

Theoretically-informed vs standard cover letter to improve participant response to mailed questionnaire: results of an embedded randomised retention trial

Colin Charles Everett

c.c.everett@leeds.ac.uk

University of Leeds <https://orcid.org/0000-0002-9788-840X>

Sarah T Brown

University of Leeds Clinical Trials Research Unit

Joanna L Dennett

University of Leeds Clinical Trials Research Unit

Howard Collier

University of Leeds Clinical Trials Research Unit

Claire L Davies

University of Leeds Clinical Trials Research Unit

Frances Game

University Hospitals of Derby and Burton NHS Foundation Trust

Andrea Nelson

Glasgow Caledonian University

Research Article

Keywords: SWAT, Study within a Trial, Retention Methods, embedded randomised controlled trial, Surveys and questionnaires, behavioural change theory, Diabetic Foot, Follow-up Studies, Quality of Life, Outcome Assessment, Health Care

Posted Date: June 17th, 2024

DOI: <https://doi.org/10.21203/rs.3.rs-4109848/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Title

Theoretically-informed vs standard cover letter to improve participant response to mailed questionnaire: results of an embedded randomised retention trial

Word count: 3576

Authors, affiliations and ORCIDs

Colin C Everett, [1] (0000-0002-9788-840X) (Corresponding Author)

Sarah T Brown, [1] (0000-0002-1840-3786)

Joanna L Dennett, [1] (0009-0009-1592-3119)

Howard Collier, [1] (0000-0002-0107-0604)

Claire L Davies, [1] (0000-0002-7969-6738)

Frances Game, [2] (0000-0002-5294-4789)

E Andrea Nelson [3] (0000-0001-6741-3078)

[1] Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom.

[2] University Hospitals of Derby and Burton NHS Foundation Trust

[3] Glasgow Caledonian University, Glasgow UK

1 **Abstract**

2 **Background**

3 Participant non-response is a source of bias in all research, especially in randomised
4 controlled trials. Participants followed-up remotely can have high non-response
5 rates. Four trials have been conducted of a cover letter with content informed by
6 behaviour-change theory to overcome hypothesised barriers to responding to a
7 mailed questionnaire. Pooled results to date have suggested further research to be
8 worthwhile. We conducted an embedded randomised study within a trial of such
9 cover letters in the hope that we would improve response rates to our postal quality
10 of life questionnaires.

11 **Methods**

12 148 participants in the CODIFI2 diabetic foot ulcer sampling trial were randomised
13 1:1 to receive one of two different cover letters at follow-up visits: either a standard
14 cover letter accompanying their postal follow-up questionnaires, or to an “enhanced”
15 (theory-informed) cover letter. Questionnaires were mailed at 39, 52 and (for some
16 participants) 104 weeks post randomisation. Outcome measures were response to
17 mailing at each timepoint. Analysis was restricted to those for whom a questionnaire
18 and letter was issued. Owing to limited recruitment, a reduced analysis plan,
19 comprising solely observed response rates and 95% confidence intervals for
20 difference in response rates was followed. Post hoc, we added our week 52 results
21 to an already-published meta-analysis.

1 **Results**

2 67/74 enhanced cover letter group (Enhanced) and 67/74 standard cover letter
3 group (Standard) participants who had not already died or withdrawn were sent their
4 first mailing at 39 weeks. The 39-week response rates were, 70.1% (47/67) and
5 58.2% (39/67) for Enhanced and Standard participants, respectively. At week 52 the
6 response rates were 70.3% (45/64) and 55.6% (35/63) for Enhanced and Standard
7 participants, respectively. At week 104, the response rates were 72.7% (24/33) and
8 57.6% (19/33) for the Enhanced and Standard participants, respectively. Adding our
9 week 52 results to a published meta-analysis increased the pooled estimate of
10 differences in response rates to 0.04 (-0.01 to 0.09) favouring enhanced letters.

11 **Conclusion**

12 While this embedded randomised trial observed greater response rates at all times
13 among those randomised to the enhanced letter, the reduced trial sample size meant
14 that these results are imprecise.

15 Trial registration: ISRCTN74929588, registered 5th March 2019.

16

Keywords:

SWAT; Study within a Trial; Retention Methods; embedded randomised controlled trial; Surveys and questionnaires; behavioural change theory; Diabetic Foot; Follow-up Studies; Quality of Life; Outcome Assessment, Health Care.

Declarations

Ethics Approval and Consent to Participate

All participants in CODIFI2 gave written informed consent to take part in the trial, and all of its sub-studies, including this SWAT. The study was submitted for – and received favourable ethical approval from West of Scotland REC 3 (Ref 18/WS/0235).

Consent for publication

This publication does not include individual participant data in any form, and so no specific consent for publication is required.

Availability of data and materials

Data supporting this work are available on reasonable request. All requests will be reviewed by relevant stakeholders, based on the principles of a controlled access approach. Requests to access data should be made to CTRU-DataAccess@leeds.ac.uk in the first instance.

Competing interests

The authors declare that they have no competing interests.

1 **Funding**

2 Funded by National Institute for Healthcare Research – Health Technology
3 Assessment Programme. Award ID: 16/163/04. The views expressed are those of
4 the author(s) and not necessarily those of the NIHR or the Department of Health and
5 Social Care.

6

7 **Authors' Contributions**

8 Colin C Everett, Lead on the embedded trial's design, analysis, interpretation and
9 drafting the manuscript, Substantial Contribution to data collection. Approved
10 submitted version.

11 Sarah T Brown, Substantial Contribution to embedded trial design, Substantial
12 Contribution to data collection, analysis, interpretation and reviewing and revising
13 manuscript. Approved submitted version.

14 Joanna Dennett, Co-lead on data collection. Substantial Contribution to embedded
15 trial design, to interpretation and reviewing and revising manuscript. Approved
16 submitted version.

17 Howard Collier, Co-lead on data collection. Substantial Contribution to embedded
18 trial design, Substantial Contribution to interpretation and reviewing and revising
19 manuscript. Approved submitted version.

20 Claire L Davies, Substantial Contribution to embedded trial design, data collection
21 interpretation, reviewing and revising manuscript. Approved submitted version.

Frances Game, Substantial Contribution to embedded trial design, Substantial Contribution to data collection, analysis, interpretation and reviewing and revising manuscript. Approved submitted version.

E Andrea Nelson, Substantial Contribution to embedded trial design, Substantial Contribution to data collection, analysis, interpretation and reviewing and revising manuscript. Approved submitted version.

Acknowledgements

We acknowledge members of the Lay ADvice on Diabetes and Endocrine Research (LADDER) Participant and Public Involvement Group, (Sheffield Teaching Hospitals NHS Foundation Trust) whose views on the cover letter SWAT and contents of the letters lead to changes to the enhanced letters used in this study.

We also acknowledge the statistical programming contributions by Joseph Lucas in support of this paper.

1 Introduction

2 If participants in clinical trials do not provide outcome data at the expected times,
3 then any analyses undertaken may become unreliable. Attrition leads to a loss of
4 information, which leads to both a loss of statistical power to detect clinically relevant
5 differences, and more importantly, potentially biased estimates of the treatment
6 effect. (1) Statistical methods exist for analysing data in the presence of
7 missingness, but must make unverifiable assumptions about the unobserved data.
8 (2) (3) (4) Consequently, it is always preferable to design and conduct a study to
9 maximise the chance of observing the expected data.

10

11 Mailed questionnaires are one possible method to collect outcome data. These can
12 be more convenient to a participant than requiring them to attend an in-person clinic
13 appointment, and hence can address a potential barrier to recruitment to trials, which
14 may be related to participant characteristics, and hence trial external validity.
15 Unfortunately, mailed questionnaires can suffer from low response rates even over
16 short durations. For example, in a 2018 randomised trial of different response
17 options to a survey mailed to parents of patients in a childhood diabetes registry,
18 Bjertnaes et al (5) reported response rates between 41.6% and 62.4% for a survey
19 administered at a single timepoint. Despite the promise of valid results if unobserved
20 values can be predicted by other observed data (the “missing at random”
21 assumption), examples such as this demonstrate the need to design the process for
22 collecting outcome data remotely (including via mailed questionnaires) so as to
23 encourage responses.

24

1 There is a long history of randomised controlled trials designed to improve response
2 to mailed questionnaires. A 2009 Cochrane Review (6) identified 481 eligible trials as
3 early as 1940 (assigning by alternation, (7)) evaluating 121 different interventions
4 aiming to improve response rates to mailed or electronic questionnaires. A 2023
5 update (8) increased this to 758 trials evaluating 187 interventions. A more specific
6 Cochrane Review by Gillies et al in 2021, tailored to improving retention in
7 randomised controlled trials (9) identified 69 studies assessing 52 interventions
8 targeting a variety of follow-up aspects, including mailed questionnaires. This latter
9 review found that evidence supporting the proposed interventions was generally
10 uncertain, per GRADE criteria. One intervention that has been previously trialled is
11 an enhanced cover letter, with content informed by behavioural change theory. (10)
12 (11) The iQUAD trial authors who devised the original intervention identified several
13 potential barriers to a participant responding to a questionnaire, and tailored a cover
14 letter to address these barriers. While the pooled evidence from four trials (9) hinted
15 at a benefit to these enhanced letters, the 95% Confidence interval for the pooled
16 effect included zero. We decided to undertake a replication of this embedded study
17 within a trial (SWAT) in a recent randomised trial, with the aim being to estimate the
18 extent to which the theoretically-informed cover letter (adapted to our own trial)
19 improved response rates to mailed questionnaires.

21 **Methods**

22 The CODIFI2 multicentre randomised controlled trial (ISRCTN74929588) included
23 an embedded multicentre, prospective, 2-arm parallel-group randomised SWAT to
24 evaluate an intervention to improve postal questionnaire response rates. The main

CODIFI2 trial recruited people with diabetes and diabetes-related foot ulcers (DFU) that were suspected to be infected, from specialist centres in England from May 2019 to April 2022. The trial's aim was to determine whether sampling potentially infected DFUs by swab sampling or by tissue curettage (to determine appropriate antibiotic usage) would result in faster DFU healing. Full eligibility criteria for CODIFI2 – and by extension this SWAT – are included as supplementary material. No additional eligibility criteria applied to this SWAT: all participants eligible for the CODIFI2 main trial were eligible to be randomised in the SWAT.

This SWAT was incorporated within the trial's ethically-approved protocol from the outset, and ethical approval for the study as a whole was obtained from West of Scotland REC 3 (Ref 18/WS/0235). The CODIFI2 trial protocol, which includes the details of this SWAT, is available from the funder at (12). Participants were informed in the participant information leaflet that there would be a trial of communication methods, but were not given further details.

Randomisation and blinding

Eligible and consenting participants were randomised to the main trial arms (swab or tissue sampling of the index DFU) by site research staff via a 24hr automated interactive central randomisation system operated and maintained at the University of Leeds CTRU. Immediately afterwards, the system randomised participants in a 1:1 allocation ratio to receive one style of cover letter (standard vs enhanced) consistently at each of their postal follow-up visits at weeks 39, 52 and 104 post randomisation, for those participants randomised in the first year of the trial's recruitment. SWAT randomisation was by minimisation with a random element

(75%), with the minimisation factors being age [65 or younger vs 66 or older), sex, randomising centre and the main trial allocation. Neither sites nor participants were informed of their cover letter allocation at the moment of randomisation. Participants did not receive their first cover letter until their first postal follow-up, 39 weeks post randomisation. Participants were not informed that their mailings were chosen as one from two possible style of mailings, that the choice of mailing style was made at random, nor that the style of mailing would be the same at each of that participant's mailed follow-up timepoints.

Interventions

At week 39, 52 and 104 (the latter for the earliest trial recruits only), participants were mailed questionnaire booklets and a cover letter, according to their randomised allocation. Cover letters were automatically generated by means of database reports, which generated the correct letter for each participant according to their randomised allocation, the timepoint of interest, expected follow-up duration and (for week 52) receipt of a response at week 39. For brevity, this article generally refers to the "Standard" and "Enhanced" cover letters in this article: the "enhanced" cover letter being based on the theoretically-informed letter identified on the SWAT repository in the SWAT24 entry (13) and provided by the Trial Forge evidence pack. (14) Samples of the enhanced and standard cover letters used in our replication of this SWAT are included as supplementary material.

A participant randomised to the standard letter arm in the SWAT received the standard cover letter, which merely reminded the participant of their involvement requesting completion and return of their booklet, and of a participant-completed

1 antibiotic diary. A participant randomised to the enhanced letter arm received a letter
2 with content hypothesised to address barriers to non-response. This letter was
3 mostly drafted along the lines of that used in the iQUAD trial (11) but tailored to the
4 requirements of CODIFI2's study design and accounted for feedback received by a
5 participant representative group. Specifically, we omitted a detailed action plan for
6 completion (owing to length), removed all references to the questionnaires being
7 short (following PPI scepticism) and did not have local site staff signatures owing to
8 difficulties in implementation. We also added to enhanced Week 52 letters a
9 sentence thanking participants for responding at Week 39 where this had happened.
10 All letters (except the reminder) included the same photograph of the same CODIFI2
11 co-chief investigator, and included contact details for a member of the CTRU trial
12 team to provide further assistance if this was required.

13 All participants were sent identical reminder letters in case of non-response. While
14 most participants opted for electronic reminders by email and/or SMS, we also
15 issued mailed reminder letters. Reminder letters were similar to the Standard group
16 letter in style and tone. At week 52, participants received slightly different cover
17 letters depending on whether they were intended to be followed up to 104 weeks. At
18 their final postal follow-up, whether at 52 or 104 weeks, all letters thanked the
19 participant for their involvement.

21 **Statistical Methods**

22 The SWAT's original sample size was determined by that of the main CODIFI2
23 study. For information, we produced a sample size calculation to illustrate the
24 potential power to the study to detect an effect of enhanced cover letters on

1 response rates. With the intended 730 recruited participants, the study would have
2 80% power to detect a difference of 10%age points in response rates with a 2-sided
3 5% significance test, allowing for analysis of all timepoints as repeated
4 measurements clustered within participant (assuming intra cluster correlation of 0.7)
5 and a control group response rate of 50%, and 10% loss to follow-up before week
6 39. No interim analyses of the SWAT were planned or undertaken.

7 The outcome measures for the trial were the proportions of mailings issued for which
8 we received the questionnaire in return for each of the three timepoints in isolation.

9 The analysis populations for each timepoint were defined as the participants
10 randomised for whom a questionnaire was issued: any randomised participants
11 dying, withdrawing from postal questionnaire follow-up or completing follow-up prior
12 to a timepoint were excluded from the analysis for that timepoint, as were
13 participants for whom questionnaires were not sent. We estimated for each group
14 the proportion of participants returning a questionnaire, and the absolute differences
15 in proportions returning. Confidence intervals for the differences in proportions were
16 by the Clopper-Pearson Exact method for single proportions (15) and the Santner-
17 Snell (16) exact interval for differences in proportions. No hypothesis testing was
18 undertaken. These analyses were performed using SAS 9.4.

19 Post hoc we updated the meta-analysis published by Gillies et al (9) to include the
20 52-week CODIFI2 findings. This was an exploratory post-hoc analysis: we did not
21 assess risk of bias, or investigate the heterogeneity of interventions and outcome
22 measures prior to adding our findings to the analysis. Taking the published numbers
23 of events reported in analysis 43 of this review, we also included the numbers from
24 our study that responded and analysed for the two cover letter groups at 52 weeks.
25 Our meta-analysis of risk differences used the DerSimonian-Laird estimator for

1 between study variance and Mantel-Haenszel Estimates in calculation of variance
2 and Cochran's Q statistic. We verified that the analysis choices were aligned with
3 those previously published in Gillies et al before proceeding to our updated analysis.
4 The post-hoc meta-analysis update used R 4.2.3 (17) and the meta package v7.0.0
5 (18).

7 **Changes to study design and outcomes**

8 CODIFI2 was closed to recruitment and follow-up before reaching its planned
9 sample size, and a truncated analysis plan was agreed with the funder.
10 Consequently, the SWAT also closed to recruitment early. We originally intended to
11 perform exploratory analyses estimating differences in times to return of
12 questionnaires, but this was complicated by the COVID19 pandemic. Questionnaires
13 were customarily date stamped on arrival at the CTRU, but national lock downs
14 meant that the date stamps reflect dates that offices were open to process mail,
15 rather than actual dates of receipt. Consequently, we did not perform any analyses
16 of time to return.

19 **Results**

20 Between 7th May 2019 and 3rd May 2022, 148 of 149 CODIFI2 participants were
21 randomly assigned to a cover letter group. One participant was not randomised
22 owing to a randomisation system failure and subsequent withdrawal prior to week 39

visit. Figure 1 illustrates the participant flow through the two arms, including the numbers still in the study at each of the follow-up timepoints.

[FIGURE 1 HERE]

The baseline characteristics of the 74 standard letter and 74 enhanced theory-informed letter participants are summarised in Table 1. The two groups were similar in most respects, the mean age was 62.8years (SD 12.55, range 31 to 93), 122/148 (82.4%) were male and 143/148 (96.6%) were of white ethnicity. 130/148 (87.8%) of participants had Type II diabetes, with median (IQR) diabetes duration 15.5 years (10 to 21.5 years) and 96/148 (64.9%) taking some oral hypoglycaemic agent and 83/148 (56.1%) taking insulin. It appeared that participants randomised to the standard cover letter were more likely to report no problems with mobility (29.7% vs 13.5%) and anxiety/depression (60.8% vs 50.0%) on the baseline EQ5D-3L questionnaire than the enhanced letter.

[TABLE 1 HERE]

Supplementary Appendix 3 summarises the baseline characteristics of those who were issued questionnaires at each of the timepoints in the two arms. The results are similar, although, it should be noted that participants who were issued the week 104 questionnaire will be from among those recruited at the beginning of the trial, and so this cohort may be systematically different to those recruited later due to unseen temporal trends.

Outcomes

The questionnaire response rates are provided together in Table 2.

[TABLE 2 HERE]

At the 39-week visit, 67/74 (90.5%) participants in both arms were analysed due to having been sent a questionnaire pack. Reasons for questionnaires not being sent for this and all timepoints are included in the flow diagram. (Figure 1) The response rates were 47/67 (70.1%) and 39/67 (58.2%) for the enhanced and standard letter groups, respectively. The estimated difference in proportions responding was 11.9% (95% CI -5.7% to 29.1%).

At the 52-week visit, 64/74 (86.5%) and 63/74 (85.1%) participants were sent a questionnaire in the enhanced and standard letter groups, respectively. Two participants at week 52 were removed from the week 52 analysis due to other reasons for not issuing a questionnaire. (Figure 1) The response rates were 45/64 (70.3%) vs 35/63 (55.6%) for the enhanced vs standard letters, respectively. The estimated difference in proportions responding was 14.8% (95% CI -3.2% to 31.2%).

At the 104-week visit, 33/74 (44.6%) participants in each group were sent a questionnaire in the enhanced and standard letter groups, respectively. The response rates were 24/33 (72.7%) 19/33 (57.6%) for the enhanced vs standard letters, respectively. The estimated difference in proportions responding was 15.2% (95% CI -10.4% to 39.3%).

Updated Meta-Analysis

In the 2021 Cochrane Review (9), 4 trials of a theoretically-informed cover letter to improve response to mailed follow-up were included, including two unpublished findings provided by personal communications. (Analysis 43 in (9)) The random effects meta-analysis of differences in response rates estimated a pooled difference in response rates (enhanced letter – standard letter) of 0.033 (95% CI -0.015 to 0.080). Incorporating our 52-week results in this analysis (assuming that no other trials have been completed at time of publication) the updated pooled random effects estimate of difference in response rates (enhanced letter – standard letter) was 0.042 (95% CI -0.009 to 0.092). (Tau-squared=0.0012, $I^2=40.0\%$).

[FIGURE 2 HERE]

Costs

We did not collect data prospectively on costs relating to this SWAT. However, we note that while there were no additional postage costs associated with the SWAT, there may have been a small additional printing cost per enhanced letter printed. We did note that the SWAT incurred additional time to draft, implement and test the database report specifications that would generate the cover letters. A total of 15 different cover letter database reports were required covering combinations of timepoints, randomised allocation, past response and expected follow-up duration. A sixteenth, overarching administration report handled letter generation, as well as identifying those participants for whom a status check was required. Each database report incurred a time cost in terms of specification, implementation and testing the report. These costs occurred solely during study set up. Staff involved in generating the cover letters noted some increased challenges occurred with generating the

1 letters: the reporting system devised to generate the corresponding letters was not
2 felt to be user-friendly, was “fiddly” and “annoying” - as it each letter to be generated
3 one at a time on request by the user - though did not add significantly more work and
4 did not allow generation of letters from the incorrect allocation group. Unfortunately,
5 it was not possible to amend the system to fix these usability issues, so the system
6 remained in place.

7
8 The only other cost to be considered was the need to perform additional ongoing
9 monitoring and validation of the randomisation system for CODIFI2, owing to the
10 need to monitor a second dynamic allocation system. This latter cost was much
11 reduced, as standardised programs to automate the checking of minimisation
12 algorithms were already in place.

13 **Harms**

14 No Adverse Events associated with the cover letter sub-study were reported.

16 **Discussion**

17 In this randomised trial of an enhanced, theoretically-informed cover letter, we found
18 that the enhanced cover letter appeared to increase the proportions of contacted
19 participants responding at all three time points compared to the standard letter.
20 However, the 95% confidence intervals for all estimated differences were wide and
21 included the null value of no difference at all time points. No harms arising from the
22 use of either cover letter were reported. The burden of running the SWAT did involve
23 a fixed cost in terms of setting up the system to automatically generate letters, and

our systems experienced usability issues, but there was not any considerable burden generated in terms of running the SWAT on a day-to-day basis.

The key strengths of this trial are that the groups were assigned at random, concealed allocation by means of a central independently-operated randomisation service which was successful in ensuring balance in important demographic characteristics. Blinding was ensured both by withholding the assigned intervention and delayed provision of the assigned intervention. We were also able to use our automated systems to efficiently generate the required cover letters.

The early termination of the CODIFI2 trial (and, consequently, this SWAT) meant that the anticipated recruitment was lower than hoped for and so is a limitation of this SWAT. The result being that our estimated differences in response rates had low precision. Despite an apparently high observed difference in response rates, confidence intervals for this difference in response rates were wide. By itself, this ought not be a concern. SWATs are necessarily undertaken as embedded trials within (and secondary to) a host trial, with a view to being able to meta-analyse results, rather than as definitive standalone trials.

We used a single subject randomisation to the same group for all cover letters, without knowledge of whether a participant would be available for follow-up, which is a possible limitation. We chose this approach to minimise the impact on delivery of the host trial. As a result of our design choice, our estimands are not those of a policy of enhanced covering letters, even in participants who are not followed up, but rather we have estimated the effect of an enhanced letter in those who were sent a questionnaire pack.

1 An alternative approach might have been to re-randomise all active participants to a
2 new letter at each available follow-up time. (19) In our case, this would have
3 introduced extra challenges by increased delay in generating each follow-up letter.
4 While the actual number recruited to CODIFI2 was small, had the trial recruited to
5 target, the extra time needed to manually perform a randomisation for each letter
6 that was due might have been substantial. In addition, from a design perspective, we
7 were concerned that there may have been a cross-over or contamination effect: a
8 participant receiving the more encouraging theory informed letter might have
9 responded negatively to receiving the less encouraging standard letter at a later visit.
10 These factors motivated our choice of a single randomisation to the same style of
11 letter at all timepoints.

12 Reflecting on our implementation of this SWAT in CODIFI2, we note that
13 implementing the SWAT at several follow-up timepoints increased the complexity of
14 the embedded trial. An argument might be made for running this SWAT only at a
15 single timepoint to minimise the set-up and running costs for the trial going forward.
16 As a point of comparison, we consider again the 2021 Cochrane Review. (9) Of the
17 four included SWATs using this intervention, the study characteristics for two studies
18 (AMBER and INTERVAL) are clear that only a single follow-up timepoint formed part
19 of the SWAT design. For the other two trials (iQUAD and OPAL) two different
20 timepoints are mentioned. For all four trials, a single estimated effect is reported,
21 rather than one for each timepoint where the SWAT was implemented. That said, our
22 SWAT appears to be the only one so far that includes an evaluation of the effect at
23 multiple distinct timepoints. Further SWATs evaluating the cover letters at multiple
24 timepoints would be indicated, in order to determine if the effect of the enhanced
25 cover letter is sustained.

1 Finally, we consider the consequences of adding our findings to the 2021 Cochrane
2 Review. While we see a slight improvement in the pooled estimated effect of
3 enhanced letters, we note that there is notable heterogeneity of effects across
4 studies to date. More and larger trials of this intervention would yield a more precise
5 estimate of the mean effect of theory-informed cover letters, and provide a clearer
6 picture of the heterogeneity of effects in other trial populations. While we could have
7 included all three timepoints in our update, we declined to do so since our results are
8 not independent: a key assumption in synthesising research findings.

10 **Conclusion**

11 Participants sent enhanced cover letters in CODIFI2 appears to have a numerically
12 higher response rate to questionnaires at all timepoints than those sent standard
13 cover letters. However, the estimated effects are uncertain, due to small sample
14 sizes. Despite this, these results of this SWAT seem compatible with other findings
15 previously reported and synthesised. The effect of adding our results to the Gillies et
16 al Cochrane Review has the effect of slightly improving the pooled estimated benefit
17 of theory informed letters. Taken together the findings from this SWAT, when
18 included alongside other replications of trials of enhanced, theoretically-informed
19 cover letters are suggestive of benefit due to enhanced cover letters exploiting
20 behavioural change theory to encourage response. However, further research in
21 more and larger trials that include multiple analysis timepoints would be required to
22 provide clearer evidence of benefit (or lack thereof) and so promote changes to
23 clinical trial conduct.

1

2 **Trial Registration:**

3 ISRCTN74929588, Registered 5th March 2019.

4

5 **List of Abbreviations**

6 AMBER: Abdominal massage for bowel dysfunction in people with multiple sclerosis

7 (Trial acronym)

8 CI: Confidence Interval

9 CODIFI2: Concordance in Diabetic Foot Infection 2 (Trial acronym)

10 COVID19: Coronavirus disease 2019

11 DFU: Diabetic Foot Ulcer

12 GRADE: Grading of Recommendations, Assessment, Development, and Evaluations

13 INTERVAL: Investigation of NICE technologies for enabling risk-variable-adjusted-
14 length (Trial Acronym)

15 iQUAD: Improving the Quality of Dentistry (Trial acronym)

16 ISRCTN: International Standard Randomised Controlled Trial Number

17 LADDER: Lay ADvice on Diabetes and Endocrine Research

18 NHS: National Health Service

19 NIHR: National Institute for Healthcare Research

20 OPAL: Optimal Pelvic floor muscle training for Adherence Long-term (trial acronym)

21 PPI: Patient and Public Involvement

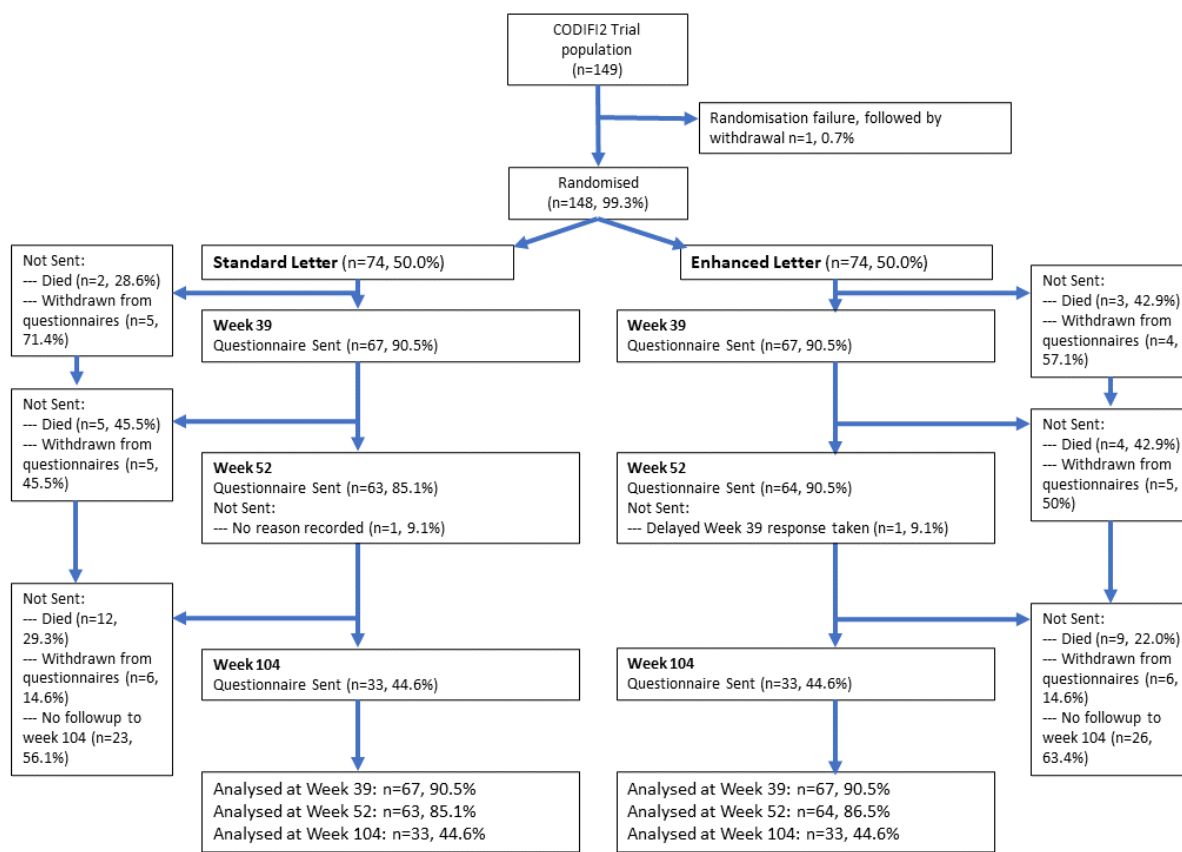
- 1 RD: Risk Difference
- 2 REC: Research Ethics Committee
- 3 SMS: Short Message Service
- 4 SWAT: Study Within A Trial
- 5 UK: United Kingdom
- 6

1 **References**

- 2 1. Little RJA, Rubin DB. Statistical analysis with missing data. Second edition.
3 ed. New York ;: Wiley; 2002.
- 4 2. Vansteelandt S, Carpenter J, Kenward MG. Analysis of incomplete data using
5 inverse probability weighting and doubly robust estimators. *Methodology: European*
6 *Journal of Research Methods for the Behavioral and Social Sciences*. 2010;6(1):37-
7 48.
- 8 3. White IR, Royston P, Wood AM. Multiple imputation using chained equations:
9 Issues and guidance for practice. *Statistics in Medicine*. 2011;30(4):377-99.
- 10 4. Mallinckrodt CH, Sanger TM, Dubé S, DeBroda DJ, Molenberghs G, Carroll
11 RJ, et al. Assessing and interpreting treatment effects in longitudinal clinical trials
12 with missing data. *Biological Psychiatry*. 2003;53(8):754-60.
- 13 5. Bjertnaes O, Iversen HH, Skrivarhaug T. A randomized comparison of three
14 data collection models for the measurement of parent experiences with diabetes
15 outpatient care. *BMC Medical Research Methodology*. 2018;18(1):95.
- 16 6. Edwards PJ, Roberts I, Clarke MJ, DiGuseppi C, Wentz R, Kwan I, et al.
17 Methods to increase response to postal and electronic questionnaires. *Cochrane*
18 *Database of Systematic Reviews*. 2009(3).
- 19 7. Sletto RF. Pretesting of Questionnaires. *American Sociological Review*.
20 1940;5(2):193-200.
- 21 8. Edwards PJ, Roberts I, Clarke MJ, DiGuseppi C, Woolf B, Perkins C.
22 Methods to increase response to postal and electronic questionnaires. *Cochrane*
23 *Database of Systematic Reviews*. 2023(11).
- 24 9. Gillies K, Kearney A, Keenan C, Treweek S, Hudson J, Brueton VC, et al.
25 Strategies to improve retention in randomised trials. *Cochrane Database of*
26 *Systematic Reviews*. 2021(3).
- 27 10. Goulao B, Duncan A, Floate R, Clarkson J, Ramsay C. Three behavior
28 change theory–informed randomized studies within a trial to improve response rates
29 to trial postal questionnaires. *Journal of Clinical Epidemiology*. 2020;122:35-41.
- 30 11. Ramsay CR, Clarkson JE, Duncan A, Lamont TJ, Heasman PA, Boyers D, et
31 al. Improving the Quality of Dentistry (IQuaD): a cluster factorial randomised
32 controlled trial comparing the effectiveness and cost-benefit of oral hygiene advice
33 and/or periodontal instrumentation with routine care for the prevention and
34 management of periodontal disease in dentate adults attending dental primary care.
35 *Health Technol Asses*. 2018;22(38):1-+.
- 36 12. CODIFI2: Randomised controlled trial of swab versus tissue sampling for
37 infected diabetic foot ulcers, and comparison of culture versus molecular processing
38 techniques [Available from: <https://fundingawards.nihr.ac.uk/award/16/163/04>].
- 39 13. SWAT Repository Store: Northern Ireland Hub for Trials Methodology
40 Research; [Available from:
41 [https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResear](https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/)
42 [ch/SWATSWARInformation/Repositories/SWATStore/](https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/)].

- 1 14. Trial Forge. Evidence pack– Retention: theory-based cover letter (ID Ret1)
2 [Available from: [https://www.trialforge.org/resource/evidence-pack-retention-theory-
4 based-cover-letter-id-ret1/](https://www.trialforge.org/resource/evidence-pack-retention-theory-
3 based-cover-letter-id-ret1/).
5 15. Clopper CJ, Pearson ES. The Use of Confidence or Fiducial Limits Illustrated
6 in the Case of the Binomial. *Biometrika*. 1934;26(4):404-13.
7 16. Santner TJ, Snell MK. Small-Sample Confidence Intervals for $p_1 - p_2$ and p_1/p_2 in 2×2 Contingency Tables. *Journal of the American Statistical Association*.
8 1980;75(370):386-94.
9 17. R Core Team. R: A language and environment for statistical computing.
10 Vienna, Austria: R Foundation for Statistical Computing; 2023.
11 18. Sara Balduzzi GR, Guido Schwarzer. How to perform a meta-analysis with R:
12 a practical tutorial. *Evidence-Based Mental Health*. 2019;22:153-60.
13 19. Goulao B, Duncan A, Innes K, Ramsay CR, Kahan BC. Using re-
14 randomisation designs to increase the efficiency and applicability of retention studies
15 within trials: a case study. *Trials*. 2023;24(1):299.

1 Figure 1: Participant Flow diagram for cover letter SWAT



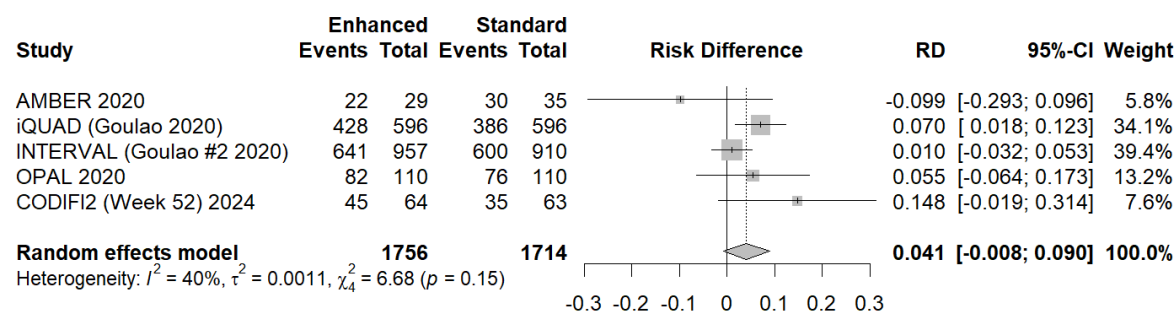
2

3

4

5

Figure 2: Forest plot of updated meta-analysis of randomised trials of theoretically-informed (Enhanced) cover letters embedded within randomised trials.



Footnote: Positive risk differences (RD) indicate increase proportions responding when assigned to the “Enhanced” (theoretically-informed) cover letter compared to the Standard letter. 95% Confidence intervals for risk difference calculated using asymptotic method, to align with Cochrane Review. (9) Unpublished AMBER and OPAL trial results reported from “personal communications” to Cochrane Review authors. CODIFI2 data taken from the week 52 timepoint.

1 Table 1: Baseline characteristics of all randomised SWAT participants

	Standard Letter (n=74)	Enhanced Letter (n=74)	Total (n=148)
Age, years			
Mean (SD)	63.1 (13.06)	62.4 (12.10)	62.8 (12.55)
Range	(31 to 93)	(31 to 92)	(31 to 93)
Gender			
Male	62 (83.8%)	60 (81.1%)	122 (82.4%)
Female	12 (16.2%)	14 (18.9%)	26 (17.6%)
Ethnicity			
White	71 (95.9%)	72 (97.3%)	143 (96.6%)
Mixed - White and Black Caribbean	-	1 (1.4%)	1 (0.7%)
Asian - Pakistani	-	1 (1.4%)	1 (0.7%)
Other Asian background	1 (1.4%)	-	1 (0.7%)
Black - African	2 (2.7%)	-	2 (1.4%)
Smoking Status			
Current smoker	5 (6.8%)	9 (12.2%)	14 (9.5%)
Former smoker	39 (52.7%)	32 (43.2%)	71 (48.0%)
Never smoked	29 (39.2%)	33 (44.6%)	62 (41.9%)
Missing	1 (1.4%)	-	1 (0.7%)
Allocation			
Swab sampling	37 (50.0%)	37 (50.0%)	74 (50.0%)

	Standard Letter (n=74)	Enhanced Letter (n=74)	Total (n=148)
Tissue sampling	37 (50.0%)	37 (50.0%)	74 (50.0%)
Diabetes Type			
Type 1	10 (13.5%)	7 (9.5%)	17 (11.5%)
Type 2	63 (85.1%)	67 (90.5%)	130 (87.8%)
Other - Monogenic	1 (1.4%)	-	1 (0.7%)
Duration of diabetes (years)			
Median (Interquartile Range)	15.5 (10.0 to 21.0)	15.5 (10.0 to 22.0)	15.5 (10.0 to 21.5)
One DFU, or multiple			
One ulcer	57 (77.0%)	50 (67.6%)	107 (72.3%)
More than one ulcer	17 (23.0%)	24 (32.4%)	41 (27.7%)
Current pain score before sampling			
No Pain	43 (58.1%)	41 (55.4%)	84 (56.8%)
Mild Pain	20 (27.0%)	16 (21.6%)	36 (24.3%)
Moderate Pain	7 (9.5%)	12 (16.2%)	19 (12.8%)
Severe Pain	4 (5.4%)	5 (6.8%)	9 (6.1%)
Euroqol EQ5D-3L Responses at baseline			
Mobility			
No problems	22 (29.7%)	10 (13.5%)	32 (21.6%)
Some problems	47 (63.5%)	60 (81.1%)	107 (72.3%)
I am confined to bed	3 (4.1%)	2 (2.7%)	5 (3.4%)

	Standard Letter (n=74)	Enhanced Letter (n=74)	Total (n=148)
No problems and Some problems selected	1 (1.4%)	1 (1.4%)	2 (1.4%)
Missing	1 (1.4%)	1 (1.4%)	2 (1.4%)
Self-care			
No problems	46 (62.2%)	42 (56.8%)	88 (59.5%)
Some problems	26 (35.1%)	26 (35.1%)	52 (35.1%)
Unable to wash or dress myself	1 (1.4%)	4 (5.4%)	5 (3.4%)
No problems and Some problems selected	-	1 (1.4%)	1 (0.7%)
Missing	1 (1.4%)	1 (1.4%)	2 (1.4%)
Usual Activities			
No problems	27 (36.5%)	24 (32.4%)	51 (34.5%)
Some problems	31 (41.9%)	37 (50.0%)	68 (45.9%)
Unable to perform my usual activities	14 (18.9%)	12 (16.2%)	26 (17.6%)
Missing	2 (2.7%)	1 (1.4%)	3 (2.0%)
Pain / Discomfort			
I have no pain or discomfort	23 (31.1%)	19 (25.7%)	42 (28.4%)
I have moderate pain or discomfort	43 (58.1%)	40 (54.1%)	83 (56.1%)
I have extreme pain or discomfort	7 (9.5%)	14 (18.9%)	21 (14.2%)
Missing	1 (1.4%)	1 (1.4%)	2 (1.4%)
Anxiety / Depression			
Not anxious or depressed	45 (60.8%)	37 (50.0%)	82 (55.4%)
Moderately anxious or depressed	27 (36.5%)	29 (39.2%)	56 (37.8%)

	Standard Letter (n=74)	Enhanced Letter (n=74)	Total (n=148)
Extremely anxious or depressed	-	6 (8.1%)	6 (4.1%)
Missing	2 (2.7%)	2 (2.7%)	4 (2.7%)

1

2 Table 2: Summary of questionnaire responses at weeks 39, 52 and 104

Was the questionnaire returned	Standard Letter		Enhanced Letter		Difference in proportions (95% CI)
	Received / Sent	Response (%, 95% CI)	Received/Sent	Response (%, 95% CI)	
Week 39	39 / 67	58.2% (45.5% to 70.2%)	47 / 67	70.1% (57.7% to 80.7%)	11.9% (-5.7% to 29.1%)
Week 52	35 / 63	55.6% (42.5% to 68.1%)	45 / 64	70.3% (57.6% to 81.1%)	14.8% (-3.2% to 31.2%)
Week 104	19 / 33	57.6% (39.2% to 74.5%)	24 / 33	72.7% (54.5% to 86.7%)	15.2% (-10.4% to 39.3%)

3

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CONSORTChecklist.pdf](#)
- [SupplementaryAppendix1Eligibility.pdf](#)
- [SupplementaryAppendix2CoverLetterBundle.pdf](#)
- [SupplementaryAppendix3Additionalbaselinechars.pdf](#)