

How Much Is the Lack of Retention Evidence Costing Trial Teams in Ireland and the United Kingdom?

Ellen Murphy (✉ ellen.murphy@ucc.ie)

TRAMS (Trials Research and Methodologies Unit), HRB Clinical Research Facility, University College Cork <https://orcid.org/0000-0001-7874-4331>

Frances Shiely

TRAMS (Trials Research and Methodologies Unit), HRB Clinical Research Facility, University College Cork

Shaun Treweek

University of Aberdeen Health Services Research Unit

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Abstract

Background

Evidence to support the use of many retention strategies in clinical trials is lacking. Despite this, trial teams still need to have some form of retention strategy in their trials to try and avoid high attrition rates. This study aimed to estimate how much this lack of retention evidence might be costing trials in Ireland and the United Kingdom.

Methods

We selected the top ten most routinely used retention strategies by Clinical Trial Units in the United Kingdom and made assumptions as to how each of these strategies was most likely to be conducted and the costs involved. We applied our costing model to a hypothetical trial scenario in both Ireland and the United Kingdom as well as to three published trial protocols. We developed the costing model and calculated the costs in Microsoft Excel.

Results

Retention strategies can be extremely expensive, some of the costliest interventions included “a timeline of participant visits for sites” (with integrated participant reminders) (€1,418.44 - €108,471.99), “routine site visits by CTU staff” (€777.67 - €14,753.48), and “data collection scheduled with routine care” (€900 - €32,503.25). Others such as “telephone reminders for questionnaire response” (€34.58 - €568.62), “inclusion of pre-paid envelopes” (€93.44 - €942.50), and “targeted recruitment of sites/GPs” (€30 - €1,620) were less costly compared to the other interventions.

Discussion

The resources invested in the use of some retention interventions may outweigh known or imagined benefits on retention. Where benefits are imagined, evaluation should be a priority.

Conclusion

More evaluation of the effectiveness and cost of trial retention strategies is needed to avoid widespread use of strategies that are both expensive and ineffective.

Background

Randomised trials can be no better than the data they collect. If retention has been poor, in other words, data are missing for many participants, then the usefulness of the trial starts to come into question. Patchy datasets can lead to a trial becoming underpowered for its primary outcome and very underpowered for its secondaries, which were anyway probably underpowered. Participants who do not provide data may differ to those who remain (1-3), making interpretation harder. It might be possible to

overturn trial conclusions by simply imagining that the results from missing participants had gone against those conclusions (4). In short, potential users of the trial results now have doubts and doubt undermines trials.

Poor retention is a major cause of research waste as it can delay the implementation (or removal) of healthcare interventions (5). Poor retention may also increase trials costs (5, 6). A recent prioritisation exercise (PRioRiTy 2) identified 20 priority unanswered research questions for research in trial retention, including questions around what motivates participants to stay involved, how to provide information and how what is done at recruitment might influence retention (7).

Although there are plenty of unanswered research questions in trial retention, trial teams nevertheless have to use some form of retention strategy in their trials. In the United Kingdom (UK), Clinical Trials Units (CTUs) registered with the United Kingdom (UK) Clinical Research Network use many approaches and Kearney et al., asked them what these strategies were. Thirty-three (70%) CTUs responded and described a total of 61 strategies, some of which were used by most CTUs (8). While evidence is available for some strategies, none have compelling evidence of benefit (9).

The current study aimed to estimate how much this lack of retention evidence might be costing trials in the UK and Ireland. To give focus, we chose to do this for the ten strategies used most often by UK CTUs (8).

Methods

The top ten most routinely used retention strategies used by UK CTUs are shown in **Table 1**, along with the percentage of CTUs that use this intervention routinely (8) and the evidence of benefit provided by the most recent Cochrane Systematic Review (9).

To estimate the cost of the retention strategies, we made assumptions as to how each of these strategies would be implemented and the costs involved. We called this our costing model for each strategy. We contacted experienced clinical trial professionals such as trial managers, clinical research nurses, and professionals working in clinical research facilities in the UK and Ireland for information to inform our costing models. We identified these individuals through workplace inquiries and personal knowledge of suitable personnel to answer specific costing queries.

We applied our costing models to each of the ten strategies in two ways. First, we created a hypothetical trial scenario (**Table 2**). We made assumptions about how the retention strategies would most likely be conducted and then calculated and applied the costs of running each of the ten retention strategies in both Ireland and the UK. The costing models for some strategies differed slightly between Ireland and the UK due to differences in the responsibilities held by staff members involved in running clinical trials and differences in how some retention strategies are conducted in each country (See **Additional File 1** for full details).

Secondly, we chose three trial protocols published in the journal *Trials* between 2020 and 2016. We chose these three for convenience reasons: they fit well into our costing model well, represented trials of various sizes and the trials had different characteristics. We used these to estimate the cost associated with each retention strategy in a “real-life” randomised controlled trial. We applied our costing model for the previously identified top 10 retention strategies to each of the three randomised controlled trials regardless of whether the trial protocol stated that these retention methods were used or not.

An example costing model for both a hypothetical trial and published trial protocol (10), with costs and assumptions, is shown in **Table 3**. A full description of the costing models and the assumptions we made to create them, together with details of the three trials selected from the *Trials* journal are outlined in **Additional File 1**.

In addition to the ten most routinely used retention strategies, we further elaborated and included additional actions that are likely to be carried out by trial units when trying to retain participants that were not specifically outlined by Kearney et al., (8). These assumptions reflect actions that are likely to be conducted by trial teams during the implementation of the listed interventions. For example, under the intervention “inclusion of pre-paid envelopes (questionnaires)” along with sending out pre-paid envelopes to enhance questionnaire response we also assumed a reminder schedule would be sent out to 30% of participants who initially did not return the questionnaire. A full list of the additional assumptions can be found in **Additional File 1**.

Where there was evidence of effectiveness of the retention strategy we calculated the cost per participant retained. For example for the ease of calculation, we calculated the cost per participant retained by using pre-paid return envelopes based on a 4% benefit (9). In the Irish hypothetical trial scenario 4% of 500 participants is 20. The total cost of “inclusion of pre-paid envelopes (questionnaires)” was €942.50. Therefore the cost per participant retained was €47.13 per 20 additional retained participants.

All our calculations were done within Microsoft Excel. **Additional File 2** contains our Excel spreadsheet with our cost calculations. For ease of comparison all our costs are presented in **Table 4** in both EUR and GBP based on exchange rates of 1 GBP = 1.16279 EUR,

1 EUR = 0.860001 GBP, 1 USD = 0.843802 EUR and 1 USD = 0.725647 GBP,

taken from [Xe Currency Converter - LIVE Foreign Exchange Rates](#) on the 7th of September 2021.

Results

We discussed the top ten most routinely used trial retention strategies in the UK, we made assumptions as to how each of these strategies would be implemented and the costs involved. We applied this costing model to our hypothetical trial scenario, (1-year trial, 10 sites, 500 participants, 3 trial visits, 1 questionnaire sent out) in the UK and Ireland, and found that the strategies ranged from very cheap to very expensive to implement. The cheapest strategy to implement in both countries would be “telephone

reminders for questionnaire response” costing €423.75 (£364.43) and €568.62 (£489.01) respectively and the most expensive strategy would be “a timeline of participant visits for sites” with integrated participant reminders costing €68,021.75 (£58,498.77) in Ireland, but “data collection scheduled with routine care” in the UK (€15,697.67 (£13,500)).

For the “real life” trials, “telephone reminders for questionnaire response” would be the cheapest strategy in the CINNAMON trial (€246.00 (£211.56)). For the MAMI and MOON trial “targeted recruitment of sites/GPs” would be the cheapest strategy in these two single centre trials costing (€30 (£25.80)) and €35.35 (£30.40) respectively. The most expensive strategy in the MAMI and the CINNAMON trial would be “a timeline of participant visits for sites”(with integrated participant reminders) costing €2,945.34 (£2,533.00) and €108,471.99 (£93,282.99) respectively. For the MOON trial the costliest intervention for the trial team to conduct would be “data collection scheduled with routine care” costing €4,834.88 (£4,158).

Newsletters were identified as the most routinely used retention strategy by CTUs in the UK (8). The cost of sending newsletters would be one of the cheaper retention strategy options ranging from €734.51 (£631.68) to €1,990 (£1,711.40) for manually posting the newsletters, and €525.93 (£452.30) to €1,036.39 (£891.27) to electronically send newsletters. However the most up-to-date evidence suggests there is no retention benefit of this strategy “RD = -0% (95% CI -4–3%); GRADE: very low” (9). This costing model has shown that “a timeline of participant visits for sites” would be a cheap option if only site reminders were used (€101.34 (£87.15) - €1,119.50 (£962.77)) but if a participant reminder schedule was also integrated into this strategies it would be one of the most expensive strategies for trial teams to implement (€1,418.44 (£1,219.86) - €108,471.99 (£93,282.99)). Regardless of which option is used neither strategy has available evidence to support its use (9) however is the second most routinely used retention strategy identified by Kearney et al., (8).

The retention strategy with the best available evidence is “inclusion of pre-paid envelopes” for questionnaire return. The cost of this retention strategy ranges from €93.44 (£80.36) to €942.50 (£810.55), one of the cheapest retention strategies trial teams can avail of. The Cochrane review found that return postage which included “preaddressed second class stamped envelope”, “high priority stamp to the mailing” and “personalised postal follow-up” all combined may lead to a 4% retention benefit “RD= 4% (95% CI -0–9%)”. However, the evidence was based on three low quality studies (n=1543), and the single study of pre-paid return envelopes itself, did not find a positive effect on retention (9).

Discussion

Our findings show that the evidence available to support the ten most-used trial retention interventions by CTUs in the United Kingdom is weak or lacking entirely but that the cost of using them can be very large.

The most routinely used intervention outlined by Kearney et al., (8) is “newsletters”, this strategy was found to be one of the cheaper retention methods particularly emailing newsletters, (€525.93 (£452.30) to €1,036.39 (£891.27)). One of the cheapest interventions across all the trials would be “telephone

reminders for questionnaire response” costing between €34.58 (£29.74) and €568.62 (£489.01). We are able to say that these interventions would be cheap but more evidence is needed to show that it is also effective at retaining trial participants.

The second most routinely used retention strategy outlined by Kearney et al., (8) is “a timeline of participant visits for sites”. The site reminder schedule alone would be cheap costing between €101.34 (£87.15) and €1,119.50 (£962.77). Integrating a participant reminder schedule would significantly increase the costs (€1,418.44 (£1,219.86) - €108,471.99 (£93,282.99)). Similarly, “routine site visits by CTU staff” (€777.67 (£668.80) - €14,753.48 (£12,688)), “investigator meetings face-to-face” (€777.67 (£668.80) - €14,753.48 (£12,688)), and “data collection scheduled with routine care” (€900 (£774.00) - €32,503.25 (£27,951.92)) would also be expensive to implement yet none of these have compelling evidence demonstrating that they are effective at retaining trial participants (9). They may be very effective. The point is that we cannot say with any certainty whether they work or not, and therefore substantial amounts of money and other resources are potentially being invested into strategies that lead to no improvement in retention.

Even some of the less costly interventions have limited evidence showing effectiveness and much of the existing evidence is from single studies often with low GRADE ratings (9). “Telephone reminders for questionnaire response” (€34.58 (£29.74) - €568.62 (£489.01)), “inclusion of pre-paid envelopes (questionnaires)” (€93.44 (£80.36) - €942.50 (£810.55)), “targeted recruitment of sites/GPs” (€30 (£25.80) - €1,620 (£1,393.20)) and “newsletters (emailed)” (€525.93 (£452.30)- €1,036.39 (£891.27)) would be less costly compared to the other interventions but not all have evidence in support of them. A cheap but ineffective intervention is still not something worth using, especially if it takes resources away from other potentially more useful interventions.

Strengths and limitations

We acknowledge that a limitation of this study is that we have had to make assumptions to calculate our cost estimates and these may not be truly representative, or the assumptions made may not be accurate depending on how trials are run, especially those outside of Ireland and the United Kingdom. However, to help to address this limitation, we have made the costing spreadsheet available as an additional file, which means readers can modify it to suit their own trial.

One of the strengths of this study is that regardless of the costs, it highlights the lack of evidence for routinely-used trial retention strategies. Even if our estimates are very wrong, no intervention costs nothing and if there is weak or no evidence in support of the intervention, we should pause and consider what we want to do. If trialists go ahead and use the strategy, we think at least some of them should use SWATs (Study Within a Trial) or other research design to investigate the impact of the strategy on retention. The combination of routine use of a strategy to support retention and a lack of evidence that the strategy actually improves retention is a recipe for research waste.

Recommendations for future research

This paper highlights the need for further research into the effects of trial retention strategies. The cost of some of the interventions that are currently routinely used are significant, and so is the lack evidence to support their use. We recommend the wider use of SWATs to evaluate the effects of retention interventions used in clinical trials to avoid persistent and widespread research waste. Replication of evaluations will add to the existing evidence to support/not support the use of these interventions.

We also think it would be useful for trial teams to include the costs of running trial retention strategies in their trial publications. Communicating the costs of retention strategies can be helpful to other trial teams to estimate budgets required for implementing similar strategies. A better idea of costs will allow for better 'cost-per-participant-retained' calculations, which in turn will give trial teams another way to compare retention strategies when making choices about which to use in their trial.

Conclusions

Without evidence regarding the effectiveness of trial retention strategies, trial teams will continue to put substantial amounts of money into strategies that potentially have no beneficial impact on participant retention. More evaluation of the effectiveness and cost of trial retention strategies is needed to avoid widespread use of strategies that are both expensive and ineffective.

List Of Abbreviations

Prioritising Retention in Randomised Trials study (PRioRiT_y 2)

Clinical Trials Units (CTUs)

United Kingdom (UK)

Studies Within a Trial (SWATs)

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: All datasets supporting the conclusions of this article are included within the articles' additional files

Competing interests: ST is an Editor-in-Chief of Trials. The other authors declare that they have no competing interests

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Authors' contributions: ST conceived the idea for the project. ST, FS and EM developed the assumptions regarding the conduct and likely costs of the retention strategies. EM reviewed the academic literature, created the costing model, and drafted the manuscript with input from all authors. All authors read and approved the final version of the manuscript.

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Tables

Table 1
Top 10 most used missing data intervention by CTUs in the United Kingdom (8)

	Missing data interventions	Number (N) and percentage of CTUs that routinely use the intervention	Evidence of reported evaluations into their effectiveness according to the most recent Cochrane Systematic Review (9).
1	Newsletters	N=23, 70%	“The evidence is very uncertain about the effect on retention of including a newsletter compared to no newsletter; RD = -0% (95%CI, -4–3%); GRADE; very low, evidence is based on four studies from various disciplines, (n=5622)”
2	A timeline of participant visits for sites	N=19, 58%	No evidence
3	Inclusion of prepaid envelopes (questionnaires)	N=19, 58%	“Various strategies compared to usual practice for return postage, such as free post versus second class stamp, high priority mail versus usual postage and personal form may increase retention slightly: RD= 4% (95% CI -0–9%), GRADE; low. Evidence is based on three studies, (n=1543)”
4	Telephone reminders	N=18, 55%	<p>“Telephone reminders compared to postal reminders may result in a large increase in retention, evidence is from one study (11) (RD= -19% (95%CI -33% to -5%) GRADE low, (-1 level: study limitations unclear risk of bias; -1 level: imprecision single study, n=148)”</p> <p>“Telephone reminders compared to usual follow-up¹ may result in little or no difference in retention, evidence from one study (12) (RD =-1% (95% -18–15%) GRADE low, (-2 levels: imprecision-single study, n = 127; wide CI crossing RD = 0))”²</p>
5	Data collection scheduled with routine care	N=18, 55%	No evidence

Notes: GRADE, grades of evidence; Low certainty: the confidence in the effect estimate is limited; the true effect may be substantially different from the estimated effect. **Very low certainty:** very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect (9).¹From this single study “usual follow-up” is as follows; “We followed-up participants by any of the means they agreed to at the start of the trial, including post, e-mail, and telephone calls to mobile, home, or work numbers [11]. We used all the effective evidence-based methods that were feasible to introduce into the procedures of the trial [12], as identified in the systematic reviews by Edwards *et al.* and Hoile *et al.* [12, 13]. These included monetary incentives, posting correspondence by recorded delivery, pre-notification, follow-up contact, unconditional advance cash incentives, short, concise questionnaires, duplicate questionnaires sent at repeat follow-up attempts, mentioning that commitment to the trial implied an obligation to respond, mention of university sponsorship, prepaid return envelopes with stamps, an assurance of confidentiality, and first-class outward mailing” (12).²We present all evidence regarding telephone reminders however we chose to select telephone reminders compared to usual follow up in Table 4 to calculate cost per participant retained as we believe it is the most relevant comparison for trial teams.

	Missing data interventions	Number (N) and percentage of CTUs that routinely use the intervention	Evidence of reported evaluations into their effectiveness according to the most recent Cochrane Systematic Review (9).
6	Site initiation training on missing data	N=18, 55%	No evidence
7	Investigator meetings face to face	N=17, 52%	No evidence
8	Routine site visits by CTU staff	N=15, 45%	No evidence
9	Targeted recruitment of sites/GPs	N=15, 45%	No evidence
10	Flexibility in appointment times	N=15, 45%	No evidence

Notes: GRADE, grades of evidence; Low certainty: the confidence in the effect estimate is limited; the true effect may be substantially different from the estimated effect. **Very low certainty:** very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect (9).¹From this single study “usual follow-up” is as follows; “We followed-up participants by any of the means they agreed to at the start of the trial, including post, e-mail, and telephone calls to mobile, home, or work numbers [11]. We used all the effective evidence-based methods that were feasible to introduce into the procedures of the trial [12], as identified in the systematic reviews by Edwards *et al.* and Hoile *et al.* [12, 13]. These included monetary incentives, posting correspondence by recorded delivery, pre-notification, follow-up contact, unconditional advance cash incentives, short, concise questionnaires, duplicate questionnaires sent at repeat follow-up attempts, mentioning that commitment to the trial implied an obligation to respond, mention of university sponsorship, prepaid return envelopes with stamps, an assurance of confidentiality, and first-class outward mailing” (12).²We present all evidence regarding telephone reminders however we chose to select telephone reminders compared to usual follow up in Table 4 to calculate cost per participant retained as we believe it is the most relevant comparison for trial teams.

Table 2

Hypothetical trial characteristics

Trial Characteristics	
Number of participants	500
Number of sites	10 sites
Duration of the trial	1 year
Number of trial visits	3
Data collection	1 questionnaire is sent out: three trial visits
Location of the trial	Ireland / United Kingdom

Table 3

Assumptions and costings for “Newsletters” – Hypothetical trial Ireland and the MAMI trial (10).

Hypothetical trial (Ireland)	
Intervention	Assumptions made
Newsletter	<ul style="list-style-type: none"> → 2 newsletters sent out over the 1-year trial period. → 5 hours to develop the newsletter. → 1 hours work to electronically send out 500 newsletters. → 7 hours to manually post out 500 newsletters. → Stamp costs in Ireland = €1.10. → Mailchimp subscription is €151.78 for 1 year. → Developing the newsletter carried out by a Research Nurse (€54 hourly rate) → Emailing/posting out the newsletter carried out by a Research Assistant (€25 hourly rate)
Costings	<p>Costings</p> <p>Staff costs for developing and manually posting out the newsletter:</p> <ul style="list-style-type: none"> → Developing newsletter: 5 hours x €54 = €270. → Manually posting newsletter: 7 hours x €25 = €175. → Total staff costs = €445 <p>Postage costs:</p> <ul style="list-style-type: none"> → 500 x €1.10 = €550 <p>Total costs: Staff hours plus postage costs x frequency of activity:</p> <ul style="list-style-type: none"> → €995 x 2 = €1990 <p>Staff costs for developing and electronically posting out the newsletter twice a year:</p> <ul style="list-style-type: none"> → Developing newsletter: 5 hours x €54 = €270. → Electronically posting newsletter: 1 hour x €25 = €25. → Total staff costs = €295. <p>Electronic postage costs: Mailchimp = €151.78</p> <p>Total costs: Staff costs x frequency of activity plus flat rate of Mailchimp:</p> <ul style="list-style-type: none"> → €295 x 2 = €590 plus €151.78= €741.78
MAMI trial (Trials Journal)	

Hypothetical trial (Ireland)	
Intervention	Assumptions made
Newsletter	<p>→ 4 newsletters sent out over the 2-year trial period</p> <p>→ 5 hours to develop the newsletter.</p> <p>→ 0.12 hours to electronically send out 60 newsletters (1 hours work to electronically send out 500 newsletters, therefore 60 newsletters is 0.12 hours)</p> <p>→ 0.84 hours of work to manually stuff and post 60 newsletters (7 hours to manually post out 500 newsletters, therefore 60 newsletters take 0.84 hours)</p> <p>→ Stamp costs in the Netherlands = €0.96</p> <p>→ Mailchimp subscription for two years is €303.56 (€151.78 for 1 year)</p> <p>→ Developing the newsletter carried out by a Research Nurse (€30 hourly)</p> <p>→ Emailing/posting out the newsletter carried out by a Research Assistant (€17 hourly)</p>
Costings	<p>Costings</p> <p>Staff costs for developing and manually posting out the newsletter twice a year:</p> <p>→ Developing newsletter: 5 hours x €30 = €150</p> <p>→ Manually posting newsletter: 0.84 hours x €17 = €14.28</p> <p>→ Total staff costs = €164.28</p> <p>Postage costs:</p> <p>→ 60 x €0.96 = €57.60</p> <p>Total costs: Staff hours plus postage costs x frequency of activity:</p> <p>→ €221.88 x 4 = €887.52</p> <p>Staff costs for developing and electronically posting out the newsletter twice a year:</p> <p>→ Developing newsletter: 5 hours x €30 = €150</p> <p>→ Electronically posting newsletter: 0.12 hours x €17 = €2.04</p> <p>→ Total staff costs = €152.04</p> <p>Electronic postage costs: Mailchimp = €151.78 x 2 = €303.56</p> <p>Total costs: Staff costs x frequency of activity plus flat rate of Mailchimp:</p> <p>€152.04 x 4 = €608.16 plus €303.56= €911.72</p>

Table 4

Total cost and cost per participant for each retention strategy for all trials

Strategy	Cost				
	Ireland	United Kingdom	MAMI trial (10)	MOON trial (13)	CINNAMON trial (14)
Strategy 1: Newsletters (posted)	€1990 (£1711.40)	€1590.58 (£1367.90)	€887.52 (£763.27)	€734.51 (£631.68)	€1874.05 (£1611.63) (\$2220.96)
Assumptions	2 newsletters per year; 500 participants; 1-year trial period.	2 newsletters per year; 500 participants; 1-year trial period.	2 newsletters per year; 60 participants; 2-year trial period ¹ .	2 newsletters per year; 154 participants; 1-year trial period.	2 newsletters per year; 428 participants; 2-year trial period.
Effect estimate²	“The evidence is very uncertain about the effect on retention of including a newsletter compared to no newsletter: RD = -0% (95% CI -4–3%); GRADE: very low”				
Cost per participant retained	Current evidence suggestions no retention benefit, unable to calculate cost per participant retained due to lack of evidence				
	Ireland	United Kingdom	MAMI trial	MOON trial	CINNAMON trial
Strategy 1: Newsletters (emailed)	€741.78 (£637.93)	€572.36 (£492.23)	€911.72 (£784.08)	€525.93 (£452.30)	€1036.39 (£891.27) (\$1228.24)
Assumptions	2 newsletters electronically sent per year; 500 participants; 1 year trial period	2 newsletters electronically sent per year; 500 participants; 1 year trial period	2 newsletters electronically sent per year; 60 participants; 2-year trial period	2 newsletters electronically sent per year; 154 participants; 1 year trial period	2 newsletters electronically sent per year; 428 participants; 2-year trial period

¹*Italic underlined font indicates the real trial information that we used e.g., number of trial participants, number of trial sites, number of trial visits and any retention methods used within the trials e.g., MOON trial sent out 2 questionnaires to participants.* The non-italic-underlined font which indicates the assumptions we applied. A full description of the trial characteristics and any retention activities conducted by the real-life trials are documented in Additional File 1. ²Evidence from the most recent Cochrane Systematic Review (9). ³We assumed benefit was applied across the whole response to all cycles. The Cochrane review found that return postage which included “preaddressed second class stamped envelope”, “high priority stamp to the mailing” and “personalised postal follow-up” all combined likely lead to a 4% benefit, so it is likely that pre-paid envelopes on their own may not provide a 4% benefit on retention. For the ease of calculation, we calculated the cost per participant retained by using pre-paid envelopes based on a 4% benefit. ⁴We chose to select telephone reminders compared to usual follow up compared to postal follow up in as we believe it is the most relevant comparison for trial teams.

Strategy	Cost				
Effect estimate	“The evidence is very uncertain about the effect on retention of including a newsletter compared to no newsletter: RD = -0% (95% CI -4–3%); GRADE: very low”				
Cost per participant retained	Current evidence suggestions no retention benefit, unable to calculate cost per participant retained due to lack of evidence				
	Ireland	United Kingdom	MAMI trial	MOON trial	CINNAMON trial
Strategy 2: A timeline of participant visits for sites (site reminder)	€791.75 (£608.91)	€1119.50 (£962.77)	€101.34 (£87.15)	€111.95 (£96.28)	€561.19 (£482.61) (\$665.07)
Assumptions	Data Manager develops reminder schedule, electronically emails the software to the sites (10 sites) Carried out once	Data Manager develops reminder schedule, electronically emails the software to the sites (10 sites) Carried out once	Data Manager develops reminder schedule, electronically emails the software to the sites (1 site) Carried out once	Data Manager develops reminder schedule, electronically emails the software to the sites (1 site) Carried out once	Data Manager develops reminder schedule, electronically emails the software to the sites (5 sites) Carried out once
Effect estimate	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				
A timeline of participant visits for sites (participant reminder)	€68021.75 (£58498.77)	€5361.36 (£4610.77)	€2945.34 (£2533.00)	€1418.44 (£1219.86)	€108471.99 (£93282.99) (\$128551.47)
<p>¹Italic underlined font <i>indicates the real trial information that we used e.g., number of trial participants, number of trial sites, number of trial visits and any retention methods used within the trials e.g., MOON trial sent out 2 questionnaires to participants.</i> The non-italic-underlined font which indicates the assumptions we applied. A full description of the trial characteristics and any retention activities conducted by the real-life trials are documented in Additional File 1. ²Evidence from the most recent Cochrane Systematic Review (9). ³We assumed benefit was applied across the whole response to all cycles. The Cochrane review found that return postage which included “preaddressed second class stamped envelope”, “high priority stamp to the mailing” and “personalised postal follow-up” all combined likely lead to a 4% benefit, so it is likely that pre-paid envelopes on their own may not provide a 4% benefit on retention. For the ease of calculation, we calculated the cost per participant retained by using pre-paid envelopes based on a 4% benefit. ⁴We chose to select telephone reminders compared to usual follow up compared to postal follow up in as we believe it is the most relevant comparison for trial teams.</p>					

Strategy	Cost				
Assumptions	Research nurse contacts each participant prior to visit and conducts preparation prior to each visit; 500 participants; 3 visits. Includes cost of site reminder schedule.	Trial manager contacts each participant prior to visit; 500 participants; 3 visits. Includes cost of site reminder schedule.	Research nurse contacts each participant prior to visit and conducts preparation prior to outpatient visit and birth; 60 participants; 1 visit but preparation work for 2 visits. Includes cost of site reminder schedule.	Trial manager contacts each participant prior to visit; 154 participants; 3 trial visits. Includes cost of site reminder schedule.	Research nurse contacts each participant prior to visit and conducts preparation prior to each visit; 428 participants; 9 visits. Includes cost of site reminder schedule.
Effect estimate	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				
	Ireland	United Kingdom	MAMI trial	MOON trial	CINNAMON trial
Strategy 3: Inclusion of pre-paid envelopes (questionnaire)	€942.50 (£810.55)	€804.12 (£691.54)	€93.44 (£80.36)	€497.31 (£427.69)	€390.10 (£335.47) (\$462.31)

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Strategy	Cost				
Assumptions	1 questionnaire to all 500 participants; 1 reminder to 30% of participants (150); overall retention	1 questionnaire to all 500 participants; 1 reminder to 30% of participants (150); overall retention	1 questionnaire to all 60 participants; 1 reminder to 30% of participants (18); overall retention	2 questionnaires to all 154 participants; 1 reminder for each questionnaire to 30% of participants (47); overall retention	1 questionnaire to all 428 participants; 1 reminder to 30% of participants (129); overall retention
Effect estimate	"Various strategies compared to usual practice for return postage, such as free post versus second class stamp; high priority mail stamp versus usual postage; and personal form may increase retention slightly: RD = 4% (95% CI -0-9%); GRADE: low" ³				
Additional participants retained	20	20	2	12	17
Cost per participant retained	€47.13 (£40.53)	€40.21 (£34.58)	€46.72 (£40.18)	€41.44 (£35.64)	€22.94 (£19.73) (\$27.19)
Strategy 4: Telephone reminders	Ireland	United Kingdom	MAMI trial	MOON trial	CINNAMON trial
Telephone reminders for trial visits	€9153 (£7871.59)	€5991.62 (£5152.80)	€203.40 (£174.92)	€1845.42 (£1587.06)	€14691.47 (£12634.27) (\$17411.04)

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Strategy	Cost				
Assumptions	<p>Research nurse contacts 500 participants – 5 minutes per call-carried out once for each visit (3-visits)</p> <p>Failed contact attempts – research nurse contacts 500 participants - 2 failed contact attempts (1 minute each) – carried out for each visit (3 visits)</p>	<p>Trial Manager contacts 500 participants – 5 minutes per call-carried out once for each visit (3-visits)</p> <p>Failed contact attempts – trial manager contacts 500 participants - 2 failed contact attempts (1 minute each) – carried out for each visit (3 visits)</p>	<p>Research nurse contacts 60 participants – 5 minutes per call-carried out once (1 trial visit)</p> <p>Failed contact attempts – research nurse contacts 60 participants - 2 failed contact attempts (1 minute each) – carried out once (1 trial visit)</p>	<p>Trial Manager contacts 154 participants – 5 minutes per call-carried out once for each visit (3-visits)</p> <p>Failed contact attempts – trial manager contacts 154 participants - 2 failed contact attempts (1 minute each) – carried out for each visit (3 visits)</p>	<p>Research nurse contacts 428 participants – 5 minutes per call-carried out once for each visit (9 trial visits)</p> <p>Failed contact attempts – research nurse contacts 428 participants - 2 failed contact attempts (1 minute each) – carried out once for each visit (9 trial visit)</p>
Effect estimate	<p>“Telephone reminders compared to usual follow-up may result in little or no difference to retention (smoking cessation (12)): RD = -1% (95% CI -18–15%); GRADE low (-2 levels: imprecision-single study, n = 127; wide CI crossing RD = 0)”⁴</p>				
Cost per participant retained	<p>With a risk difference of negative 1 there are no participants retained with this strategy so cost per participant retained cannot be calculated</p>				
Telephone reminders for questionnaire response	<p>€423.75 (£364.43)</p>	<p>€568.62 (£489.01)</p>	<p>€34.58 (£29.74)</p>	<p>€356.33 (£306.44)</p>	<p>€246.00 (£211.56) (\$291.54)</p>

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Strategy	Cost				
Assumptions	Research assistant contacts 30% of participants (150) – 5 minutes per call – carried out once	Research assistant contacts 30% of participants (150) – 5 minutes per call – carried out once	Research assistant contacts 30% of participants (18) – 5 minutes per call – carried out once	Research assistant contacts 30% of participants (47) – 5 minutes per call – carried out twice	Research assistant contacts 30% of participants (129) – 5 minutes per call – carried out once
	Failed contact attempts – research assistant contacts 150 participants – 2 failed attempts - 1 minute per attempt – carried out once	Failed contact attempts – research assistant contacts 150 participants – 2 failed attempts - 1 minute per attempt – carried out once	Failed contact attempts – research assistant contacts 18 participants – 2 failed attempts - 1 minute per attempt – carried out once	Failed contact attempts – research assistant contacts 47 participants – 2 failed attempts - 1 minute per attempt – carried out twice	Failed contact attempts – research assistant contacts 129 participants – 2 failed attempts - 1 minute per attempt – carried out once
Effect estimate	“Telephone reminders compared to usual follow-up may result in little or no difference to retention (smoking cessation(12)): RD = -1% (95% CI -18–15%); GRADE low (-2 levels: imprecision-single study, n = 127; wide CI crossing RD = 0)”				
Cost per participant retained	With a risk difference of negative 1 there are no participants retained with this strategy so cost per participant retained cannot be calculated				
Telephone reminders for at home data collection	€244.08 (£209.91)				

¹*Italic underlined font indicates the real trial information that we used e.g., number of trial participants, number of trial sites, number of trial visits and any retention methods used within the trials e.g., MOON trial sent out 2 questionnaires to participants.* The non-italic-underlined font which indicates the assumptions we applied. A full description of the trial characteristics and any retention activities conducted by the real-life trials are documented in Additional File 1. ²Evidence from the most recent Cochrane Systematic Review (9). ³We assumed benefit was applied across the whole response to all cycles. The Cochrane review found that return postage which included “preaddressed second class stamped envelope”, “high priority stamp to the mailing” and “personalised postal follow-up” all combined likely lead to a 4% benefit, so it is likely that pre-paid envelopes on their own may not provide a 4% benefit on retention. For the ease of calculation, we calculated the cost per participant retained by using pre-paid envelopes based on a 4% benefit. ⁴We chose to select telephone reminders compared to usual follow up compared to postal follow up in as we believe it is the most relevant comparison for trial teams.

Strategy	Cost												
Assumptions	Research nurse contacts 30% of participants (18) – 5 minutes per call - 1 reminder for each at home data collection (4 in total)												
Effect estimate	“Telephone reminders compared to usual follow-up may result in little or no difference to retention (smoking cessation (12)): RD = -1% (95% CI -18–15%); GRADE low (-2 levels: imprecision-single study, n = 127; wide CI crossing RD = 0)”												
Cost per participant retained	With a risk difference of negative 1 there are no participants retained with this strategy so cost per participant retained cannot be calculated												
	<table border="1"> <thead> <tr> <th></th> <th>Ireland</th> <th>United Kingdom</th> <th>MAMI trial</th> <th>MOON trial</th> <th>CINNAMON trial</th> </tr> </thead> <tbody> <tr> <td>Strategy 5: Data collection scheduled with routine care</td> <td>€20250 (£17415.02)</td> <td>€15697.67 (£13500)</td> <td>€900 (£774.00)</td> <td>€4834.88 (£4158)</td> <td>€32503.25 (£27951.92) (\$38520)</td> </tr> </tbody> </table>		Ireland	United Kingdom	MAMI trial	MOON trial	CINNAMON trial	Strategy 5: Data collection scheduled with routine care	€20250 (£17415.02)	€15697.67 (£13500)	€900 (£774.00)	€4834.88 (£4158)	€32503.25 (£27951.92) (\$38520)
	Ireland	United Kingdom	MAMI trial	MOON trial	CINNAMON trial								
Strategy 5: Data collection scheduled with routine care	€20250 (£17415.02)	€15697.67 (£13500)	€900 (£774.00)	€4834.88 (£4158)	€32503.25 (£27951.92) (\$38520)								

¹*Italic underlined font indicates the real trial information that we used e.g., number of trial participants, number of trial sites, number of trial visits and any retention methods used within the trials e.g., MOON trial sent out 2 questionnaires to participants.* The non-italic-underlined font which indicates the assumptions we applied. A full description of the trial characteristics and any retention activities conducted by the real-life trials are documented in Additional File 1. ²Evidence from the most recent Cochrane Systematic Review (9). ³We assumed benefit was applied across the whole response to all cycles. The Cochrane review found that return postage which included “preaddressed second class stamped envelope”, “high priority stamp to the mailing” and “personalised postal follow-up” all combined likely lead to a 4% benefit, so it is likely that pre-paid envelopes on their own may not provide a 4% benefit on retention. For the ease of calculation, we calculated the cost per participant retained by using pre-paid envelopes based on a 4% benefit. ⁴We chose to select telephone reminders compared to usual follow up compared to postal follow up in as we believe it is the most relevant comparison for trial teams.

Strategy	Cost				
Assumptions	Carried out by a research nurse during a routine care visit – 15 minutes – carried out 3 times for each participant (once for each trial visit)	Carried out by a research nurse during a routine care visit – 15 minutes – carried out 3 times for each participant (once for each trial visit)	Carried out by a research nurse during a routine care visit – 15 minutes – carried out twice for each participant (outpatient clinic data collection and data collection at birth)	Carried out by a research nurse during a routine care visit – 15 minutes – carried out 3 times for each participant (3 trial visits)	Carried out by a research nurse during a routine care visit – 15 minutes – carried out 9 times for each participant (9 trial visits)
Effect estimate	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				
	Ireland	United Kingdom	MAMI trial	MOON trial	CINNAMON trial
Strategy 6: Site initiation training on missing data	€7000 (£6020.00)	€7376.74 (£6344)	€400 (£344.00)	€388.83 (£334.40)	€2953.31 (£2539.76) (\$3500)

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Strategy	Cost				
Assumptions	Prep, site training and report per site @€400 per day plus travel and overnight costs. Carried out once for each site (10 sites)	Prep, site training and report by Trial manager (11 hours of work) – plus travel and overnight costs. Carried out once per site (10 sites)	Prep, site training and report per site @€400 per day. Carried out once (1 site)	Prep, site training and report by Trial Manager (11 hours of work) Carried out once (1 site)	Prep, site training and report per site @€400 per day plus travel and overnight costs. Carried out once for each site (5 sites)
Effect estimate	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				
	Ireland	United Kingdom	MAMI trial	MOON trial	CINNAMON trial
Strategy 7: Investigator meetings face to face	€14000 (£12040.01)	€14753.48 (£12688)	€1600 (£1376)	€777.67 (£668.80)	€11813.22 (£10159.06) (\$14000)

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Strategy	Cost				
Assumptions	Prep, meeting, and report per site @€400 per day plus travel and overnight costs. Carried out twice per site over 1 year trial period (10 sites)	Prep, meeting, and report by Trial manager (11 hours of work) – plus travel and overnight costs. Carried out twice per site over 1 year trial period (10 sites)	Prep, meeting, and report per site @€400 per day Carried out 4 times for each site over 2-year trial period (1 site)	Prep, meeting, and report by Trial manager (11 hours of work). Carried out twice per site over 1 year trial period (1 site)	Prep, meeting, and report per site @€400 per day plus travel and overnight costs. Carried out 4 times for each site over 2-year trial period (5 sites)
Effect estimate	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				
	Ireland	United Kingdom	MAMI trial	MOON trial	CINNAMON trial
Strategy 8: Routine site visits by CTU staff	€14000 (£12040.01)	€14753.48 (£12688)	€1600 (£1376)	€777.67 (£668.80)	€11813.22 (£10159.06) (\$14000)

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Strategy	Cost				
Assumptions	Prep, site visit and report per site @€400 per day plus travel and overnight costs. Carried out twice per site over 1 year trial period (10 sites)	Prep, site visit and report by Trial manager (11 hours of work) – plus travel and overnight costs. Carried out twice per site over 1 year trial period (10 sites)	Prep, site visit and report per site @€400 per day Carried out 4 times per site over 2-year trial period (1 site)	Prep, site visit and report by Trial manager (11 hours of work). Carried out twice per site over 1 year trial period (1 site)	Prep, site visit and report per site @€400 per day plus travel and overnight costs Carried out 4 times per site over 2-year trial period (5 sites)
Effect estimate*	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				
	Ireland	United Kingdom	MAMI trial	MOON trial	CINNAMON trial
Strategy 9: Targeted recruitment of sites/GPs	€1620 (£1393.20)	€1060.46 (£912)	€30 (£25.80)	€35.35 (£30.40)	€506.28 (£435.39) (\$600)

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Strategy	Cost				
Assumptions	Research nurse carries out site selection and investigation (1 hour work per site) – 30 sites are targeted	Trial manager carries out site selection and investigation (1 hour work per site) – 30 sites are targeted	Research nurse carries out site selection and investigation (1 hour work per site) – single centre so only 1 site targeted	Trial manager carries out site selection and investigation (1 hour work per site) – single centre so only 1 site targeted	Research nurse carries out site selection and investigation (1 hour work per site) – 15 sites are targeted
Effect estimate	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				
	Ireland	United Kingdom	MAMI trial	MOON trial	CINNAMON trial
Strategy 10: Flexibility in appointments	€4050 (£3483.00)	€3139.53 (£2700)	€270 (£232.20)	€1004.65 (£864)	€2177.01 (£1872.17) (\$2580)
Assumptions	Research nurse carries out out-of-hours visits for 10% of participants (50) – 1.5-hour visit	Research nurse carries out out-of-hours visits for 10% of participants (50) – 1.5-hour visit	Research nurse carries out out-of-hours visits for 10% of participants (6) – 1.5-hour visit	Research nurse carries out out-of-hours visits for 10% of participants (16) – 1.5-hour visit	Research nurse carries out out-of-hours visits for 10% of participants (47) – 1.5-hour visit
Effect estimate	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				
<p>¹Italic underlined font <i>indicates the real trial information that we used e.g., number of trial participants, number of trial sites, number of trial visits and any retention methods used within the trials e.g., MOON trial sent out 2 questionnaires to participants.</i> The non-italic-underlined font which indicates the assumptions we applied. A full description of the trial characteristics and any retention activities conducted by the real-life trials are documented in Additional File 1. ²Evidence from the most recent Cochrane Systematic Review (9). ³We assumed benefit was applied across the whole response to all cycles. The Cochrane review found that return postage which included “preaddressed second class stamped envelope”, “high priority stamp to the mailing” and “personalised postal follow-up” all combined likely lead to a 4% benefit, so it is likely that pre-paid envelopes on their own may not provide a 4% benefit on retention. For the ease of calculation, we calculated the cost per participant retained by using pre-paid envelopes based on a 4% benefit. ⁴We chose to select telephone reminders compared to usual follow up compared to postal follow up in as we believe it is the most relevant comparison for trial teams.</p>					

Supplementary Files

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- [AdditionalFile1.docx](#)
- [AdditionalFile2.xlsx](#)