serious brain injuries that resulted in severe impairment were excluded.

Comment 4
Unfortunately we did not collect data on the number of individuals who were screened so are unable to present this. We have included a sentence at the beginning of the participants section within the methods to provide information for how individuals were initially screened.

Comment 5
As discussed above we have decided to keep our original analytic strategy.

Comment 6
We have changed the word 'co-morbid' to 'other mental health difficulties'.

Comment 7
As stated above because we did not employ an RCT design and instead used a within subject design and had missing data we were advised to continue to use the current analytic approach.

Comment 8
As suggested we have removed the sentences on page 12, line 41-48.

Comment 9
We have added a sentence into the results to state that 13% of participants PSSI scores remained the same or got worse, 27% scores reduced between 1-9 points, 30% between 10-19 points and 30% more than 20 points. We have updated the discussion to reflect this (within paragraph one of the discussion) and made comparison to another study.

Comment 10
We have added the word 'statistically'.

Comment 11
We have removed the word 'complex'

Comment 12
We have condensed page 15 to take into the reviewer's comments to exclude information that is not needed.

Comment 13
As suggested we have included the references of two recent meta-analyses of pharmacological treatments for PTSD.

Comment 14
We understand the reviewer's comments that gains reported were modest. However, we believe

comparison needs to be made between our intervention and others offered to veteran populations around the world to help with the interpretation of results. For example, we reported a reduction in PSSI and IES-R scores at 6 months that was greater than one standard deviation in baseline score. In comparison, studies of Australian veterans reported more most reductions in PCL score by less than one standard deviation2;3, and pre and post baseline scores in US studies show little change4. We have attempted to do this within the discussion, and as mentioned above have added new information related to the interpretation of scores and taken a more cautious approach to the interpretation of our results. We have also updated our limitations to acknowledge that the gains reported were modest and have explicitly stated that we have evidence for a reduction in PTSD severity rather than remission.

As suggested by the reviewer we have provided information related to different rates of PSSI score changes within the results. In the future we hope to answer questions related to cost-effectiveness, and understand the impact of group sessions further by starting to offer outpatient TF-CBT. However, at present we are unable to comment on the cost-effectiveness of treatment.

We would like to acknowledge that table four may have been unclear and that the figures presented for changes between time points relate to the slope of the line between time points (i.e. the rate of change) rather than the change in PSS-I score between the time points. We have changed the labelling in the table to reflect this. The aim of presenting this data was because we wanted to explore whether health scores increased at six month follow up as this pattern has been observed in studies of US veterans with PTSD.

Comment 15
We have updated the abstract to take the reviewers comments into account.

Comment 16
We have updated our strengths and limitations to add the suggested comment about broad-based assessments and the lack of women and more complicated groups of PTSD. Further, we have modified our exclusion criteria to make it clear that individuals with brain injuries were not excluded (only those with severe cognitive impairment) and that having a current alcohol problem or having uncontrolled active psychotic symptoms did not permanently exclude individuals. Rather, these individuals would have been offered further support and then re-assessed. As such, our sample did include certain groups that are considered to have complicated presentations (e.g. BI, those with psychosis and a history of alcohol problems).

Comment 17
We were not able to collect information on psychiatric medication. We have updated our inclusion and exclusion criterion to reflect that participants had to be stable on any medication prior to being enrolled on the ITP. In addition, we have updated our limitations to reflect that we were unable to collect this data.

We hope that we have been able to address the reviewers' comments with the changes we have made to the manuscript and that the paper is now ready to be accepted for publication.

Yours Sincerely

Dr Dominic Murphy

Reference List

(1) Creamer M, Bell R, Failla S. Psychometric properties of the Impact of Event Scale - Revised. Behaviour Research & Therapy 2003; 41(12):1489-1496.
(2) Creamer M, Morris P, Biddle D, Elliot P. Treatment outcome in Australian veterans with combat-related posttraumatic stress disorder: a cause for cautious optimism? Journal of Traumatic Stress 1999; 12(4):545-558.
(3) Forbes D, Lewis V, Parslow R, Hawthorne G, Creamer M. Naturalistic comparison of models of programmatic interventions for combat-related post-traumatic stress disorder. Australian and New Zealand Journal of Psychiatry 2008; 42:1051-1059.
(4) Currier J, Holland J, Drescher K. Residential treatment for combat-related posttraumatic stress disorder: identifying trajectories of change and predictors of treatment response. PLoS ONE 2014; 9(7):e101741. doi:10.1371/journal.pone.0101741.

VERSION 2 – REVIEW

REVIEWER	Don Richardson Parkwood Operational Stress Injury Clinic, Western University, London Ontario I personally know one of the authors:Busuttil, Walter
REVIEW RETURNED	18-Feb-2015

GENERAL COMMENTS	Thank you for addressing my concerns in your most recent revised manuscript. Sincerely

REVIEWER	Jonathan Davidson Duke University Medical Center Durham USA Consulting fees from Tonix, Edgemont, Lundbeck Pharmaceuticals, University of California San Diego. Speaker honorarium, University of Tennessee Royalties from Guilford and McFarland Publications, Rating scales (Davidson Trauma Scale, Connor-Davidson Resilience Scale, Social Phobia Inventory, MINI-SPIN). Author of A Century of Homeopaths, Springer publishers
REVIEW RETURNED	13-Feb-2015

GENERAL COMMENTS	The authors have responded commendably to the reviewers' comments. At this stage, I have two remaining issues. 1. In that one of the main purposes of the study was to compare health profiles of completers to dropouts, and the analysis plan so determined, I believe the title should be modified slightly to take into account this goal. 2. Even accepting that the IES and PSS thresholds were based on different samples, the question will still be asked how to interpret the scores. According to the author of the PSSI, a cut off score of 10 or

	less corresponds to remission. Since remission is a widely acknowledged goal of treatment, it would enhance the paper if the authors can report the number (%) who met this criterion at the 12 week and 6 month times.

VERSION 2 – AUTHOR RESPONSE

We have made revisions as directed by amended the paper title and by adding two sentences within the results section to indicate overall changes in rates of participants meeting case criteria for PTSD. These changes have been marked in red with the review manuscript