APPENDIX: PEP-TALK SUB-STUDY

Printing the primary outcomE on Pink PapER versus standard paper to increase participant engagement to postal questionnaires (PEPPER): protocol for an embedded retention trial

PEP-TALK ISRCTN Number: 29770908

PEP-TALK IRAS Number: 245306

Contributors to this protocol:

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1. BACKGROUND AND RATIONALE

Missing data on the primary outcome of a randomised control trial (RCT) risks introducing bias, reducing the sample size and statistical power of the study and affects the validity, reliability and generalisability of the findings [1, 3-6]. There are currently numerous ways to deal with missing data, for instance data imputation [38]. The easiest means to negate this issue is to not have data missing in the first place.

Given the trend towards using patient reported outcome measures (PROMs) for the primary outcome measure in RCTs, many trials collect their primary outcome on paper-based questionnaires, sent by post. Numerous strategies are used by trialists to improve response rates. However these are often adopted without being subjected to rigorous evaluation, leading to a relative absence of evidence-based interventions [3, 7-9]. There is a need to develop and rigorously evaluate strategies for improving the return of postal questionnaires by embedding them in real-life 'host' trials [10, 11]. Recently, initiatives such as Systematic Techniques for Assisting Recruitment to Trials (START) [12-14], Studies Within A Trial (SWAT) [15, 16] and Trial Forge [17] have promoted the development and reporting of embedded recruitment and retention trials, across ongoing multiple host trials.

Whilst previous evidence has provided guidance on how to effectively design a questionnaire [37], missing data remains a problem. The primary outcome is the most important piece of information to be collected in a RCT, so emphasis should be placed on participants completing and returning this above all else [39].

Human perception (attention) and consequent cognition (thoughts), emotion and behaviour can be influenced by colour. From a bottom-up aspect, neurophysiological models of perception suggest coloured objects are attended to for saliency more than grey-scale objects [45]. From a top-down aspect, we are primed to attend to colours which match our beliefs and expectations [46]. From these models we surmise that automatic visual attention is drawn to coloured objects in preference to grey-scale and that if we expect (believe) an object to be in grey-scale, for example a letter or questionnaire, then when it is not our attention is moved to examine this mismatch.

This principle has been tested in both pragmatic psychological and market research. A study undertaken of 1.4 million customers by Zviran et al (2006) [42] showed that using background colour in email messages can result in a higher percentage of emails being clicked upon and read. When choosing colour we are advised to check for cultural specific connotations [47]. For example using the colour green, which holds sacred associations in Islam, could be perceived as inappropriate. The idea of using coloured paper to increase response rates in research is not new. It has been around for a long time, in an array of settings from direct mail advertising [34], to use in sports management [35]. Most studies have reported no significant effects from using coloured paper [40]. However, some have

found positive results [41]. A meta-analysis has been conducted collating all the known studies, at the time, on the topic and it was found that pink paper had the greatest effect [36]. It has been hypothesised that if colour is psychologically appealing to respondents, the response rates for an initial mailing of a questionnaire should be higher, there is also a reduced chance of the questionnaire being misplaced [41].

Despite there being a large evidence pool on the use of colour in questionnaires as a whole, there has been no test done on only colouring only one question and examining the impact that may have on response rates. Having just one question printed on coloured paper should make that question in particular more appealing than the rest of the questionnaire printed on white paper. Colour, in marketing, is a powerful tool that significantly influences consumer purchases [44]. So much so that one study [43] found that it that it accounts for 85% of the reason why someone decides to purchase a product. So printing the primary outcome measure on coloured paper should improve response and retention rates.

The addition of printing the primary outcome questionnaire on pink paper is a simple, cost-effective and easily implemented way of potentially making the questionnaire more engaging to the participant and hence increasing compliance. It also may make the questionnaire as a whole more appealing so could reduce the number of other, secondary, questions skipped and improve the overall response rate. Adding colour may also make participants less likely to need prompting to fill in and return the questionnaire.

Our main objective is to test the effectiveness of the low-cost pink paper strategy (PEPPER) of printing the primary outcome on coloured paper on completion of that primary outcome measure using a randomised controlled trial embedded within the PEP-TALK trial. PEP-TALK (a behaviour change physiotherapy intervention to increase physical activity following hip and knee replacement) is a randomised controlled trial which assesses the impact of a behaviour change intervention on patients' activity level and psychological state following total hip and total knee replacements (http://www.isrctn.com/ISRCTN29770908). The study is funded by the National Institute of Health Research– Research for Patient benefit.

2. OBJECTIVE

The aim of the PEPPER sub-study is to evaluate the effectiveness of printing the primary outcome on pink paper, versus printing the primary outcome on white paper on overall completion of the primary outcome measure (for PEP-TALK the primary outcome measure is the UCLA activity scale). Compliance rates to completing the rest of the questionnaire, overall response rates to the questionnaires, and number of times the patient was reminded to fill in the questionnaire will also be assessed.

3. TRIAL DESIGN

The general methodology of this embedded study within the PEP-TALK trial, of an intervention to improve completion of the primary outcome in postal questionnaires, will be guided by methodology developed and published by START [12, 13]. The sub-study will use a RCT design. Participants will be randomised (1:1) to receive one of two interventions:

1) The UCLA activity scale printed on white paper in their 6 month follow-up questionnaire (control group)

2) The UCLA activity scale printed on pink paper in their 6 month follow-up questionnaire (intervention group)

4. METHODS – PARTICIPANTS, INTERVENTIONS AND OUTCOMES

4.1. Participant recruitment

All participants in the PEPPER sub-study will have consented and be enrolled in the PEP-TALK trial which will act as the host trial. Participants will be included into the PEPPER sub-study if they meet the inclusion criteria for the PEP-TALK trial, there are no addition inclusion criteria for the sub-study.

4.2. Interventions

Participants will be randomised to receive either a six month follow-up questionnaire printed on only white paper (control group), or a six month follow-up questionnaire with the UCLA activity score printed on pink paper and all other sections printed on white paper (intervention group). Both arms' questionnaires will be sent to trial participants 6 months post-randomisation as stated in the PEP-TALK protocol. If patients do not return completed questionnaires the steps specified in the PEP-TALK protocol will be followed in the same way for both the control and the intervention arms. The white paper used for both arms will be standardised in weight and quality.

The questionnaires both groups receive will be identical in every way except the primary outcome is printed on pink paper for the intervention group. The handling of the questionnaires once returned to the central trials office will be the same for both groups and consistent with the PEP-TALK protocol.

4.3. Outcomes

Primary Outcome

The primary outcome measure will be UCLA activity score completion rate, defined as the raw number of UCLA activity score questionnaires returned by participants.

Secondary Outcomes

The secondary outcome measures will be:

- UCLA activity score completion rate adjusting for the number questionnaires received per arm.
- The proportion of participants reminded to fill in the questionnaire.
- The proportion of the remaining questions in the questionnaire completed.
- Overall return rate of the 6 month questionnaire.

5. METHODS – ASSIGMENT OF INTERVENTIONS

5.1. Randomisation

Participants will be assigned a unique trial identification (ID) number by the PEP-TALK trial. A computer generated randomisation list will be used to list all participants that are in the PEP-TALK trial. Half of the participants will be randomly allocated (1:1) to the intervention group and half to the control group. Generation of the allocation sequence and assignment of the intervention and control groups will be undertaken independently by a researcher not involved with sending the postal questionnaires. To avoid imbalance, block randomisation with equal probabilities of assignment to the intervention and control groups will be used.

For practical reasons, participants will be randomised to the PEPPER sub-study soon after being randomised to the PEP-TALK host trial rather than being randomised when they are due to be sent their six month follow up questionnaire. This could potentially add a bias as there is a 6 month gap from randomisation to being sent the questionnaire, participants could withdraw or drop out from the PEP-TALK study in this time giving unequal numbers between the two groups. However, the bias this could introduce is negligible so not a concern on the validity of the results from the PEPPER sub-study.

5.2. Blinding

PEP-TALK trial participants will be blinded to the nature and objectives of the PEPPER sub-study. The trial team will not be blinded to the allocation of groups.

5.3. Sample size

As is usual with an embedded trial within a trial, no formal power calculation will be undertaken as the sample size will be constrained by the number of participants included in the PEP-TALK trial receiving follow-up questionnaires. Based on anticipated recruitment and follow up rates, we anticipate an analysable sample size of approximately 250 participants (125 per group). If this sample size is not large enough to detect an effect, other similar studies using PROMs for their primary outcome, could perform the same sub-study and a meta-analysis be performed.

6. STATISTICAL ANALYSIS

All eligible participants will be included in the analysis on an intention-to-treat basis. The analyses will be conducted in Stata (StataCorp) or R. Completion of the primary, whether a reminder follow up questionnaire is sent, the proportion of the rest of the questionnaire being completed, overall return rates of the 6 month questionnaires, and the completion of the primary adjusting for the number questionnaires received per arm will all be compared using a chi-square test and reported as risk ratios and 95% confidence intervals. When there is withdrawal/drop out between randomisation and mailout in the PEPPER sub-study then these participants will be retained in the intention to treat analysis and categorised as incomplete for the primary outcome (then no bias except for dilution effects will be introduced).

7. APPROVAL AND DISSEMINATION

7.1. Ethical approval

Ethical approval will be obtained from the South Central – Oxford B Research Ethics Committee (REC) in the form of a substantive amendment to the PEP-TALK trial (REC Ref: 18/SC/0423; Integrated Research Application System (IRAS) ID 245306). The PEP-TALK trial has been registered on the ISRCTN clinical trial register (ISRCTN Number: 29770908); the PEPPER sub-study will be registered as a sub-study of PEP-TALK on the ISRCTN register. The sub-study will be conducted in accordance with the principles of the Declaration of Helsinki and the Medical Research Council's GCP guidelines.

7.2. Informed consent

Due to the nature and objective of the PEPPER sub-study participants will not be asked to consent specifically to take part in this sub-study of PEP-TALK. However, we do not consider this to be a major ethical issue as we consider this to be a low-risk sub-study and informing participants that we are looking at questionnaire response and completion rates might impact the impartiality of our results. All participants that consented to be in the PEP-TALK study will be explicitly asked if they consent to being contacted for the purposes of follow up by the central PEP-TALK team.

7.3. Publication

The findings of the PEPPER sub-study will be published in a peer-reviewed journal and will be reported following the Consolidated Standards of Reporting Trials guideline (CONSORT, www.consort-statement.org). In addition, data from the PEPPER sub-study will contribute to the Study Within A Trial (SWAT) initiative to improve trial recruitment (www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInfor

mation/) and to the Cochrane review of strategies to improve trial retention (http://onlinelibrary.wiley.com/doi/10.1002/14651858.MR000032.pub2/abstract). It will help to increase the evidence base on the retention of participants to trials. To facilitate this fully anonymised data from the PEPPER sub-study will be shared, on written request, in order to undertake a meta-analysis of individual patient data in accordance with the 'Good Practice Principles for Sharing Individual Participant Data from Publicly Funded Clinical Trials' [33].

9. PEPPER SUB-STUDY PROJECT TEAM

- Dr Toby Smith (Oxford Clinical Trials Research Unit, University of Oxford) is the chief investigator for the PEP-TALK trial, assisting in the design of the intervention for the PEPPER sub-study.
- Alexander Ooms (Oxford Clinical Trials Research Unit, University of Oxford) is trial statistician for the PEP-TALK trial and project lead the PEPPER sub-study with overall responsibility for its design and implementation.
- Dr Scott Parsons (Oxford Clinical Trials Research Unit, University of Oxford) is trial manager for the PEP-TALK trial and project co-ordinator for the PEPPER sub-study with responsibility for its day to day implementation.
- Dr Bethany Fordham (Oxford Clinical Trials Research Unit, University of Oxford) is co-applicant and investigator for the PEP-TALK trial, assisting in the design of the intervention for the PEPPER sub-study.
- Dr Vicki Barber (Oxford Clinical Trials Research Unit, University of Oxford) is hub manager for the Oxford Clinical Trials Research Unit supporting the infrastructure for the PEPPER sub-study.
- Professor Sarah Lamb (Oxford Clinical Trials Research Unit, University of Oxford) is a co-investigator for the PEP-TALK trial.

10. TIMELINE

Predicted* timelines:

March 2019 – March 2020	PEP-TALK trial recruitment period
September 2019 – September 2020	6 month follow up period for PEPPER sub-study
October 2020 – December 2020	Analysis of PEPPER sub-study
January 2021 – February 2021	Final report for PEPPER sub-study
March 2021	Sharing of anonymised patient level data for PEPPER sub-study

**Based on predicted timelines for host PEP-TALK trial and so subject to change*

11. COSTINGS

Total cost = £3,467.29

Staff costs:

Grade 7 – Trial Manager / Trial Statistician – 3 weeks equivalent of 100% FTE for 1 year (£2,857.29)

Associated tasks include:

- Initial set up of PEPPER sub-study (e.g. set up and testing of RRAMP randomisation system, incorporating SWAT into existing protocol and subsequent submission of amended Protocol to Sponsor, HTA and REC) – approx. 4-5 days.
- Activities involved per questionnaire sent (e.g. randomisation of each patient into SWAT, printing UCLA activity score onto pink paper) approx. 10 minutes per questionnaire - approx. 5-6 days.
- Analysis of PEPPER sub-study, preparation of final report and preparing anonymised patient level data set – approx. 10 days.

Other costs:

Pink Paper (£10)

Conference attendance to disseminate findings from PEPPER (£600)

12. PEP-TALK SUB-STUDY REFERENCES

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