

28 APPENDIX 1 – SUB-STUDY 3: STUDY WITHIN A TRIAL (EVALUATION OF THE IMPACT OF A THEORETICALLY INFORMED COVER-LETTER ON QUESTIONNAIRE RESPONSE RATES)

28.1 BACKGROUND

Many trials collect outcome data direct from participants using mailed questionnaires. A low response rate to these questionnaires puts the validity and generalisability of the trial results in jeopardy [1-5].

Triallists recognise the challenge and use many interventions to improve retention but it is generally difficult to predict their effect. The Cochrane systematic review of strategies to improve retention [6] found only a handful of interventions with high quality evidence of benefit. Given how central recruitment and retention are to all trials, it is crucial that more rigorous evaluations of retention interventions are done.

One way of doing this is to do a Study Within a Trial, or SWAT (See, for example, [7]). A SWAT provides a protocol for the evaluation of an intervention to improve some part of the trial process, such as recruitment or retention. This evaluation is then embedded within a host trial, such as the present trial, CODIFI2. Several teams can follow the same SWAT protocol, meaning the results can be combined in a meta-analysis. This coordinated and collaborative approach means triallists will have faster access to high-quality evidence to inform their trial design, conduct, analysis and reporting decisions.

Since returning the questionnaire is a behaviour, this opens up the possibility of designing a behaviour change intervention to influence the willingness of participants to do that behaviour. To that end, we would like to make use of SWAT 24 [8] in CODIFI2, which describes the use of a theory-based [9-11] cover letter to improve response rates to mailed questionnaires used to collect trial data. The theory-based letter shows promise as a way of improving retention [12] but requires evaluation in more trials before we can conclude that it is effective.

This SWAT 24 study is part of the Trial Forge initiative to improve trial efficiency [13].

28.2 AIMS AND OBJECTIVES

To estimate the effect on mailed questionnaire response rates of a covering letter designed with reference to behavioural change theory to encourage response compared to a standard cover letter merely requesting a response over 52 weeks (to a maximum of 104 weeks for relevant participants) post randomisation.

28.3 TRIAL DESIGN

28.3.1 Sub-Study 3: Trial Design

The embedded cover letter sub-study is a 2-arm parallel group randomised controlled trial comparing the response rates to postal questionnaires when accompanied by either a short standard cover letter requesting response to those accompanied by an “enhanced” cover letter, designed with reference to behavioural change theory [9-11]. The effect will be estimated at each time point where a questionnaire is mailed to the participant.

Eligible and consenting patients who are randomised within study 1 will be randomised 1:1 to either standard or enhanced cover letter. Participants’ cover letters will be according to randomised group at all mailed questionnaire timepoints: there will be no cross-over and no re-randomisation to different letters.

28.3.2 Blinding

Neither the randomising site nor the participant will be informed of their cover letter allocation at randomisation. The participant will become aware of their cover letter once they receive their first mailing. Site may become unblind to that patient’s allocation should the participant bring the entire questionnaire pack to clinic for their clinical follow-up. To mitigate possible biases, participants will be informed that the trial will look at the effect of a communication intervention on their data completeness, but they will not be informed of the exact nature of this intervention.

28.3.3 Randomisation

Immediately after randomisation in the main CODIFI2 study is complete, randomisation to the “cover letter” sub-study will occur. Participants will be allocated to receive either the standard or the “Enhanced” cover letter with their postal questionnaire. A second minimisation

algorithm, also incorporating a random element will be used to ensure that the sampling strategy groups are well balanced for the following characteristics:

- Randomising centre
- Sampling strategy allocation (Swab vs Tissue)
- Participant age (65 or younger, 66 or older)
- Gender (Male, Female)

Participants will retain the participant identifier already allocated.

28.4 INTERVENTIONS

28.4.1 Sub-study 3: Comparison of “Enhanced” Theory-Based Cover Letter Vs Standard Cover Letter

The interventions to be assessed in this sub-study are covering letters sent in addition to the mailed questionnaire booklet of quality of life questionnaires. All mailed questionnaire packages will comprise a blank questionnaire booklet for completion, a stamped addressed envelope for return and a covering letter addressed to the participant. The content of the cover letter will differ according to the patient’s randomised group within this sub-study, and the wording will differ slightly for each follow-up time point. (eg: “please find enclosed the 39 week / 52 week / 104 week questionnaire”).

28.4.2 “Enhanced” theory-based cover letter

The Theoretical Domains Framework (TDF) is a tool for identifying theoretical targets for behaviour change interventions [9-11]. The TDF and behaviour change techniques were used by the IQuaD trial team [12] to produce a template that trial teams can use to structure a theory-informed cover letter to send together with their trial questionnaires. Examples of relevant theoretical domains and behavioural change techniques include “Motivation and Goals” (providing general encouragement and information about others support and approval), “Beliefs about consequences” (Providing information on the benefits of action or costs of inaction) and “Knowledge” (Providing information on behaviour and outcomes, i.e. why are we asking these questions and what it means for the study) This template has been adapted for use in the CODIFI2 trial as the intervention cover letter in this study.

At the 39 week follow-up visit, participants randomised to the “enhanced” cover letter group will be sent cover letter A (filename xxxxxxxxxxxx_letter A) in addition to the questionnaire booklet and a stamped addressed envelope. At 52 weeks, cover letter B (filename xxxxxxxxxxxx_letter B) will be sent in addition to the booklet and envelope. Participants eligible for the 104 week follow-up will receive cover letter C with their final questionnaire pack. (filename xxxxxxxxxxxx_letter C).

28.4.3 Standard cover letter

The standard comparator cover letter conveys the usual information provided by the CTRU to mailed questionnaire respondents: the title of the study, a reminder that they are taking part in the study, contact details for a staff member and that a questionnaire is enclosed for their completion and return. At week 39, participants randomised to the control cover letter group will receive follow-up letter I (filename xxxxxxxxxxxx_letter I) with their questionnaire pack. At 52 weeks, cover letter II (filename xxxxxxxxxxxx_letter II) will be sent with the pack. Participants eligible for the 104 week follow-up will receive cover letter III (filename xxxxxxxxxxxx_letter III) with their pack.

28.5 OUTCOME ASSESSMENT

The return of questionnaire either by mail to the Clinical Trials Research Unit, or by hand at a clinic visit will be recorded. The date of receipt at clinic or at the Clinical Trials Unit will be recorded for determining time to response.

For the sub-study, the full analysis set is based on questionnaires issued to the participant. This population will include all participants randomised to take part in the CODIFI2 study. However, if a participant withdraws or dies before the first questionnaire is mailed, no questionnaires will be included in the analysis set for this participant.

28.5.1 Sub-study 3: outcome measures

Primary outcome measure: Return of mailed questionnaire at 39, 52 and 104 weeks.

Exploratory outcome measure: Time from mailing to return of questionnaire at the same timepoints.

28.6 SUB-STUDY 3: OUTCOME MEASURE ANALYSES

Multivariable logistic regression – accounting for repeated measures clustered within each participant – with fixed effects for randomised cover letter, age, sex, CODIFI Sampling arm, time-point and timepoint-by-cover letter interaction and random effects for randomising centre (if feasible), participant and participant -by-timepoint. The odds ratio for the overall effect of the enhanced letter on return (with 95% confidence interval) will be presented, along with the same for the effect at each time point.

An exploratory analysis taking a time-to-return approach (accounting for repeated measures clustered within patients) will be considered, if feasible. Such an analysis – multivariable time-to-event regression – will adjust for the sub-study minimisation factors, if feasible.

28.7 SAMPLE SIZE CALCULATION

Sub-Study 3: Questionnaire response rate

Outcome measure	Return of questionnaire
Outcome measure analysis method	Comparing proportions (logistic regression)
Fixed Sample Size	365 per arm
Control Group return rate	50%
Assumptions	ICC of response rates = 0.7 (Note unit of allocation=patient, unit of analysis = questionnaire. Multiple questionnaires per patient); Constant intervention effect over all follow-ups; All participants attend 2 follow-ups.
Type I error rate / alpha	5%
1 or 2-sided significance test	2-sided
Type II error rate (Power)	20% (ie 80% Power)
Resource	nTerim 3.0 (Statistical Solutions Ltd, Republic of Ireland), table "Fixed Term, Cluster randomised two proportions inequality"
Attrition / loss to follow-up allowed for	10% (from the main study 1)
Effect size (absolute difference in proportions Control - Enhanced)	10.03%

Expected ICC of 0.7 justified by repeated measures within patient (rather than many different patients clustered within a hospital) so expect high correlation of outcomes between patients. For example, Essers et al [61] found that in 12 month longitudinal quality of life outcomes in ankylosing spondylitis, the ICC ranged from 0.58 to 0.73. Detectable effect decreases as ICC decreases. Control group return rate 50% as worst case scenario (maximum variance occurs when both return rates are 50%)

28.8 REFERENCES

1. Walters, S.J., et al., *Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme*. BMJ open, 2017. **7**(3): p. e015276.
2. Sully, B.G., S.A. Julious, and J. Nicholl, *A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies*. Trials, 2013. **14**(1): p. 166.
3. McDonald, A.M., et al., *What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies*. Trials, 2006. **7**(1): p. 9.
4. Foy, R., et al., *How evidence based are recruitment strategies to randomized controlled trials in primary care? Experience from seven studies*. Family practice, 2003. **20**(1): p. 83-92.
5. Sutherland, H., et al., *A randomized trial of the total design method for the postal follow-up of women in a cancer prevention trial*. European journal of cancer prevention: the official journal of the European Cancer Prevention Organisation (ECP), 1996. **5**(3): p. 165-168.
6. Brueton, V.C., et al., *Strategies to improve retention in randomised trials*. Cochrane Database of Systematic Reviews, 2013(12).
7. Smith, V., et al., *SWAT 1: what effects do site visits by the principal investigator have on recruitment in a multicentre randomized trial?* Journal of Evidence-Based Medicine, 2013. **6**(3): p. 136-137.
8. Anne Duncan, C.R., Debbie Bonetti, Jan Clarkson. *SWAT 24: Using a theoretically informed cover letter to improve response rates to annual postal questionnaires*. 23rd May 2018]; Available from: <https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/FileStore/Fileupload,545010,en.pdf>.
9. Michie, S., et al., *Making psychological theory useful for implementing evidence based practice: a consensus approach*. BMJ Quality & Safety, 2005. **14**(1): p. 26-33.
10. Michie, S., et al., *From Theory to Intervention: Mapping Theoretically Derived Behavioural Determinants to Behaviour Change Techniques*. Applied Psychology, 2008. **57**(4): p. 660-680.
11. Abraham, C. and S. Michie, *A taxonomy of behavior change techniques used in interventions*. Health psychology, 2008. **27**(3): p. 379.
12. Duncan, A., et al., *Improving trial questionnaire response rates using behaviour change theory*. Trials, 2015. **16**(2): p. P92.
13. Treweek, S., et al., *Making randomised trials more efficient: report of the first meeting to discuss the Trial Forge platform*. Trials, 2015. **16**(1): p. 261.
14. Essers, I., et al., *Fluctuations in patient reported disease activity, pain and global being in patients with ankylosing spondylitis*. Rheumatology, 2016. **55**(11): p. 2014-2022.