PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Testing a support programme for opioid reduction for people with chronic non-malignant pain: The I-WOTCH randomised controlled trial protocol
AUTHORS	Sandhu, Harbinder; Abraham, Charles; Alleyne, Sharisse; Balasubramanian, Shyam; Betteley, Lauren; Booth, Katie; Carnes, Dawn; Furlan, Andrea; Haywood, Kirstie; Iglesias, C; Lall, Ranjit; Manca, Andrea; Mistry, Dipesh; Nichols, Vivien; Noyes, Jennifer; Rahman, Anisur; Seers, Kate; Shaw, Jane; Tang, Nicole; Taylor, Stephanie; Tysall, Colin; Underwood, Martin; Withers, Emma; Eldabe, Sam

VERSION 1 – REVIEW

REVIEWER	Joseph W. Frank University of Colorado School of Medicine, Aurora, Colorado, USA
REVIEW RETURNED	07-Mar-2019

GENERAL COMMENTS	Comments: This is a well-written protocol and an important trial. My only major recommendation is to clarify the context in which potential participants will consider study participation as it relates to opioid dose reduction. Important questions include: Is opioid dose reduction mandatory for study participants? For participants who are unable or unwilling to reduce medication dose during study participation, how will study participation be impacted? More broadly, can the authors comment on any other concurrent initiatives that may be implementing involuntary opioid dose reduction at participating sites? Abstract: -- Methods and analysis: Specify control condition (self-help booklet and relaxation CD) which is first mentioned on page 9 -- Page 5, line 41: Consider using person first language (e.g., patients with chronic pain) -- Page 6, line 5: Specify that pre-specified effectiveness threshold is for co-primary outcome of pain interference Methods/Design: -- Include dates of study enrollment -- Trial setting: Recommend brief description of any concurrent initiatives that may affect chronic pain management and/or opioid medication management at recruitment sites. For example, many US health systems have undertaken initiatives to support (or mandate) opioid dose reduction, which could confound between-group comparisons for co-primary outcome of opioid use -- Eligibility and informed consent:

	-- Recommend description of how goals of study (opioid medication reduction specifically) are communicated to potential participants at time of enrollment. Is opioid dose reduction mandatory for study participants? How might potential participants expect their access to opioid medications to be impacted if they decline to participate? -- Consider including model consent form as noted in SPIRIT checklist -- Opioid tapering procedures: -- Specify whether there are criteria by which the tapering regimen will be paused or stopped. -- Facilitator training: -- Page 16, line 42: Consider revising for clarity. ("... to take home and watch. This DVD has been integrated throughout..." -- Study outcomes: -- Page 20, line 27: Period missing at end of sentence -- Power and sample size: -- Page 20, line 50: The final recruitment target of 542 participants differs from the target of 468 participants in Figure 1 on page 10 -- Randomisation methods: -- Page 21, line 38: Recommend stating the cut-offs by which randomisation has been stratified by baseline pain severity and baseline opioid use. Clarify stratification by group. -- Health Economic Evaluation: -- Page 25, line 6: Add reference as noted References: -- References 17 & 18 are redundant

REVIEWER	Dalila Veiga Centro Hospitalar Universitario do Porto Portugal
REVIEW RETURNED	24-Mar-2019

GENERAL COMMENTS	This is a very interesting and well-designed research work protocol. However, in Methods section you refer that you accept self-referrals. How do you check chronic non-cancer pain diagnosis and strong opioid prescription in these cases? Are all patients opioid prescription´s checked in these situations?

REVIEWER	Mike Clarke Northern Ireland Methodology Hub Queen's University Belfast Northern Ireland UK
REVIEW RETURNED	30-Apr-2019

GENERAL COMMENTS	This is a well written, very good plan for an important randomised trial. I hope that the following suggestions are helpful in finalising the paper for the journal: 1. It would be helpful to include more information on how the groups will be formed and how they will run. For instance: a) When will the randomisation be done? This could be mentioned in the "Eligibility and informed consent" section and although it is clear from the randomisation section that you are building batches to be randomised (which I very much agree with), it is not clear if you will check with participants just before randomisation that they

	are still willing to be randomised. Perhaps the consent process is done at that point (ie when you have an adequate batch), but this is not clear. b) How many people would be in a group, and is there a minimum size below which the group might become ineffective? This might be important for any subgroup analyses relating to the "dose" of the group-based activities and for any adjustments to the analyses due to clustering effects within the groups. c) Does everyone need to join the group at the start or can people join later in the 8-10 weeks? d) How long is the interval from randomisation to the first day of group-based intervention? This may be important because the participants allocated to control will begin their "intervention" immediately, while the experimental group might need to wait for a group to form. 2. The control intervention seems to be "augmented" usual care. If outcomes are similar between the two randomised groups and both show improvements, will this augmentation need to enter routine practice? 3. Will patients who withdraw from the group-based intervention revert to "usual" usual care or the augmented usual care being used for the control group. 4. Will you stratify for, or at least record, the strength of desire of the participant to come off the opioids? 5. It is great to see that you are using a core outcome set. 6. Have you considered how the evidence in the Cochrane Reviews of recruitment (Treweek S, et al. Strategies to improve recruitment to randomised trials. Cochrane Database of Systematic Reviews 2018;(2):MR000013) or retention (Brueton VC, Strategies to improve retention in randomised trials. Cochrane Database of Systematic Reviews 2013;(12):MR000032) might help? 7. Have you considered embedding a SWAT into the trial (Treweek S, et al. Trial Forge Guidance 1: what is a Study Within A Trial (SWAT)? Trials 2018;19(1):139)? 8. You will have a DMC but it is not clear what recommendations these might be able to recommend and it would be good to have more information about this. For instance, will the collection of data be fast enough to allow them to stop recruitment, randomisation, intervention, or follow-up; or merely to accelerate dissemination of the findings? 9. Page 25 of the manuscript (page 27 of the BMJ Open pdf), line 6 contains a leftover "[add ref]". Should this be changed to a call out to reference 20 or to another paper?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments

My only major recommendation is to clarify the context in which potential participants will consider study participation as it relates to opioid dose reduction. Important questions include: Is opioid dose reduction mandatory for study participants? For participants who are unable or unwilling to reduce medication dose during study participation, how will study participation be impacted? More broadly, can the authors comment on any other concurrent initiatives that may be implementing involuntary opioid dose reduction at participating sites?

Thank you for this useful comment. We added more clarity to address these points under eligibility and informed consent. We have specifically added detail on what information participant are given to consider the study, which is background and aims of opioid reduction. We have also clarified that opioid reduction is not mandatory.

We are aware that a limited number of pain clinics around the UK are now offering opioid reduction services. However such efforts remain small scale and we are not aware of any around the study recruitment regions. Any difference or benefit we will show will be in addition to anything else that is available.

Abstract:
Methods and analysis: Specify control condition (self-help booklet and relaxation CD) which is first mentioned on page 9

Thank you, this additional information has been added to the abstract (Page 5).

Page 5, line 41: Consider using person first language (e.g., patients with chronic pain)

Thank you we have now amended this sentence as suggested.

Page 6, line 5: Specify that pre-specified effectiveness threshold is for co-primary outcome of pain interference

Thank you for this comment we have now made this change to reflect the two primary outcomes.

Methods/Design:
Include dates of study enrolment

Thank you the dates have now been added to this section.

Trial setting: Recommend brief description of any concurrent initiatives that may affect chronic pain management and/or opioid medication management at recruitment sites. For example, many US health systems have undertaken initiatives to support (or mandate) opioid dose reduction, which could confound between-group comparisons for co-primary outcome of opioid use

Thank you for this comment as stated above we are aware that a limited number of pain clinics around the UK are now offering opioid reduction services. The aim of this study however is to provide a specific opioid reduction programme in addition to anything else that is available to participants in this pragmatic trial. Current services for opioid reduction do remain small scale in the UK and we are not aware of any around the study recruitment regions.

Eligibility and informed consent:
Recommend description of how goals of study (opioid medication reduction specifically) are communicated to potential participants at time of enrollment. Is opioid dose reduction mandatory for study participants?

Thank you for this comment, we have now included further information about the telephone check in which study information is communicated with potential participants. We have also clarified that opioid reduction is not mandatory.

How might potential participants expect their access to opioid medications to be impacted if they decline to participate?

Thank you, we have now included a sentence: “Participants are informed that if they decline to take part on the study or are found to be ineligible there is no impact on their usual form of care or access to opioid medication.”

Consider including model consent form as noted in SPIRIT checklist

Thank you we have provided a copy of the participant consent form.

Opioid tapering procedures:
Specify whether there are criteria by which the tapering regimen will be paused or stopped.

Thank you for this comment, our North East external pilot uncovered a large variability in the need to pause tapering. We therefore elected to give the study nurse the freedom to pause tapering where appropriate (as judged by intolerance to withdrawal symptoms) following communication with the study team. We did not encourage the complete stoppage of tapering unless specifically requested by the participant. We have therefore included a sentence which specifies that the there is an element of negotiation between the nurse and participant dependent on the participant circumstances.

Facilitator training:
Page 16, line 42: Consider revising for clarity. ("... to take home and watch. This DVD has been integrated throughout..."

Thank you for this comment, we have now inserted more information clarifying the use of the DVD during the intervention and at home.
Study outcomes:
Page 20, line 27: Period missing at end of sentence

Thank you for this comment, we have made the necessary amendment (Page 23, of the current manuscript).

Power and sample size:
Page 20, line 50: The final recruitment target of 542 participants differs from the target of 468 participants in Figure 1 on page 10

Thank you the figure has now been updated with the new recruitment target of 542.

Randomisation methods:
Page 21, line 38: Recommend stating the cut-offs by which randomisation has been stratified by baseline pain severity and baseline opioid use. Clarify stratification by group.

Thank you, we have now included cut-offs by which randomisation was stratified as requested.

Health Economic Evaluation:
Page 25, line 6: Add reference as noted

Thank you the correct reference has now been added.

References:
References 17 & 18 are redundant

Thank you, the correct order of references have now been inserted and duplications removed.

Reviewer 2 Comments
In Methods section you refer that you accept self- referrals. How do you check chronic non-cancer pain diagnosis and strong opioid prescription in these cases?

Are all patients opioid prescription´s checked in these situations?

Thank you for this comment, we have now included information which describes the process of eligibility checking for participants who were self-referrals. We have also added information confirming that all medications reported on the baseline questionnaire are checked again with the participant at time to consent.

Reviewer 3 Comments
It would be helpful to include more information on how the groups will be formed and how they will run. For instance:
a) When will the randomisation be done? This could be mentioned in the "Eligibility and informed consent" section and although it is clear from the randomisation section that you are building batches to be randomised (which I very much agree with), it is not clear if you will check with participants just before randomisation that they are still willing to be randomised. Perhaps the consent process is done at that point (ie when you have an adequate batch), but this is not clear.

Thank you for this comment, we have further information in “eligibility and informed consent” as to when randomisation happens.
There is no check point to see if participants can still make the dates after consent has already been taken.

If the delay was longer than expected then we would contact participants again to check they were still willing to be randomised but this was on ad-hoc basis.
b) How many people would be in a group, and is there a minimum size below which the group might become ineffective? This might be important for any subgroup analyses relating to the "dose" of the group-based activities and for any adjustments to the analyses due to clustering effects within the groups.

Thank you for this comment, due to the pragmatic nature of this trial, we would run a group with a minimum of 2 people but always aim to randomise to a full group. We have added this information in the “Randomisation methods and blinding” procedures section.

c) Does everyone need to join the group at the start or can people join later in the 8-10 weeks?

Thank you we have included the sentence: Attendance at Day One is mandatory for accessing subsequent elements of the programme, in the Experimental Intervention section of the paper for clarity.

d) How long is the interval from randomisation to the first day of group-based intervention? This may be important because the participants allocated to control will begin their "intervention" immediately, while the experimental group might need to wait for a group to form.

Thank you, we have specified the minimum time frame we aim for, between randomisation and the first day of the group (two weeks). During the recruitment phase we will record the actual time taken
2. The control intervention seems to be "augmented" usual care. If outcomes are similar between the two randomised groups and both show improvements, will this augmentation need to enter routine practice?

Thank you for this comment, we have included as a limitation at the beginning of the paper that: We acknowledge that the proposed best usual care method is not always embedded in current NHS practice. If results are similar in both groups we would consider use of “My Opioid Manager” and the relaxation CD in routine practice.

3. Will patients who withdraw from the group-based intervention revert to "usual" usual care or the augmented usual care being used for the control group.

Thank you, we have clarified that under experimental intervention, participants who withdraw from the group based intervention are sent all the additional materials they would have received if they had attended the group.

4. Will you stratify for, or at least record, the strength of desire of the participant to come off the opioids?

Thank you, we have now included a sentence under Process evaluation and intervention fidelity which clarifies that:
“Process evaluation includes outcomes around motivation, expectation and confidence in ability to reduce opioids.”

5. It is great to see that you are using a core outcome set.

Thank you

6. Have you considered how the evidence in the Cochrane Reviews of recruitment (Treweek S, et al. Strategies to improve recruitment to randomised trials. Cochrane Database of Systematic Reviews 2018;(2):MR000013) or retention (Brueton VC, Strategies to improve retention in randomised trials. Cochrane Database of Systematic Reviews 2013;(12):MR000032) might help?

Thank you for this suggestion. At the time of designing the trial we considered available evidence as well as experience from running complex trials with group based interventions to maximise recruitment and retention. The references you provide are useful texts for our future studies.

7. Have you considered embedding a SWAT into the trial (Treweek S, et al. Trial Forge Guidance 1: what is a Study Within A Trial (SWAT)? Trials 2018;19(1):139)?

Thank you again for this useful suggestion. We did not consider this publication when designing this trial as the trial was designed before the paper quoted was published. However we will consider this in future trial designs.

8. You will have a DMC but it is not clear what recommendations these might be able to recommend and it would be good to have more information about this. For instance, will the collection of data be fast enough to allow them to stop recruitment, randomisation, intervention, or follow-up; or merely to accelerate dissemination of the findings?

Thank you, we have now amended the paragraph outlining the aims of the DMC with information on recommendations that DMC will make. The frequency of meetings are in line with data recruitment and a minimum of once a year.

9. Page 25 of the manuscript (page 27 of the BMJ Open pdf), line 6 contains a leftover "[add ref]". Should this be changed to a call out to reference 20 or to another paper?

Thank you the reference has now been added.

VERSION 2 – REVIEW

REVIEWER	Mike Clarke Northern Ireland Methodology Hub, Queen's University Belfast, UK (Northern Ireland)
REVIEW RETURNED	07-Jun-2019

GENERAL COMMENTS	Thank you for revising this manuscript. I am happy with the changes you have made in response to my earlier comments. I am happy to leave it to the Editor to decide if the manuscript needs copy editing for grammar and consistency (e.g. the use of abbreviations).