

**Strategies to Improve Retention:
Effectiveness and Use in Randomised
Trials**

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Philosophy

by

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“I, Valerie Catherine Brueton, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.”

Signed: _____

This thesis is dedicated to my parents Ita J. Fox and the late Thomas A. Fox.

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Abstract

Background

Loss to follow-up from randomised trials (RCTs) can affect the reliability of results.

Objectives

To quantify the effect of strategies to improve retention in RCTs, explore their use, and develop best practice guidance.

Methods

Systematic review: including retention RCTs nested in RCTs.

Qualitative study: in-depth interviews with RCT personnel.

Consensus development: workshops with RCT personnel.

Results

Systematic review:

38 RCTs evaluated RCT retention strategies. Most aimed to improve questionnaire response. Questionnaire response was improved by: adding monetary incentives (RR 1.18;1.09-1.28), higher value monetary incentives (RR 1.12;1.04-1.22) and offering monetary incentives (RR 1.25;1.14-1.38). There is some evidence that recorded delivery (RR 2.08;1.11-3.87), a specialised postal strategy (RR 1.43;1.22-1.67) and an open RCT design (RR 1.37;1.16-1.63) also improve questionnaire response.

There is no clear evidence that, when compared to usual follow-up procedures, questionnaire response / retention is improved by: sending questionnaires early, more disease-relevant questionnaires, shorter, or long and clear questionnaires, offering charity donations, giving or offering gifts, "enhanced" letters, priority post, additional reminders, questionnaire order, reminders to sites, behavioural or case management strategies. There was no clear effect for monetary incentives when compared to offering entry into a prize draw, or telephone surveys when compared to a monetary incentive with a questionnaire.

Qualitative study:

Communication and incentive strategies are routinely used to improve retention / response. There was uncertainty about their effectiveness. Non-monetary incentives, although used, were not thought to be effective. Efforts are made to improve questionnaire layout. Other strategies are seldom used. Factors thought to impact upon retention were identified.

Consensus development:

Best practice guidance was agreed for monetary incentives and postage.

Conclusion

Giving and offering small monetary incentives can be used to improve questionnaire response in RCTs. Second class postage can also be used. Application of the results would depend on RCT context and follow-up procedures.

Lay summary

A randomised clinical trial is a type of research study that involves people and compares one treatment to another. The people who take part are placed by chance into groups for comparison. This is called randomisation and is usually done by a computer program. In each trial one group is given the treatment to be tested and their progress is compared to the group having the current or a dummy treatment. Information is collected from all of the people in each group to find out which treatment is the best. That information is gathered by questionnaires or through face to face meetings. This is known as “follow-up”. However, sometimes follow-up information is missing because the people taking part are too busy to return a questionnaire, or they are unable to attend a follow-up appointment. Researchers call this “loss to follow-up”. Different ways are used to try to prevent loss to follow-up because too much missing information can lead to incorrect results. Researchers have used trials to compare different ways to prevent loss to follow-up in clinical trials to see which work best. For example a questionnaire sent with a pen could be compared with a questionnaire sent without a pen.

This PhD is about finding the best ways researchers can use to improve follow-up in trials. To do this, databases that store research reports were searched for trials that compared different ways to prevent loss to follow-up in clinical trials. The information gathered from the reports were grouped and tested to find the ways that do improve follow-up. Researchers who collect follow-up information from people in trials were also asked about the different ways that they use to improve follow-up. They were asked about why they thought people do not return questionnaires or return to clinics to be follow-up. The results of these two studies were then presented to researchers who work on trials. These researchers discussed the results, and they agreed on the best ways researchers can use to improve follow-up in trials.

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Glossary of terms

| | |
|--------------|--|
| CENTRAL | Cochrane Central Register of Controlled Trials |
| C2SPECTRE | Campbell Collaboration's Social, Psychological, Educational and Criminological Trials Register |
| CINAHL | Cumulative Index to Nursing and Allied Health Literature |
| CMR | Cochrane Methodology Register |
| CMG | Cochrane Methodology Group |
| CTU | Clinical Trials Unit |
| CI | Chief Investigator |
| DARE | Database of Abstracts of Reviews of Effects |
| EMBASE | Excerpta Medica Database |
| ERIC | Education Resources Information Centre |
| GPRF | General Practice Research Framework |
| GP | General Practitioner |
| HIV | Human Immunodeficiency Virus |
| ICC | Intracluster Correlation Coefficient |
| MRC | Medical Research Council |
| <i>m</i> RCT | Current Controlled Trials <i>meta</i> Register |
| NGT | Nominal Group Technique |
| NIHR | National Institute of Health Research |
| PC | Primary Care |
| PICO | Participants Interventions Comparisons Outcomes |
| PCRN | Primary Care Research Network |
| PO | Primary Outcome |
| PI | Principal Investigator |
| PPI | Patient and Public Involvement |
| RTN | Regional Training Nurse |
| RCT | Randomised Controlled Trial |
| RN | Research Nurse |
| SOP's | Standard Operating Procedures |
| TM | Trial Manager |
| TMN | Trial Managers Network |
| UKCRN | United Kingdom Clinical Research Network |
| WHO | World Health Organisation |

CHAPTER 1: INTRODUCTION

1.1. BACKGROUND

Randomised trials (RCTs) are the gold standard for evaluating the effectiveness of interventions in clinical and social research (Pocock 1983, Torgerson et al. 2008). Following recruitment to an RCT, the participants are randomised to either an intervention group or a control group and subsequently followed-up for a length of time to determine the pre-specified intervention effect. This is measured through the primary outcome, often at a pre specified time point. Data for the primary outcome can be collected either at the study site through biomedical tests and face to face interviews, or by postal or electronic questionnaires. Data can also be collected via the internet, telephone or Short Message Service (SMS) text message.

1.1.1. *WHAT IS LOSS TO FOLLOW-UP?*

Protocol deviations in RCTs can occur when participants do not attend follow-up appointments or do not return their questionnaires (Pocock 1983). This is known as loss to follow-up, and retention is 1-loss to follow-up. Loss to follow-up is described in different ways in the literature, for example as “drop-out”, “withdrawal”, or “non-response”. Reporting of loss to follow-up is often variable and difficult to interpret, perhaps because there is no clear definition of what constitutes loss to follow-up in standard statistics and epidemiology text books (Armitage 2005, Last 1983). This could be because of the variability in opinion and understanding in the research community of what constitutes loss to follow-up (Toerien et al. 2009). The outcome of loss to follow-up in RCTs is attrition which was defined by Akl in 2009 as: “incomplete ascertainment of the primary outcome for participants randomised in a trial” (Akl et al. 2009).

Reasons for loss to follow-up can include a change in the participants’ location, withdrawal from treatment and subsequent RCT dropout, or loss of interest or commitment to the RCT, for example due to complicated treatment / medicine regimens (Janson et al. 2001).

1.1.2. *WHY IS IT IMPORTANT TO REDUCE LOSS TO FOLLOW-UP?*

It is important for researchers to reduce loss to follow-up in RCTs because this can lead to incomplete outcome data for the final analysis. Incomplete outcome data can bias the results of the RCT particularly where there is an imbalance in the number of participants followed-up in each RCT arm. Schulz (2002) suggests that less than 5% loss to follow-up

may lead to minimum bias in RCTs while 20% loss to follow-up can threaten RCT validity (Schulz et al. 2002). Missing outcome data can compromise RCT findings in two main ways. First, by reducing the power of an RCT to detect a true difference between the control group and the intervention group and second, where there is differential loss to follow-up between RCT arms, this can lead to bias through exaggerated effects in favour of the treatment or the control group. Such biases can affect the internal validity of the RCT and the generalisability of results because the participants who are lost to follow-up may not be representative of the participants retained in the RCT (Fewtrell et al. 2008, Moher et al. 2001, Schulz et al. 2002).

Missing data can be dealt with statistically in different ways during the RCT analysis phase. The methods employed to deal with missing data include imputation, where data for missing values in intention to treat analysis are replaced (imputed) based on assumptions about the true value for the missing data. However, the risk of bias still remains because RCTs do not always collect adequate data to give accurate estimates (Hollis et al. 1999) and therefore the true value of the missing data will not be known (Sterne et al. 2009). The impact of the different assumptions made for the missing data can be assessed in sensitivity analyses, however guidance on the interpretation of these analyses in the face of conflicting results is lacking. A more practical way to address the problem of loss to follow-up in RCTs is to use strategies to encourage participants to return to study sites for measurement of primary and secondary outcomes, or to encourage RCT participants to return their completed outcome assessment tool. This may be a questionnaire or biomedical specimen. However, the spectrum of populations, diseases, health care and social settings through which RCTs are conducted means that participant retention can be complex. Therefore, different approaches to improve follow-up in RCTs are used to engage and motivate participants to return data for measurement of the primary outcome (Good et al. 1997).

1.2. TYPES OF PARTICIPANT RETENTION STRATEGIES

Retention strategies can target the study site by engaging site staff through training and improved communication with the trial coordinating centre (Bruzzese et al. 2009, Cooley et al. 2003, Leathem et al. 2009). Other retention strategies target participants in an RCT once they have been randomised. Some of these retention strategies are designed to help participants to identify more with the RCT and to encourage a sense of value and belonging to the RCT (Villacorta et al 2007). For example, participants may be given T-shirts, mugs or fridge magnets with a study logo to remind them about the RCT (Senturia

et al. 1998). Other retention strategies are designed to keep participants informed about the progress of the RCT in which they are participating for example; participants can be sent newsletters with RCT progress updates (Given et al. 1990). Some retention strategies are designed to remind participants to return RCT outcome information to the coordinating centre or to return to the clinical site for RCT follow-up. These strategies are usually in the form of letters, emails, and/or telephone calls (Constantine et al. 1993, Goldberg et al. 2005, Northouse et al. 2006, Sprague et al. 2003).

Different retention strategies have been used in RCTs of different disease treatments. In a mental illness treatment RCT, Furimsky (2008) made follow-up more convenient for participants by streamlining clinical and research assessments (Furimsky et al. 2008). In an RCT of treatments for Bell's palsy, the participants were given the option to be followed-up up at home to improve retention (McKinstry et al. 2007). Sometimes retention strategies are used in combination to improve retention, for example Couper (2007) used telephone calls by trained interviewers and monetary incentives to improve responses in a weight loss RCT (Couper 2007). Goldberg (2005) used birthday cards, flexible appointment schedules and telephone contact to improve responses in a behavioural weight loss RCT (Goldberg et al. 2005). In a behavioural intervention RCT to reduce smoking, depression and intimate partner violence during pregnancy, El Khorazaty (2007) used incentives to compensate participants for their time and effort. A data management system was also developed to track the participants and to send reminders for forthcoming follow-up assessments (El Khorazaty et al. 2007).

Strategies have also been used to improve retention of target minority ethnic groups in RCTs. For example among Latino participants in a primary care based RCT of a physical activity and dietary intervention, Eakin (2007) requested alternative contact numbers, and followed participants up at home. In a diabetes treatment RCT that evaluated a dietary self-management intervention among rural African Americans, Loftin (2005) used telephone and postcard reminders and gift incentives to improve retention (Eakin et al. 2007, Loftin et al. 2005,). Retention strategies have also been used in RCTs that include vulnerable groups of participants e.g. elderly people. Burns (2008) describes using home visits by the same person to improve retention in a community based counselling intervention for older rural African American women (Burns et al. 2008). While in a nutritional intervention RCT involving people with human immunodeficiency virus (HIV) and chronic diarrhoea, flexible appointment times and a reminder telephone call before each follow-up visit were used to improve retention (Anastasi et al. 2005). The different RCT retention strategies used can be grouped into broad categories as summarised below.

1.2.1. MOTIVATIONAL STRATEGIES

Motivational retention strategies include monetary incentives or gifts given to reimburse participants for their time, or as compensation for travel expenses. These strategies are thought to encourage retention by motivating participants to return to RCT and study sites for further follow-up visits (Loftin et al. 2005, Robinson et al. 2007). Promotional gift items can include calendars, mouse mats, note pads, pens, T-shirts, mugs and fridge magnets (Eakin et al. 2007, El Khorazaty et al. 2007, Furimsky et al. 2008, Robinson et al. 2007, Senturia et al. 1998). Often these promotional items are designed to give participants a sense of belonging to an RCT (Villacorta et al. 2007). Logos and trade marks on such gifts are thought to encourage commitment and to raise the profile of the RCT among the participants (Aitken et al. 2003).

1.2.2. COMMUNICATION STRATEGIES

Communication strategies include different methods of postal communication for example sending participants personalised letters, study enrolment anniversary cards and birthday cards (Goldberg et al. 2005). Telephone calls, short message service (SMS) text messages, and emails to remind participants of future study visits are also included in this group (Senturia et al. 1998, Free 2011).

1.2.3. METHODOLOGICAL STRATEGIES

Methodological strategies to improve retention in RCTs include such strategies as modifying the frequency and duration of RCT follow-up visits. Costenbader (2005) followed-up participants once a year in a feasibility RCT of prevention strategies for atherosclerosis in patients with Systemic Lupus Erythematosus, and Schulz (2002) suggests streamlining RCT follow-up procedures to move participants more quickly through follow-up (Costenbader et al. 2005, Schulz et al. 2002).

1.2.4. SOCIAL SUPPORT STRATEGIES

Social support retention strategies include those that encourage family support through involvement of other family members in RCT follow-up (De Sousa et al. 2008). Another strategy that can be included in this category is the provision of child friendly waiting rooms at study sites to encourage mothers with small children to attend RCT follow-up appointments (Loue et al. 2008). Combined scheduling of research and clinical assessments to reduce the number of RCT follow-up visits for participants could also be included in this category (Furimsky et al. 2008).

1.2.5. MANAGEMENT FOCUSED STRATEGIES

Management focused retention strategies include those used to target RCT management teams at study sites e.g. sending site specific reports of study activity progress to each RCT site. Such reports can highlight progress and potential follow-up problems to be acted upon by site staff (El Khorazaty et al. 2007, Senturia et al. 1998). Comparisons of retention figures sent regularly to RCT sites (blinded by site) may stimulate competition between sites and so increase retention (Senturia et al. 1998). Senturia (1998) used regular telephone contact between the coordinating centre and clinical sites to discuss RCT monitoring and follow-up strategies to improve retention. Other management focused strategies may include the exclusion of potential RCT participants thought likely to move or not return for follow-up before randomisation. However, such a strategy could affect the generalisability of results because those who remain in the RCT may not be representative of the study population as a whole (Schulz et al. 2002).

1.3. PREDICTORS OF LOSS TO FOLLOW-UP

Some studies have retrospectively examined the predictors of loss to follow-up in RCTs (Arnow et al. 2007, Snow et al. 2007). Arnow (2007) in an RCT for treatment of depression that compared pharmacotherapy with psychotherapy found that the predictors of drop-out were those participants from ethnic and racial minorities, and those with comorbid anxiety. In a lung health study which examined the impact of smoking cessation and bronchodilator use on chronic obstructive airways disease, Snow (2007) found that older females who smoked less heavily were more likely to attend for follow-up visits (Snow et al. 2007). Knowing the predictors of loss to follow-up in an RCT for a particular group of participants may help researchers target and match retention strategies to help improve retention of participants from such at risk groups.

1.4. STRATEGIES TO IMPROVE RECRUITMENT AND RETENTION

Similar strategies may be used in an attempt to increase recruitment and to improve retention of RCT participants. Such strategies include giving incentives and providing extra information to participants during recruitment. Treweek's (2010) Cochrane systematic review identified strategies to improve recruitment to RCTs. Telephone reminders, opt out rather than opt in recruitment procedures, and an open RCT design were found to improve recruitment to RCTs. RCT recruitment can present different challenges to researchers than retention in RCTs. For example, the strategies used to market an RCT and to win over participants during the recruitment phase (Francis et al.

2007) may be different to the strategies needed to keep participants engaged in an RCT for follow-up. An intensive marketing strategy is ideal for recruitment to create awareness and buy-in among potential RCT participants (Anastasi et al. 2005, Bruzzese et al. 2009, Bull et al. 2008, Francis et al. 2007). However, intensive marketing could be inappropriate and even off putting if continued once participants are recruited and randomised to an RCT. Nevertheless, there are common strategies that can be used for recruitment and retention in RCTs, for example sending reminders (Anastasi et al. 2005, Bruzzese et al. 2009, Bull et al. 2008) and giving small incentives (Bull et al. 2008, Parra-Medina et al. 2004). This thesis will focus on the strategies that improve retention in RCTs.

1.5. CRITICAL REVIEW OF REVIEWS OF RETENTION STRATEGIES

To date there have been five literature reviews of strategies to improve retention in different health and non-health care research contexts (Booker et al. 2011, Davis et al. 2002, Edwards et al. 2009, Nakash et al. 2006, Robinson et al. 2007). Four of these are reported as systematic reviews (Booker et al. 2011, Edwards et al. 2009, Nakash et al. 2006, Robinson et al. 2007) one of which is a Cochrane systematic review (Edwards et al. 2009) registered with the Cochrane methodology group. One review is a narrative review (Davis et al. 2002). Systematic reviews differ from narrative reviews in that the research question for a systematic review is focused, clear objectives are defined, and the search strategy is comprehensive and replicable. A risk of bias assessment of the included studies is also conducted in a systematic review to assess the validity within and across all of the studies included. A quantitative assessment and systematic presentation of summary evidence is also reported to help clinicians and researchers to keep up to date with current practice (Green et al. 2008).

To evaluate the strengths and weaknesses of each of the reviews of strategies to improve retention conducted to date, the preferred reporting items for systematic reviews and meta-analyses guidelines (PRISMA) were used (Liberati et al. 2009). These guidelines, which are endorsed by the Cochrane collaboration, provide a checklist for systematic review authors to report the results of such reviews in a complete and transparent way (Liberati et al. 2009). Table 1 shows the PRISMA items reported for the five retention reviews identified.

Table 1 Checklist of PRISMA items reported for reviews of retention strategies

| PRISMA items | Davis (2002) | Robinson (2007) | Booker (2011) | Nakash (2006) | Edwards (2009) |
|--|--------------|-----------------|---------------|---------------|----------------|
| Title | | | | | |
| Systematic review mentioned in title | - | ✓ | ✓ | ✓ | ✓ |
| Abstract | | | | | |
| Structured summary | ✓ | ✓ | ✓ | ✓ | ✓ |
| Introduction | | | | | |
| Rationale | ✓ | ✓ | ✓ | ✓ | ✓ |
| Objectives | ✓ | ✓ | ✓ | ✓ | ✓ |
| Methods | | | | | |
| Protocol and registration | - | - | - | - | ✓ |
| Eligibility criteria | ✓ | ✓ | ✓ | ✓ | ✓ |
| Information sources searched | - | ✓ | ✓ | ✓ | ✓ |
| Search strategy | - | ✓ | ✓ | ✓ | ✓ |
| Study selection - screening process | - | ✓ | ✓ | ✓ | ✓ |
| Data collection process | - | ✓ | ✓ | ✓ | ✓ |
| Data items extracted | - | ✓ | - | - | ✓ |
| Risk of bias assessment | - | - | - | ✓ | ✓ |
| Summary measures e.g. Risk Ratios | - | - | - | ✓ | ✓ |
| Synthesis of results | - | - | - | ✓ | ✓ |
| Risk of bias across studies e.g. publication bias | - | - | - | - | - |
| Additional analyses e.g. sensitivity analyses | - | - | - | ✓ | ✓ |
| Results | | | | | |
| Numbers of studies screened and selected with flow diagram | - | ✓ | ✓ | ✓ | - |
| Study size, participants, intervention, control, and outcomes measured | - | ✓ | ✓ | ✓ | ✓ |
| Risk of bias within studies | - | - | - | - | ✓ |
| Results of individual studies with forest plot | - | - | - | ✓ | ✓ |
| Results of meta-analysis | - | - | - | ✓ | ✓ |
| Risk of bias across studies | - | - | - | - | ✓ |
| Additional analysis e.g. sub-group or sensitivity analysis | - | - | - | ✓ | ✓ |
| Discussion | | | | | |
| Summary of main findings | - | ✓ | - | ✓ | ✓ |
| Limitations e.g. risk of bias at outcome and review level | - | - | ✓ | - | ✓ |
| Conclusions | ✓ | ✓ | ✓ | ✓ | ✓ |
| Funding | | | | | |
| Funding source described | - | ✓ | ✓ | ✓ | ✓ |

Note: ✓ = item reported; - = item not reported.

Davis and colleagues conducted a broad literature review to identify the effectiveness of retention strategies used in community based RCTs published from 1990-1999 (Davis et al. 2002). The inclusion criteria were community based RCTs, excluding drug RCTs, reporting strategies used for retention and the associated retention rates. This narrative review has several substantial limitations. Neither the sources searched nor the search strategies were reported. Furthermore, the searches were restricted to English language publications and it is unclear how the included RCTs were selected. A tabulated summary of the 21 included RCTs is provided. These RCTs were rank ordered by retention rates which ranged from 44% - 99%. However, the retention strategies used in the RCTs are not clearly reported in the review summary. There is no synthesis of results in the form of a meta-analysis because the retention strategies were not evaluated in nested retention RCTs. Furthermore, a risk of bias assessment of the included RCTs is not reported. The authors suggest that community based RCTs with the highest retention rates used a combination of retention strategies. However, there is little evidence to support this suggestion from the methods used and the results reported.

Building on the work of Davis (Davis et al. 2002), Robinson (Robinson et al. 2007) conducted a systematic review to identify the strategies used for participant retention across all areas of research not limited to community based RCTs. The eligibility criteria for this review were clearly defined as: studies that followed-up participants and reported the retention strategies used and corresponding retention rates. Five databases were searched including PubMed, EMBASE and CENTRAL as recommended by the Cochrane Collaboration. The search strategy used is clearly defined in an appendix to the published report. The reference lists of included studies and relevant reviews were also searched (see Table 2). It is unclear from the review report if the databases were searched through to 2005 or if these searches were limited to a specific time period as seen in the review by Davis (2002). However, one of the included studies dates from 1985 which indicates that the time intervals searched were broader than those for Davis's review, which spanned publications over one decade (Davis et al. 2002). A flow diagram of the results for each of the databases searched is provided. Overall, 21 eligible studies that met the inclusion criteria were identified. There were thirteen RCTs and eight cohort studies. None of the included studies had a nested RCT that evaluated the effectiveness of the retention strategy used. Therefore, synthesis of the results in a meta-analysis was not feasible. The mean retention rate for the included studies is the only summary statistic reported i.e. 86%. Robinson's (2007) review summarises in tabular form the different types of strategies used to improve participant retention in studies using face to face follow-up at

Table 2 Reviews of retention strategies: areas of overlap and difference

| Review | Objective | Included studies | Setting | Searches | Number of eligible studies | Retention strategies identified | Meta-analysis yes / no | Effective strategies |
|------------------------|--|--|---------------------|---|--|--|-------------------------------|-----------------------------|
| Davis (2002) | To determine the effects of retention strategies on participant retention | Community based clinical trials | Community | Not reported | 21 RCTs that describe the use of strategies to improve retention | Study design Incentives Communication Staff training Trial management Marketing | No | - |
| Robinson (2007) | To identify and describe studies that use retention strategies to maximise in person follow-up | Studies that describe retention strategies for health care research and that include retention rates | Health care studies | PubMed; EMBASE; CENTRAL CINAHL; Cochrane Methodology Register Reference lists | 21 RCTs that describe the use of strategies to improve retention | Communication Marketing Incentives Trial management | No | - |
| Booker (2011) | To determine the effectiveness of retention strategies in population based cohort studies | Studies that evaluated retention methods in population based cohort studies | Population based | MEDLINE; EMBASE; CENTRAL; CINAHL DARE; PsycINFO; ISI; PsycABSTRACTS; AMED Health development agency literature Reference lists | 11 retention RCTs embedded in longitudinal cohort studies | Incentives Communication | No | - |

| Review | Objective | Included studies | Setting | Searches | Number of eligible studies | Retention strategies identified | Meta-analysis yes / no | Effective strategies |
|-----------------------|---|--|---|--|--|---|------------------------|--|
| Nakash (2006) | To identify effective methods to improve response to postal questions in health care research | Randomised trials of methods to improve response to postal questionnaires in clinical studies | All health care settings and disease areas | MEDLINE; EMBASE; CENTRAL; Cochrane database of systematic reviews ; PsycINFO National Research Register | 15 retention RCTs embedded in surveys and RCTs | Incentives Communication Questionnaire format | Yes | Reminders (OR 3.7: 2.3-5.97) Shorter questionnaires (OR 1.35: 1.19-1.54) |
| Edwards (2009) | To identify effective strategies to increase response to postal and electronic questionnaires | Randomised trials of methods designed to increase response to postal and electronic questionnaires | All health care and non-health care research settings | MEDLINE; EMBASE; CENTRAL; PsycINFO; CINAHL; ERIC; PsycLit; Spectre; EconLit Dissertation abstracts Social Science and Science citation index Sociological Abstracts Index to Scientific and technical proceedings. Journal hand searches Contact with authors Reference lists | 513 retention trials embedded in surveys cohort studies and RCTs | Incentives Communication Questionnaire format | Yes | Postal questionnaires: Monetary incentives (OR 1.87;1.73 - 2.04) Recorded delivery (OR 1.76; 1.43 - 2.18) Teaser on envelope (OR 3.08; 1.27 - 7.44) More interesting topic (OR 2.00;1.32 -3.04) Electronic questionnaires: Picture in an e-mail (OR 3.05; 1.84 - 5.06) Non-monetary incentives (OR 1.72; 1.09 - 2.72) |

sites rather than follow-up through questionnaires. The review also provides a useful summary of the factors thought to influence retention in health care studies (Robinson et al. 2007). The author suggests that using several retention strategies simultaneously could improve participant retention and that further evidence for the effectiveness of different strategies is needed.

A more recent systematic review by Booker (2011) aimed to determine the effectiveness of retention strategies used in prospective population-based cohort studies (Booker et al. 2011). Population based cohort studies that describe at least one retention method and report method specific retention rates were eligible for inclusion in this review. Clinical RCTs evaluating treatment regimens and interventions were excluded. Nine databases were searched and the bibliographies of relevant studies and grey literature (see Table 2). However, the searches were limited to English language publications and only five broad search terms used to identify the studies were reported. These search terms included “recruitment” as a search term. This is considered a separate subject area to participant retention and would have generated additional abstracts and titles that were not appropriate to meet the review aim (Treweek et al. 2010). Overall, 28 studies met the inclusion criteria, 11 of which were RCTs of retention strategies embedded in longitudinal cohort studies. Nine of these RCTs evaluated incentives, one RCT evaluated interview length and one RCT evaluated postal methods. A risk of bias assessment of the included RCTs was not reported. All of the included studies were described qualitatively and the authors reported that a meta-analysis was not conducted because of heterogeneity in the included study designs. However, a meta-analysis may have been possible for the incentive, communication and questionnaire strategies that had been evaluated in nested RCTs in cohort studies. The authors suggest that incentives improved retention in longitudinal cohort studies. However, there is no evidence to suggest this from the analyses conducted.

The systematic review by Nakash (Nakash et al. 2006) focused on ways to increase response to postal questionnaires used in health care research. Eligible studies were RCTs of any method of improving response to postal questionnaires embedded within health care research studies and not necessarily RCTs. Although the three main databases recommended by Cochrane were searched (i.e. MEDLINE, CENTRAL and EMBASE), the search dates were time limited. For instance the MEDLINE search was limited to the years 1996 to 2004, and the searches of EMBASE, CENTRAL and the Cochrane database of systematic reviews limited to the years 1980 to 2004. The search strategy and database filters used were presented in tabular form. The search terms focused on RCT retention and were reported for the MEDLINE search only. Only one register i.e. the national

research register was searched. None of the allied professional literature database e.g. CINAHL were searched. The reference lists of relevant RCTs and reviews were also searched for further potentially eligible RCTs. There was also no reference to grey literature searches and the language restrictions for the searches were not reported. The authors of relevant RCTs and reviews were contacted in order to identify eligible unpublished RCTs.

Fifteen eligible RCTs were identified and a quality assessment of the included RCTs based on the Cochrane risk of bias assessment was conducted. Five of the RCTs were assessed as good quality, and six of moderate quality. For four included RCTs there was insufficient information to make a judgment about the risk of bias. A meta-analysis was conducted appropriate for the groups of strategies identified. The strategies found to improve response to postal questionnaires in health care research were: reminder letters (OR 3.7, 2.30 - 5.97), and short questionnaires (OR 1.4, 1.19 - 1.54). Monetary incentives (OR 1.09: 0.94-1.27) and re ordering questionnaire questions (OR 1.00:0.91-1.09) were not effective in this review. Nakash (2006) correctly concluded that all strategies used to improve response to postal questionnaires used in health care research require further evaluation.

The Cochrane systematic review by Edwards (2009) aimed to identify effective strategies to increase response to postal and electronic questionnaires. This review included all RCTs of methods to increase response to postal and electronic questionnaires in health and non-health care research studies and was not limited to evaluations embedded in RCTs. A key strength of this review is that it collates all the empirical evidence about ways to improve response to postal and electronic questionnaires in different research settings. The search strategy and the number of databases searched are more comprehensive than any of the other reviews. Furthermore, the search strategy is reported in enough detail to be replicated across all of the databases searched. The review report meets most of the criteria required by PRISMA, apart from a risk of bias assessment across studies which may be accounted for by the large number of RCTs identified. Overall, 513 RCTs were included in the review and these reported 137 different strategies that evaluated ways to improve response to postal and electronic questionnaires. The strategies found were: communication, incentive, and questionnaire format strategies. The most effective strategies to improve postal questionnaire response were: monetary incentives (OR 1.87; 1.73 - 2.04), recorded delivery (OR 1.76; 1.43 - 2.18), a teaser on an envelope (OR 3.08; 1.27 - 7.44) and having a more interesting questionnaire topic (OR 2.00; 1.32 - 3.04). Different strategies were found to be effective for increasing response to electronic questionnaires. These included a picture in an e-mail (OR 3.05; 1.84 - 5.06) and non-

monetary incentives (OR 1.72; 1.09 - 2.72). The authors conclude that the results can be used for evaluations in health care. However, most of the included RCTs were embedded in surveys in non-health care contexts, for example among student populations or factory workers. These results are therefore not generally applicable to research in health care settings. It is also unclear which of the retention strategies identified are the most effective for use in either RCTs, cross sectional surveys or longitudinal cohort studies.

In summary, the systematic reviews by Edwards (2009) and Nakash (2006) were broad and included nested randomised or quasi randomised evaluations of strategies to improve retention in research conducted in different settings. The retention strategies identified were designed to improve response to questionnaires in surveys, cohort studies and RCTs (Edwards et al. 2009, Nakash et al. 2006). Robinson identified a range of strategies used for in person follow-up in community based RCTs (Robinson et al. 2007). The review by Booker identified retention strategies used in longitudinal cohort studies (Booker et al. 2011). Nevertheless, the effectiveness of strategies to improve retention in RCTs remains unknown because none of these literature reviews have specifically examined the effectiveness of strategies to improve retention in RCTs. There is therefore a strong case for such a systematic review.

1.6. BARRIERS TO CONDUCTING NESTED RCTS

It is clear from these retention reviews that few retention strategies have been evaluated in nested RCTs (Booker et al. 2011, Davis et al. 2002, Edwards et al. 2009, Nakash et al. 2006, Robinson et al. 2007). Nested RCTs require a second randomisation of the participants in a host RCT to a control group or an intervention group and can therefore be complex to manage. The nested RCT can be embedded in one or all arms of the host RCT after the host RCT participants have been recruited, consented and randomised. Therefore, while there is efficient use of participants, nested RCTs may add further complexity to the planning and management of both host and nested RCTs.

There are therefore potential barriers to conducting nested RCTs. Graffy (2010) examined stakeholders i.e. funders, principal investigators, trial managers and ethics committee members perspectives on the practicality and acceptability of nesting RCTs of different recruitment methods in RCTs. The findings suggest that, although researchers recognised the need for nested RCTs of recruitment strategies, they thought that these were challenging to implement because of the additional work for trial management teams. They also thought that the resources available for nested RCTs may be limited compared to those available for host RCTs. Furthermore, they felt that the competition for resources between the host RCT and the nested RCT could challenge relationships between clinical

collaborators where more resources are available for the administration of the host RCT compared with the nested RCT.

There is little information on the barriers to embedding nested retention RCTs in host RCTs. However, there may be some overlap with the barriers to embedding nested recruitment RCTs in host RCTs, for instance the availability of funding, the additional work for the RCT management team, and the extra burden of nested RCT participation for the host RCT participants (Graffy et al. 2010).

Extra resources will be required to set up a nested retention RCT if this is not anticipated when a grant application for the host RCT is submitted for funding. Therefore, an additional funding application is usually required. However, there are few methodology research funding bodies compared with clinical research funders. The additional work associated with applying for funding for a nested methodology RCT can be arduous for the host RCT management team thus limiting the number of nested RCT funding applications and potentially limiting the number of nested retention RCTs. Limited funding and the burden on staff resources can have implications for the conduct of both the host and the nested RCTs in terms of the equitable use of resources to ensure that both host and nested RCTs are completed to publication.

A successful funding application for a nested RCT will trigger an extra tranche of work for the RCT management team. Nested RCTs can be complex to operationalise and experienced staff with the practical skills required to set up such RCTs would need to be recruited. Once additional staff are recruited applications for ethics and research and development approvals for the nested RCT are commenced. These activities require time to design specific data collection tools e.g. information sheets and consent forms for potential nested RCT participants. Training on additional procedures related to the nested RCT will be required for data collectors, administrators, and budget managers.

The design and implementation of the nested RCT should not compromise the conduct or interpretation of the host RCT. Therefore, complex methodological decisions for the nested RCT will need to be addressed and consensus reached on these. For instance, decisions about: which participants to recruit into the nested RCT from the host RCT, which arm/s of the host RCT to recruit from, the optimal time to commence the nested RCT, and the research outcomes to measure. The length and frequency of follow-up, management of follow-up and data monitoring also need planning.

In addition to the extra funding and trial management arrangements needed to conduct nested RCTs, the host RCT could be at risk of losing participants because of the additional

time required from participants for recruitment and follow-up in the nested RCT. The additional data collection required for a nested RCT may compromise an already established rapport between key members of the management team (e.g. trial managers and data collectors) and the host RCT participants. This could lead to loss to follow-up and missing data for the primary outcome for both host and nested RCTs. Once recruited to the nested RCT the participants may have a preference for participating in one RCT over the other because of the perceived benefits of participation e.g. if the host RCT offers treatment for a chronic disease. This could lead to drop out in the nested RCT and affect the power to demonstrate a difference between the groups being compared in the nested RCT.

Beyond the difficulties in initiating and conducting a nested RCT, there is also the risk that the results will not be published or disseminated because of the priority given to outputs for the host RCT. As a result, a detailed analysis of data for the nested RCT, beyond analysis for the primary outcome may be delayed as outputs for the host RCT required by funding bodies are prioritised.

In summary, nested RCTs are complex to manage. The barriers to conducting such RCTs include applications for additional funding and research governance, and the additional staff required. The barriers to conducting nested methodology RCTs can be overcome with skilful planning and management of the host RCT.

1.7. FEASIBILITY STUDY

In order to understand the problem that loss to follow-up presents for researchers conducting RCTs, informal one to one preliminary information gathering meetings were arranged with key RCT personnel working at the Medical Research Council, Clinical Trials Unit (MRC CTU). The MRC CTU conducts RCTs in developed and developing countries, in the areas of treatments for cancer and infections. The purpose of these meetings was:

1. To determine if loss to follow-up remained a concern to researchers conducting RCTs.
2. To ascertain if strategies to improve retention were used in RCTs conducted at MRC CTU.
3. To determine the feasibility of recruiting interviewees to discuss retention and loss to follow-up in RCTs in a more formal qualitative study.
4. To gain an understanding of loss to follow-up that would inform the development of a protocol for a systematic review on strategies to improve retention in RCTs.

The meetings were arranged with ten principal investigators and trial managers who were working on RCTs. They were asked if loss to follow-up was a problem in RCTs, and how this was dealt with when it occurred. The ten meetings were held between 16.04.2009 and 8.06.2009. A summary of the discussions for each meeting is presented in Table 3.

The meetings highlighted some of the challenges researchers encountered retaining participants in RCTs conducted in cancer and infections in secondary care settings. It was clear from these meetings that the level of loss to follow-up from RCTs appears to be disease and outcome specific. For example, for RCTs of cancer treatments conducted in secondary care, loss to follow-up was not necessarily a problem if, as in the case of overall survival, the primary outcome could be sourced from national disease registers or hospital records. Loss to follow-up in cancer RCTs with patient-assessed quality of life data was, however, a more substantial and less easily solved problem probably because of the frequency of data collection, and the acceptability of collecting such data to clinicians at sites. A factor thought to contribute to keeping in touch with RCT participants who change address is a global network of specialist clinicians in cancer and infectious disease research who can follow-up participants if they move to their region. Other factors thought to contribute to RCT retention were: good RCT management, good rapport between clinicians and participants, good communication with participants, and good communication between RCT sites and the RCT coordinating centre.

The discussions demonstrated that researchers were unsure of any clear definition for attrition. They highlighted the importance of obtaining a measurement for the

Table 3 Summary of feasibility study meetings

| Researcher role | Key points about loss to follow-up in RCTs | Trial setting | Disease area |
|------------------------|--|--|---------------------|
| Principal Investigator | Thought loss to follow-up should not happen in cancer RCTs. Many ways to keep in contact with participants even if they migrate. Worldwide medical networks for participants to be followed up at other centres. Good trial management important. Communication with clinicians important; unanswered emails followed up with letters, phone calls and meetings. A clear definition of attrition is needed. Are withdrawals included in attrition rates? Withdrawal from treatment versus withdrawal from study follow-up. Participants can withdraw from treatment but are still followed up for primary outcome measurement. Clinicians may feel that a different treatment is better and withdraw a participants from an RCT. | Secondary care Developed countries | Cancer |
| Principal Investigator | Loss to follow-up funding related in the USA. Nurse needed to follow-up participants, contract based. Management strategies to improve retention: compare recruitment and create competition between sites. Have monthly teleconferences with sites. Generate lists of participants to co-ordinate follow-up visits. | Secondary care developed and Developing countries | Infections |
| Principal Investigator | Participants may complete quality of life questionnaires every 1-2 weeks in cancer RCTs. Doctors and nurses ask participants to complete forms at clinic. Some clinicians reluctant. Resources needed to send reminders. Trial specific questions added to diary cards to fill in gaps in questionnaires returned with missing data. Text messaging or telephone calls to participants to collect QOL data, specialist nurses do this rather than trial nurses, high response. | Developed countries | Cancer |
| Principal investigator | Little loss to follow-up from phase II RCTs – usually shorter length of follow-up Participants should be asked to take responsibility for being followed-up; commitment to research once consented. 10% loss to follow-up built into sample size calculation but not based on evidence. No clear guidance on what to do with data from participants who withdraw data altogether. Long term outcomes can be obtained from Office for National Statistics (ONS). Not so good for evaluating disease progression League tables of recruitment. Give a prize to the unit that wins. Burden of involvement for participants may contribute to loss to follow-up. Attrition rates in RCTs not published enough. Explanation for loss to follow-up would be helpful. Principal investigator (PI) may be unaware of retention strategies used to improve follow-up. May be removed from running of RCT. | Developed countries | Cancer |
| Principal investigator | Find out why participants are dropping out. Then do something about it. Dropout could be for socio cultural reasons. Strategies to increase retention used: involving family members, incentives, food supplements, reimburse travel costs, restrict length of follow-up. More intensive follow-up can lead to low loss to follow-up. Reimburse participants e.g. in South Africa participants have to be reimbursed 150 Rand. Participants may enrol for incentives. Attrition / loss to follow-up poorly reported in papers e.g. one or two lines. Important to report loss to follow-up. | Developing countries | Infections |

| Researcher role | Key points about loss to follow-up in RCTs | Trial setting | Disease area |
|------------------------|--|------------------------------------|----------------------|
| Operations manager | Thought education at site important for site clinicians to create awareness of different ways to reduce loss to follow-up. Loss to follow-up depends on the population group, some groups thought to be more prone to loss to follow-up than others | Developed and developing countries | Infections Cancer |
| Operations manager | Change of address problematic in paediatric RCTs Network of investigators and sites to follow-up participants who move. | Developed countries | Infections |
| Trial Manager | 20 % dropout factored into protocol for HIV RCT in Africa. Healthy volunteers more prone to dropping out. Work with social scientists, community teams and local non-government organisations to highlight barriers to retention in RCTs . | Developing countries | Infections |
| Trial Manager | Retention thought to be related to the social circumstances of participants. Participants move location in developing countries. Change of foster parents of children in RCTs can change consent status if new foster parents do not wish for child to continue to participate. | Developing countries | Infections Cancer |
| Trial Manager | RCT protocols allow loss to follow-up between 30 - 33% Higher in one site due to staff turnover A definition of attrition required. Is it: a) complete loss to follow-up where there is no data provided after the date of withdrawal or b) are people that have withdrawn from treatment but who attend follow-up appointments included? Good relationships between clinician and participant important for retention of participants. Perceived benefit of participation to the participant could be important. Standard operating procedures (SOPs) developed to keep people engaged in RCTs. Reminder letters used. Number of reminders agreed by an ethics committee. | Developed countries | Other diseases |

primary outcome for participants who withdrew from treatment in RCTs. They thought that this was important because missing values can bias RCT results. They also noted that loss to follow-up is poorly reported, and that this is only sometimes reported in the CONSORT diagram of the RCT publication (Moher et al. 2010). They mentioned that an anticipated rate for loss to follow-up was factored into power calculations to determine an adequate sample size for RCT recruitment.

The researchers thought that it was important to ascertain why loss to follow-up was happening and to act on this. Examples were given of some of the social barriers to follow-up such as changes in participant circumstances, for example a change of foster parents for children in paediatric HIV treatment RCTs that may bring about a change in consent to participate. The researchers also mentioned that involving other family members to support RCT participants during follow-up helped to improve retention. For RCTs conducted in developing countries, collaborations were forged locally with non-government organisations and centrally with experts in sociology to try to identify culturally appropriate ways to control losses to follow-up.

Most of the incentive strategies mentioned were used in the context of developing country RCTs. These included giving food supplements, or reimbursing travel costs. Some methodology strategies were mentioned e.g. restricting the length of follow-up. Most of the different communication strategies mentioned were used in developed country RCTs.

1.7.1. HOW THE FEASIBILITY STUDY INFORMED THE MAIN STUDY

This short feasibility study demonstrated that there was concern among researchers about loss to follow-up in RCTs. This was primarily because loss to follow-up leads to missing data and can reduce RCT power and precision. However, some researchers reported that loss to follow-up was not a problem in the RCTs that they conduct particularly in the field of cancer treatment where survival is the outcome measured. This is in part because participants tend to return to clinical RCT sites in secondary care settings for cancer monitoring, treatment and RCT follow-up to determine disease progression. Furthermore, mortality data can be obtained from disease registers for time to event outcomes thus reducing the amount of missing / censored data for cancer RCTs.

The researchers used multi-pronged approaches to reduce loss to follow-up in RCTs. However, there is no evidence that the retention strategies that they use are effective in RCTs. A Cochrane systematic review of the literature to determine the effectiveness of the strategies to improve retention in RCTs would answer this.

There is also no indication from the feasibility study about the different types of strategies and factors that affect loss to follow-up in other RCT settings for example in RCT conducted through primary care. Retaining relatively healthy participants in primary care based RCTs can be more problematic than for RCTs of treatments for terminal illnesses. RCTs conducted through primary care GP practices can span several population groups and disease areas including for example; dependency, musculoskeletal disorders, mental health, gynaecology, cardiovascular and neurology. Loss to follow-up can range from 8-37% depending on the disease area and the population group (Dennis et al. 2000, Hall et al. 2007). The reasons for such high losses to follow-up may be because participants are relatively healthy compared to participants in RCTs conducted through secondary care but there may be other contributing factors.

Because of the range of diseases and population groups seen by clinicians in primary care, many different strategies may be used to retain participants in RCTs conducted in this setting. However, to date, these have not been well documented. Graffy (2009) identified factors that are important to researchers for successful recruitment and retention in UK primary care research. As that study was not specifically about strategies to improve retention in primary care RCTs more information is needed about the use of strategies to improve retention in RCTs conducted in UK primary care settings. The results of such a study would also help to explain the results of a systematic review of the effectiveness of retention strategies used in RCTs.

This feasibility study demonstrated that it was possible to recruit and interview researchers who were in general keen to discuss loss to follow-up and ways to overcome this. The feasibility study also provided a greater understanding of loss to follow-up and the multiple efforts made to reduce this in RCTs. It informed the methods for the Cochrane systematic review, notably the search strategies which are reported in Chapter 2 of this thesis, and also informed the design of the qualitative study reported in Chapter 5.

1.8. THESIS AIMS AND OBJECTIVES

It is clear from the feasibility study and the literature, that loss to follow-up can compromise the validity of RCT findings, delay results, and increase research costs. It is also clear that there is a gap in the knowledge concerning the effectiveness of the strategies used to improve retention in RCTs. Therefore, the overarching aim of this thesis is:

To establish the effectiveness and use of strategies to improve retention in RCTs, and to provide guidance for the use of these in future RCTs.

A protocol for the project is provided in Appendix 10. Mixed methods were used to establish the effect and use of strategies to improve retention and to provide guidance for the future use of retention strategies in RCTs. The methods used were:

1. A systematic review of the literature and meta-analysis to describe and quantify the effectiveness of strategies to improve retention in RCTs.
2. A qualitative study based on a series of in-depth interviews with members of UK primary care research teams to explore the strategies used to improve retention in primary care RCTs.
3. Consensus development workshops to develop best practice guidance for the future use of strategies to improve retention in RCTs.

A Cochrane systematic review methodology was chosen to identify and synthesise all published and unpublished literature on the effectiveness of the strategies used to improve retention in RCTs. In-depth interviews were chosen for the qualitative study because these can facilitate a deep exploration of a topic, in this instance the retention strategies used. The in-depth interviews will help provide a better picture of the complexity of retaining participants in primary care RCTs than structured interviews (Denzin et al. 1994) and will also help to identify any potential barriers to implementing the results of the systematic review.

Therefore the specific objectives of my thesis were:

1. To identify the retention strategies that have been evaluated in RCTs.
2. To determine if the strategies that have been evaluated are used to improve retention in primary care RCTs.
3. To identify barriers to the use of strategies to improve retention in primary care RCTs.
4. To identify retention strategies for further evaluation in RCTs.
5. To make recommendations for the use of effective strategies to improve retention in RCTs.

The work for my PhD was undertaken between 2009 - 2013 as part of a cross unit project between three MRC (Medical Research Council) units; GPRF (General Practice Research Framework), MRC SPHRU (Social and Public Health Research Unit) and CTU (Clinical Trials Unit). The project was funded by the MRC Population Health Sciences Research Network.

1.9. MY ROLE IN THE PROJECT

I was the research fellow on the retention in RCTs project between Jan 2009- March 2012. Three groups were established to oversee the project:

1. **The project group** included two PhD supervisors Dr Greta Rait (GR) (MRC GPRF) and Prof Sally Stenning (SS) (MRC CTU). Dr Jayne Tierney (JT) (MRC CTU meta-analysis unit) was also a member of this group.
2. **The qualitative study group** included two PhD supervisors Dr Greta Rait and Dr Fiona Stevenson (FS) (UCL Primary Care and Population Health). Dr Claire Vale (CV) (MRC CTU meta-analysis unit) was also a member of this group.
3. **The management group** oversaw both the project group and the qualitative study group. This group included all the members of the qualitative and project groups and Dr Sarah Meredith (MRC CTU), Prof Irwin Nazareth (MRC GPRF), and Prof Seeromanie Harding (MRC SPHRU).

I led the meetings for all groups.

Cochrane systematic review of the effect of strategies to improve retention in RCTs

I wrote the protocol for the systematic review with comments from all members of the management group. I designed and conducted the searches with advice from Dr Jayne Tierney. I screened all of the abstracts generated by the searches, and any full papers of potentially eligible RCTs for eligibility. Potentially eligible RCT papers were also screened independently by Dr Greta Rait. I designed the data extraction and screening forms with input from Dr Jayne Tierney, and Prof Sally Stenning. The data extraction was conducted by myself and checked independently by Dr Jayne Tierney. I developed the analysis plan with Dr Jayne Tierney with additional statistical advice from Prof Sally Stenning. I conducted the analysis with comments on interpretation of results from Dr Jayne Tierney, Dr Greta Rait, Prof Sally Stenning, and Prof Irwin Nazareth.

Qualitative study to determine the use of strategies to improve retention in primary care RCTs

I wrote the proposal for the qualitative study and obtained ethics approval from UCL ethics committee. I designed the participant information sheet, consent form, and topic guide with comments from Dr Fiona Stevenson, Prof Sally Stenning, and Prof Irwin Nazareth. I recruited and interviewed all of the interviewees. The tape recorded interviews were transcribed by a MRC approved transcription service. I checked and

anonymised the transcripts. I conducted the analysis with comments on interpretation by Dr Fiona Stevenson and Dr Claire Vale.

Consensus study to develop best practice guidance for retention in RCTs

I arranged and chaired the consensus development workshops. I prepared the abstract that was used to advertise the workshops. I also prepared and delivered the presentation of the results of the systematic review and the qualitative study at each consensus workshop. I organised the group discussions at each workshop and analysed the consensus discussion notes and transcripts.

1.10. THESIS OUTLINE

In Chapter 1, I have given an introduction to the types of strategies used to improve retention in RCTs and I have critiqued existing reviews of the literature on retention in research. I have identified gaps in the knowledge about the effectiveness and use of strategies to improve retention in RCTs, identified potential barriers to conducting nested RCTs and I have ascertained that it will be feasible to recruit and interview researchers about the ways to improve retention in RCTs. In Chapter 2, I describe the methods used to conduct a Cochrane systematic review of the literature on strategies to improve retention in RCTs. This includes formulating the research question and designing the search strategies. The method of data extraction and assessment of risk of bias for included RCTs are also described. In Chapters 3 and 4, the results of the searches and meta-analyses of included RCTs are presented. The methods used to identify and interview researchers from RCTs conducted in primary care for the qualitative study are described in Chapter 5. The results of the qualitative study are presented in Chapter 6. In Chapter 7 the methods and results of the best practice guidance consensus workshops are presented. Finally, in Chapter 8, a discussion of the implications of the results is presented with conclusions and recommendations for future research based on the findings.

CHAPTER 2: SYSTEMATIC REVIEW METHODS

2.1. INTRODUCTION

In Chapter 1 (section 1.1) we saw that RCTs are the gold standard for evaluating the effectiveness of different social and healthcare interventions. To establish the consistency of the findings of RCTs, the findings can be integrated in systematic reviews to examine the generalizability of results to other populations (Mulrow 1994). Systematic reviews conducted by the Cochrane collaboration aim to identify and synthesise all published and unpublished literature on a given topic in an unbiased way. Cochrane methodology reviews are different to disease specific reviews conducted by the collaboration. Rather than focus on a particular disease or treatment, Cochrane reviews of methodology studies focus on the effect of methods used in the conduct of RCTs and meta-analyses of health care evaluations (The Editorial Team.Cochrane Methodology Review Group. 2011). These reviews may encompass different disease areas and may or may not have wide applicability.

In this chapter, the methods underpinning the Cochrane systematic review of the literature to examine the effect of strategies to improve retention in RCTs are described. This includes the aim of the review, a description of the development of the research question, the type of RCTs included, and how these were identified and screened for eligibility. The data extraction process and data analysis plan are also described.

2.2. DEVELOPMENT OF THE COCHRANE SYSTEMATIC REVIEW PROTOCOL

For any Cochrane systematic review, a protocol defining the research problem is prepared in a prescribed format facilitated by the RevMan5 (Review Manager) program and published by the Cochrane library. In the protocol, the intervention/s and how these might work are explained, and objectives and methods for the review are outlined (Green et al. 2008a). The protocol for this review was published by the Cochrane Methodology Group in 2011 (Bructon et al. 2011), see Appendix 7.1.

2.3. REVIEW AIM

The aim of the Cochrane systematic review was to examine the effectiveness of strategies to improve retention in RCTs.

2.4. DEVELOPMENT OF THE RESEARCH QUESTION

For all Cochrane systematic reviews a clear research question is to be formulated to underpin the search strategy. This helps to identify relevant studies, prevent bias and to plan the data for extraction from each RCT included in the review (O'Connor et al. 2008). The PICO acronym is used to formulate the research question. This includes the participants, interventions, comparators and outcomes relevant to end users that are to be included in the review.

For our systematic review the participants were from RCTs from any disease area and health care setting. The interventions considered for evaluation were strategies to improve retention in RCTs. The comparators were other strategies to improve retention or usual follow-up procedures in RCTs and the outcome was retention, which was defined as the proportion of patients retained in the RCT at the time point(s) of interest.

Cochrane review questions are stated as precise statements of the primary objective of the review. Therefore the primary objective for this review was:

To assess the effects of strategies to reduce attrition¹ compared with other strategies or usual follow- on RCT retention in RCTs.

This question was broad, which has the advantage of being comprehensive and generalisable. However, broad systematic reviews are time consuming, often costly, and can be difficult to interpret due to heterogeneity between studies (Counsell 1997). For this reason, subgroup analysis to explore heterogeneity was built into the analysis plan (see section. 2.11.2 Subgroup analysis). The research question was registered as a title with the Cochrane Methodology Group in April 2009 as the protocol was being developed.

2.5. INCLUDED STUDIES

The research question was designed to focus on strategies to reduce attrition / improve retention in RCTs. Similar types of strategies can be used to improve retention in observational studies, for example, giving incentives or providing extra information to participants (Booker et al. 2011, Edwards et al. 2009). However, reasons for loss to follow-up from cohort studies and surveys could differ from the reasons for loss to follow-up from RCTs. In RCTs, for participants with a medical condition requiring treatment, the motivation to comply with RCT follow-up may differ from the motivation to comply with

¹ The title registered with the Cochrane Methodology group in April 2009 was: "Strategies to reduce attrition in randomised trials". This was changed to "Strategies to improve retention in randomised trials" in response to peer reviewers comments on the review in December 2012.

observational study follow-up. This could be affected by the participants' treatment allocation, particularly if they were not allocated to their preferred choice of treatment. Therefore, strategies that improve retention in cohort studies and surveys may not be suitable to increase follow-up in RCTs. As a result, in this review only completed randomised or quasi randomised RCTs evaluating strategies to improve retention (retention RCTs) which were embedded within RCTs (host RCTs) were included.

The retention RCTs had to include at least one randomised comparison of either one or more strategies to improve retention, or compare one or more strategies with no strategy or usual follow-up procedures. Strategies should have been designed for use or impact after participants were recruited and randomised to either the intervention or the control arm of the host RCT.

For the embedded retention RCT to be included in the review the host RCT had to be fully randomised as a measure of quality and not quasi randomised. Quasi randomised RCTs were defined as RCTs where the method of allocation was not strictly random, for example the use of alternation, date of birth or case record number as a method of allocating participants (Lefebvre et al. 2008). Quasi randomised retention RCTs were included to maximise the number of comparative studies identified as it was anticipated these would be few because of the potential barriers of conducting and reporting such RCTs. RCTs from all disease areas and health care settings including primary, secondary, tertiary, and long term care were included. Participants from all age, gender, ethnic, and cultural groups were also included, as were RCTs conducted in all languages and set in different geographical areas.

2.6. EXCLUDED STUDIES

Retention RCTs embedded in cohort studies were excluded from the review primarily because they did not meet the inclusion criteria and also because these were the subject of a separate systematic review by Booker and colleagues (See Chapter 1 section 1.5) (Booker et al. 2011).

2.7. SEARCHES

2.7.1. ELECTRONIC SEARCHES

A preliminary literature search and the meetings with researchers identified several strategies used to improve retention (Chapter 1 sections 1.2. and 1.7.). Any combination of strategies to improve retention and directed toward the clinician, researcher or participant could be included in the review. The retention strategies could be compared to

each other or to usual RCT follow-up procedures. Other retention strategies identified during the review process could also be included. The strategies identified a priori were divided into participant focused and management focused strategies as follows:

Participant focused strategies:

1. Motivational strategies, for example monetary incentives or gifts (Eakin et al. 2007, El Khorazaty et al. 2007, Furimsky et al. 2008, Senturia et al. 1998), provision of medical test results (Loftin et al. 2005), and reimbursement for research expenses (Robinson et al. 2007).
2. Communication strategies, for example personalised letters, anniversary and birthday cards (Goldberg et al. 2005).
3. Social strategies, for example provision of child friendly facilities at follow-up centres and/or support with child care while participants were being followed up (Loue et al. 2008).
4. Methodological strategies for example, adjustments to the frequency and duration of follow-up visits (Costenbader et al. 2005, Schulz et al. 2002).

Management focused strategies to encourage sites to improve retention:

1. Site specific reports on study activities (El Khorazaty et al. 2007, Senturia et al. 1998).
2. Training for trial specific staff at site (Davis et al. 2002).

The bibliographic search strategy was designed to identify all published and unpublished RCTs that assessed strategies to improve retention in RCTs in health care, education, and social science settings (see Appendix 1.4 for terms searched). When building the searches to be used for the bibliographic databases, the terms used to describe retention were: “retention”, “follow-up” and “compliance”. Because authors could have reported attrition rather than retention, the terms “attrition”, “dropout” and “withdrawal” were also included. The terms “improve”, “promote”, “maximise”, and “encourage”, were combined with the term “retention”. Terms used to control “attrition” were also used e.g. “minimise”, “decrease”, “prevent”, “lessen”, and “reduce”. The Boolean term “ADJ2” was used to combine terms to identify potentially eligible RCTs with both terms within two words of each other in the title or abstract, for example ways to “minimise” RCT “attrition” (Lefebvre et al. 2008). All of the search terms identified were agreed with the management and project groups.

Free text search terms were combined with a search filter to identify RCTs in MEDLINE, EMBASE, PsychINFO, CINAHL, and ERIC databases (Lefebvre et al. 2008). The search

syntax was tailored for each database depending on the syntax recommended. To avoid very large numbers of non-relevant abstracts and titles, the sensitivity and precision maximising search filter specific to each database was used, as recommended by the Cochrane Collaboration (Lefebvre et al. 2008). For MEDLINE this was the sensitivity and precision maximising search filter described in the Cochrane handbook (Lefebvre et al. 2008). For EMBASE, the sensitivity and specificity maximising search filter described by Wong was applied (Wong et al. 2006a), and for CINAHL the best optimisation of sensitivity and specificity filter also described by Wong 2006 was used (Wong et al. 2006b). No language restrictions were applied to the searches. All the electronic databases searched are listed in Table 4.

Table 4 Databases searched

| Database | Search platform | Initial search date | Search update date |
|--|--|------------------------|--------------------|
| MEDLINE | OVID | 1950 to April 2009 | May 2012 |
| PreMEDLINE non-indexed citations | OVID | 1950 to April 2009 | Not updated |
| EMBASE | OVID | 1980 to April 2009 | May 2012 |
| PsycINFO | OVID | 1806 to April 2009 | May 2012 |
| Database of Abstracts of Reviews of Effects (DARE) | The Cochrane Library | Searched to April 2009 | May 2012 |
| Cochrane Central Register of Controlled Trials | Cochrane CENTRAL | Searched to April 2009 | May 2012 |
| CINAHL (Cumulative Index to Nursing and Allied Health) | EBSCOHost | 1981 to April 2009 | May 2012 |
| Campbell Collaboration's Social, Psychological, Educational and Criminological Trials Register (C2-SPECTR) | http://geb9101.gse.upenn.edu/; | Searched to April 2009 | Not updated |
| Education Resource Information Centre (ERIC) | Dialog Datastarweb | 1966 to April 2009 | Not updated |

A number of changes to the search strategy were made both in response to the peer reviewers' feedback on the review protocol submitted to the Cochrane Methodology group, and also in response to our experiences of conducting the initial searches. Because the searches were run while the protocol was being peer reviewed, the initial search conducted was slightly different to the search published in the protocol (Brueton et al. 2011). The initial search did not include the search term "response", this was added to the search update. Most un-truncated "response" search terms were also removed for the search updates because hits relating to "response" were captured by the search term "response*". To reduce the number of references for screening that referred to response to disease treatment, the search term "questionnaire" was added to the search terms "response" or "response*" to make the searches more specific to questionnaire response. The search term "compliance" was removed for the search updates because treatment compliance was not a focus of the review.

The search updates (2009-2012) for EMBASE, MEDLINE and PsycINFO were de-duplicated in OVID. MEDLINE and EMBASE duplicate records were excluded from the

search of the CENTRAL database. C2 Spectre and ERIC searches were not updated from 1.05.2009 because: the URL for the C2-SPECTR website available at: <http://geb9101.gse.upenn.edu/>: was not accessible, and also because the search platform for ERIC changed from Datastarweb to Proquest in December 2011. As the latter limits searches to 10 lines of text the search terms were not modified for those search updates.

2.7.2. OTHER RESOURCES SEARCHED

Reference lists of relevant publications and reviews were hand searched to identify further eligible retention RCTs. In addition, the Current Controlled Trials *metaRegister* of Controlled Trials (*mRCT*) was searched (Current Controlled Trials LTD 2013). This is a register of current, on-going and recently completed RCTs. The register pools together several international RCT sources, for example the International Standard Randomised Controlled Trial Number register (ISRCTN) and ClinicalTrials.gov. In addition, the World Health Organisation (WHO) trials platform which is a network of international clinical trials registers (World Health Organisation 2013) was searched. The Cochrane Methodology Register (CMR), which stores studies relevant to the methods of systematic reviews of healthcare and social interventions (UK Cochrane Centre 2013) was also searched.

The Society for Clinical Trials Annual Conference is the major international conference for those involved in trial conduct methodology. The abstracts of the Society for Clinical Trials meetings from 1980-2012 were searched manually for potentially eligible RCTs. Abstracts for all RCTs conducted through the MRC General Practice Research Framework and MRC Clinical Trials Unit were also screened for eligibility.

2.7.3. SURVEY OF UK CLINICAL TRIALS UNITS

While screening the GPRF database for RCTs to include in the qualitative study sampling frame (see Chapter 5 section 5.3.5.), one potentially eligible retention RCT was identified (Smeeth et al. 2001) which was not identified through the initial search strategy used.

In response to this, and in the hope of identifying other eligible retention RCTs, during April 2010, all 49 clinical trial units in the United Kingdom (UK) (registered and those pending registration) were surveyed by email to identify retention RCTs that were not identified through the other sources searched. A database of contacts was collated from the UKCRN (United Kingdom Clinical Research Network) now the UKCRC (United Kingdom Clinical Research Collaboration) (UK Clinical Research Collaboration 2013). The contact person for each unit was sent a personalised email with:

1. A two page summary protocol outlining the purpose of the Cochrane systematic review and detailing the inclusion / exclusion criteria for eligible retention RCTs.
2. A short personalised reply slip with seven questions. The questions were designed to determine if the unit had potentially eligible RCT/s for inclusion. All seven questions fitted on one side of the A4 reply slip for ease of completion. (Appendix 2.3)

One reminder letter was sent via email to non-responders after three weeks.

2.7.4. SOCIETY FOR CLINICAL TRIALS 2010

As a further means of identifying potentially eligible RCTs outside the UK, the review was advertised at the Society for Clinical Trials 31st conference, Baltimore, USA (May 2010) via a poster describing the methods (Brueton et al. 2010). The message board notice read "Our review needs you!" (Appendix 1.5). During the poster session on the 18.05.2010, business cards, A3 copies of the poster and reply slips similar to the one sent to UK clinical trials units were available for delegates to complete with details of potentially eligible RCTs they may have been engaged with. Although this novel strategy for identifying potentially eligible RCTs generated interest in the review, no new eligible RCTs were identified through the advertisement.

2.8. IDENTIFICATION OF RETENTION RCTs

The Cochrane process for selecting studies was used to assess RCTs for inclusion in the review (Higgins et al. 2008a). The results of the nine database searches were downloaded in units of 1000 abstracts / titles into Microsoft Office Word 2003.

A retention RCT eligibility screening form (Appendix 1.1.) was developed based on the inclusion criteria outlined in section 2.5. of this chapter. This form was used to screen the full paper for inclusion. To be included, retention RCTs had to meet the following criteria:

1. Describe strategies to improve retention in RCTs.
2. Be randomised or quasi randomised.
3. Be embedded in a host RCT.
4. Compare strategies to improve retention, or compare strategies to improve retention with no strategy.

All titles and abstracts were read by me (VB). Potentially eligible titles and abstracts were selected. The full text of all potentially eligible RCTs was sourced from UCL library. Author(s) were contacted directly or The British Library used to source difficult to access papers. Potentially eligible RCTs were reviewed for inclusion by two reviewers (VB, GR).

Disagreements were resolved by discussion with a third reviewer (SS). Where necessary, information was sought from authors of potentially eligible RCTs to clarify eligibility. Potentially eligible RCT papers were logged and tracked on a Microsoft Office 2003 Excel spread sheet to ensure all potentially eligible RCTs were accounted for.

2.9. DATA EXTRACTION

The data extraction form (Appendix 1.2.) was developed based on Cochrane guidelines for data extraction (Higgins et al. 2008a). The review protocol and examples of MRC CTU Meta-analysis unit data extraction forms were used to guide the design of the form. The Cochrane risk of bias tool was incorporated into the data extraction form to assess the validity of each included retention RCT (Higgins et al. 2008). The form summarised data for entry to RevMan 5. It was designed to record data extracted for analysis on the following: the type of retention strategy, when the retention RCT commenced in relation to the host RCT, and the frequency of administration of the retention strategy e.g. how often an incentive was given to participants. The following data were extracted for all included retention RCTs and associated host RCTs.

2.9.1. DATA EXTRACTED FROM RETENTION RCTs

1. Aim.
2. Type of retention or attrition measured: for example questionnaire response, attendance for follow-up appointments, return of biomedical test kits.
3. Definition of retention or attrition used.
4. Number of participants randomised to each retention RCT arm.
5. Number of participants included in the analysis.
6. Number of participants retained in each group.
7. Type of strategy used to improve retention.
8. Primary outcomes. Retention rates at the primary analysis point as defined by each retention RCT, or at the first time point recorded if the primary analysis point was undefined.
9. Secondary outcomes. Retention rates at secondary analysis points.
10. Risk of bias assessment based on the five domains of the Cochrane risk of bias assessment tool i.e. sequence generation, allocation concealment, blinding of participants, selective outcome reporting, and other biases were recorded (Higgins et al. 2008).
11. The CONSORT diagram.

2.9.2. DATA EXTRACTED FROM HOST RCTS

1. Aim.
2. Disease area.
3. Participant inclusion criteria.
4. Randomisation sequence generation.
5. Concealment of sequence generation.
6. Context.
7. Primary and secondary outcomes (to identify the retention RCT outcome for example questionnaire response) including where applicable the time point(s) at which they were assessed.
8. Comparators.
9. Number of participants randomised to each group.
10. Definition of attrition and retention used.

Data extraction was piloted on four eligible retention RCTs that illustrated the complexity and range of both the retention RCT designs and the corresponding host RCT designs included in the review. The pilot exercise was conducted on papers associated with the following RCTs:

1. A 2x2 factorial retention RCT that compared the effectiveness of two different lapel pin types plus an incentive compared with no incentive (Bowen et al. 2000).
2. A host RCT with randomisation to different cervical screening options, and further randomisation in one arm to two different treatment management options (TOMBOLA Group 2009a, TOMBOLA Group 2009b).
3. A cluster randomised host RCT to assess care of patients with whiplash injuries (Gates et al. 2009).
4. A primary care management host RCT comparing computerised templates for the treatment of asthma, diabetes and angina (Tai et al. 1999).

Minor amendments were made to the data extraction form prior to data extraction. These included the addition of a space to record data for multi-armed RCTs, tick boxes for unclear and other categories, and changes to the order of questions in the form.

Data was extracted by myself and checked independently by another project group member (JT). Consensus was reached on any disparities with a member of the project management team (SS).

2.10. RISK OF BIAS ASSESSMENT

Each included retention RCT was assessed against the five domains of the Cochrane risk of bias assessment tool (Higgins et al. 2008). Selection bias was judged by assessing allocation, sequence generation, and methods used to conceal the allocation. Performance bias was assessed at outcome level by recording the methods used to blind participants and researchers. Both data extraction reviewers (VB and JT) judged whether or not it was appropriate to blind participants and researchers to the intervention and outcome, and assessed performance bias in this context. For some strategies to improve retention, participants could not be blinded to the intervention for example when vouchers, cash, or gifts were used. However, they could be blinded to the outcome retention. RCT personnel could also be blinded to the intervention if administration was carried out by a third party unaware of the allocation. Primary and secondary outcomes for the retention RCT i.e. retention, attrition, and response, were used to judge any evidence of selective outcome reporting bias. The number of participants randomised, the number included in the primary analysis and the number retained at the primary analysis point were recorded to give precise estimates of retention based on the numbers randomised to each arm of the retention RCT.

For completed host RCTs, how the randomisation sequence was generated and how the allocation was concealed were assessed to ensure randomisation was adequately preformed. The details were recorded in the risk of bias table for each included retention RCT in the risk of bias assessment tables of the Cochrane review.

2.10.1. MISSING DATA

RCT authors were contacted for information where there was missing data with the potential to bias the review outcome. Individualised letters were sent with up to three reminders (Appendix 1.3.). For non-responders, other authors named on the associated RCT publication were contacted. The outcomes of any retention RCTs with missing data after this process were described qualitatively.

2.11. DATA ANALYSIS

The meta-analyses for the review focused on the primary endpoint of retention (the proportion of participants retained) at the primary analysis point, as defined in each individual retention RCT. This was easier to interpret than attrition i.e. proportion lost. Where the time point for measurement of the primary outcome was not clearly defined in the retention RCT publication, the first time point reported was used for analysis.

As retention is a binary outcome, risk ratios, and their 95% confidence intervals were calculated to determine the effect of strategies on retention. The unit of analysis was the individual for cluster randomised trials that ignored clustering in the analysis and the standard errors (SEs) were inflated as described in the Cochrane handbook 16.3.4. (Higgins et al. 2008b) See Appendix 5.3. for calculations. The effect estimate and the new updated SE were entered into RevMan5 using the generic inverse variance. The Cochrane handbook states that values of less than 0.05 are typical for the intracluster correlation coefficient (ICC). For one retention RCT (Land unpublished) the mean ICC was used for appropriate external estimates. This was the mean of estimates for the return of Euroqol questionnaires (ICC=0.054) from a source recommended by the Cochrane handbook section 16.3.4. (Higgins et al. 2008b) available at URL <http://www.abdn.ac.uk/hsru/documents/iccs-web.xls> (University of Aberdeen 2013). Where the number of participants randomised was not clearly stated in the included retention RCT report, the trial authors were contacted for this information.

2.11.1. ANALYSIS OF FACTORIAL AND MULTI-ARM RCTS

Where possible, data for comparisons in factorial RCTs were divided and each within-stratum comparison labelled (a-h) so that all comparisons could be considered individually in the analysis. This was done for two retention RCTs by Kenton (2007) and Sharp (2006). For a 2x2 factorial RCT, comparing the addition of intervention X and Y to control C, the four strata were:

1. C versus C+X
2. C versus C+Y
3. C+Y versus C+Y+X
4. C+X versus C+Y+X

Comparisons 1 and 3 address the addition of “X” and comparisons 2 and 4 address the addition of “Y”. Where the numbers randomised within each stratum were not available at the time of analysis that is, where only the data from the main effect comparisons were given, the comparison arms were collapsed and treated as separate RCT comparisons in the appropriate analyses. This was the case for the retention RCT by Renfroe (2002).

The individual arms were compared to the relevant control arm to examine the different effects. In factorial RCTs, each participant contributes to more than one randomised comparison and where two or more comparisons of interest lay within the same intervention category (for example different types of non-monetary incentives), inclusion of the same groups of participants more than once leads to in appropriate variance

estimates. To address this (i.e. double counting) it was necessary to collapse the experimental arms so each participant contributed only once in each subgroup. Therefore, for retention RCTs with three and four arms comparing for example different values of incentives with a single control arm, the treatment arms were combined for the main analysis and compared with the control arm to examine the overall effect. Subsequently the individual RCT arms were compared to the control arm to examine the individual effects. The RCT comparisons were labelled a, b, c, etc. to identify the different arms for comparison. This approach was also used for the multi-arm trial by Bowen (2000) because the three incentives used had the same comparator i.e. no incentive see Table 6 Chapter 3 (Bowen et al. 2000). This approach to the analysis of multi armed retention RCTs allowed a complete exploration of the data and also avoided double counting in the main analyses. As a result of this, there are a greater number of RCT comparisons than retention RCTs in the analyses.

For retention RCTs, where retention data was read off a survival curve for example in the three RCTs by Chaffin et al. (2009), Sutherland et al. (1996) and Land (unpublished), the final time point reported was used. The number of participants retained in each RCT arm was then read off the curve. This number was used as the numerator to calculate the proportion retained, the denominator was the number of participants randomised to the specific arm. The data was checked with the retention RCT authors before it was entered into RevMan5 for analysis.

To assess the robustness of the results, sensitivity analyses were conducted with and without quasi randomised trials. Heterogeneity of the intervention effect was measured by the χ^2 statistic at a significance level of 0.10 and the I^2 statistic (Higgins et al. 2003)

2.11.2. SUB GROUP ANALYSIS

The greater than expected diversity of retention RCTs and interventions identified through the searches meant that some of the pre-specified analyses outlined in the original protocol were not possible (Bructon et al. 2011). Therefore the different types of strategies used to increase retention were broadly categorised and new subgroups were defined within these prior to analyses as follows.

Incentive strategies

1. Monetary incentives given up front: were defined as money given to the participant prior to data collection in cheque, cash or voucher format.

2. Offers of monetary incentives: were defined as a promise of the incentive after return of outcome data through attendance for scheduled follow-up at the RCT site or through receipt of follow-up questionnaires.
3. Non-monetary incentives given up front: were defined as gifts for example pens or certificates.
4. Offers of non-monetary incentives: were defined as a promise of the non-monetary incentive after return of outcome data.

Retention RCTs comparing different values of monetary incentives were sub grouped into:

- a) Offers of incentives.
- b) Those giving and then offering an incentive for return of a questionnaire or specimen collection kit.

Communication strategies

Retention RCTs or RCT comparisons of the effect of different communication strategies were grouped into letter, post, and reminder strategies for analysis as follows:

Communication strategies focusing on participants

1. Enhanced versus standard letters.
2. Priority versus regular post.
3. Additional reminders versus usual follow-up procedures.
4. Multiple postal communication strategies e.g. the type of stamp used, the colour of envelope versus standard postal communication strategies.
5. Early versus late administration of questionnaires e.g. sending questionnaires 2-3 weeks after a follow-up visit versus 1-4 months after a follow-up visit.
6. Recorded delivery versus a telephone reminder.
7. Face to face interview versus a postal questionnaire.

Communication strategies focusing on sites

1. Additional reminders versus usual reminders to sites.

For factorial retention RCTs that evaluated both communication and incentive strategies together (e.g. follow-up by telephone versus the addition of a monetary incentive), these strategies were analysed separately.

New questionnaire structure / format

These retention RCTs were sub-grouped into length of questionnaire, clarity of meaning, order of questions and layout, and relevance of the questionnaire to the condition as follows:

1. Short versus long questionnaire.
2. Long and clear questionnaire versus short and condensed questionnaire.
3. Questionnaires with the medical condition questions first versus questionnaires with the generic questions first.
4. Relevance of questionnaires: alcohol versus mental health questionnaires.

In general, each subgroup looked at the addition of a strategy to either standard practice or another strategy. The RCTs that directly compared retention strategies, or looked at the addition of a combination of retention strategies taken from several subgroups, were analysed and reported separately.

The results of the searches are presented in the next Chapter and the results of the meta-analyses are presented in Chapter 4.

Chapter 3: Literature Search Results

3.1. INTRODUCTION

In this chapter the results of the different searches to identify eligible retention RCTs are presented. The methodological quality of each included retention RCT, and the main characteristics of excluded studies are also presented.

To identify retention RCTs that met the inclusion criteria outlined in Chapter 2 (section 2.5.), nine bibliographic databases and three trial registers were searched. Conference abstracts were also searched and the reference lists of relevant papers and included retention RCTs. A survey of UK clinical trials units was also conducted to identify eligible retention RCTs in progress or completed and unpublished to include in the review.

3.2. RESULTS

Twenty four thousand three hundred and four unique records were identified from all the sources searched (see PRISMA flow diagram Appendix 6.2.). From these records, 735 full text papers were screened and 38 eligible retention RCTs met the inclusion criteria. From the 735 full text manuscripts, 169 (23%) were reviewed by two reviewers (VB, GR) and twenty nine (4%) were reviewed by three reviewers (VB, GR, SS). Of the 38 eligible retention RCTs, 28 were published in full, one as an abstract (Kenton et al. 2007). Nine retention RCTs were unpublished one of which was a PhD thesis (Edwards, Svoboda, Letley, MacLennan, Land, Bailey 1, Bailey 2, Marson, Nakash 2007). Four retention RCT publications reported two retention RCTs each (Khadjesari et al. 2011, McCambridge et al. 2011, McColl et al. 2003, Severi et al. 2011). The earliest published retention RCT was from 1989 (Hughes 1989). All included retention RCTs were published in English.

The number of abstracts identified from each source searched is presented in Table 5. The initial database searches were conducted between February and May 2009 and updated to May 2012. A description of the characteristics of the included retention RCTs design, intervention, comparator and the outcomes measured is presented in section 3.3. of this chapter. The characteristics of the participants in each eligible retention RCT together with the disease / condition, intervention and setting of the corresponding host RCT are summarised in Appendix 6.1.

Eleven eligible retention RCTs were identified from three bibliographic data bases; MEDLINE, CINAHL and CENTRAL. Fourteen eligible RCTs were identified by hand searching reviews, conference abstracts, and references lists of eligible papers. Thirteen

eligible RCTs were identified through word of mouth or correspondence with clinical trials units, see Table 5.

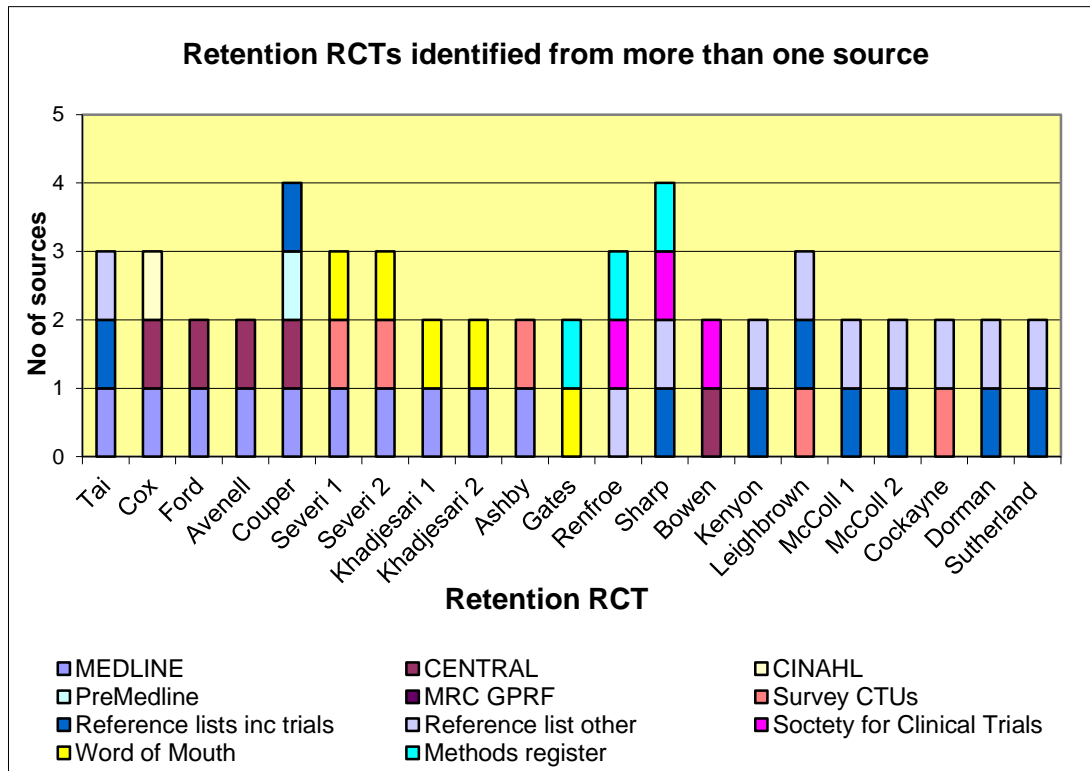
Table 5 Number of abstracts identified by source searched

| Initial search (2009) | | | | Updated search (2012) | | | |
|---|-------------------|-----------------|--|-----------------------|-----------------|--|--|
| Source searched | Number of records | Number screened | Number of unique retention trials included | Number of records | Number screened | Number of new unique retention trials included | Total number of unique retention trials included |
| 9 databases | 13564 | 329 | 8 | 2972 | 25 | 3 | 11 |
| 3 registers | 115 | 0 | 0 | 223 | 20 | 0 | 0 |
| SCT abstracts 1980-2011 | 4048 | 47 | 4 | 781 | 3 | 0 | 4 |
| 25 reference lists of included trials | 669 | 145 | 6 | 39 | 1 | 0 | 6 |
| GPRF database of published trials | 21 | 1 | 0 | 0 | 0 | 0 | 0 |
| 26 Reference lists of reviews and relevant papers | 1828 | 148 | 4 | 1 | - | 0 | 4 |
| Survey of 49 UK CTUs | 16 | 8 | 6 | - | - | 0 | 6 |
| Word of mouth/networking | 8 | 8 | 7 | - | - | 0 | 7 |
| Total | 20269 | 686 | 35 | 4035 | 49 | 3 | 38 |

Twenty one of the 38 eligible RCTs were identified from more than one source, see Figure 1. Two retention RCTs by Sharp (2006) and Couper (2007) were identified through four of the sources searched. Six retention RCTs were identified through three of the sources searched, and thirteen eligible RCTs were identified through two sources.

Nine of the seventeen retention RCTs identified from one source only were unpublished (Edwards, Svoboda, Letley, MacLennan, Land, Bailey 1, Bailey 2, Marson, Nakash) (see Figure 2). Four of these retention RCTs were identified through the reference lists of related systematic reviews (see Figure 2). Three each were identified through the survey of clinical trials units and MEDLINE. The remaining retention RCTs were identified through word of mouth, SCT abstracts, CINAHL or the reference lists of included retention RCTs.

Figure 1 Retention RCTs identified from more than one source

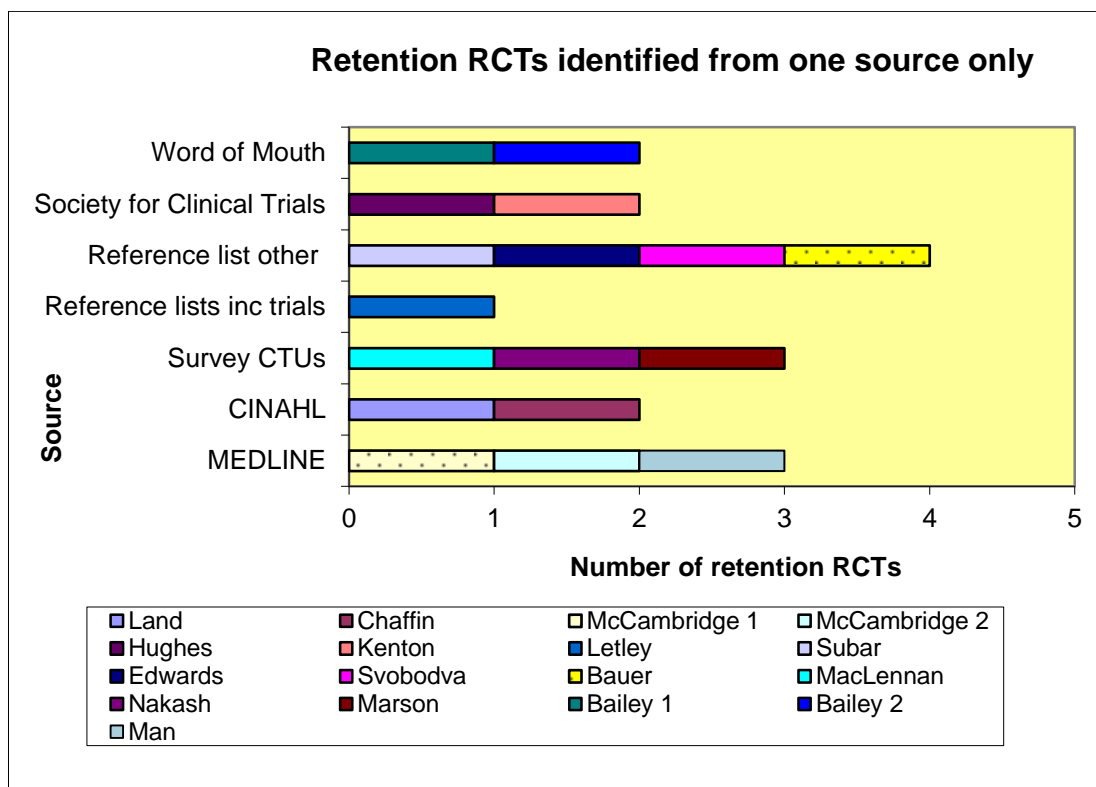


3.2.1. Bibliographic database search results

Eleven eligible retention RCTs were identified from the nine bibliographic databases searched (see Table 5). The initial database searches to April 2009 identified 13,564 records. Three hundred and twenty nine full text papers were screened and eight eligible retention RCTs were identified. Five RCTs were identified through MEDLINE / PreMEDLINE (Avenell et al. 2004, Couper et al. 2007, Cox et al. 2008, Ford et al. 2006, Tai et al. 1997). The PreMEDLINE search returned one duplicate retention RCT (Couper et al. 2007). One retention RCT was identified through CENTRAL, (Bowen et al. 2000) and four duplicate RCTs (Avenell et al. 2004, Couper et al. 2007, Cox et al. 2008, Ford et al. 2006). Two further retention RCTs we identified through CINAHL (Chaffin et al. 2009, Land unpublished) and one duplicate RCT (Cox et al. 2008). Five databases returned no eligible retention RCT. These databases were: EMBASE, PsycINFO, Database of Abstracts of Reviews of Effects (DARE), Campbell Collaboration’s Social, Psychological, Educational and Criminological Trials Register (C2-SPECTR), and Education Resource Information Centre (ERIC). The updated bibliographic searches from 2009 to May 2012 identified 4035 records, 2972 of these records were from database searches. Twenty five papers were screened from the updated searches and three further eligible retention RCTs identified

(Man et al. 2011, McCambridge et al. 2011)². All of these were identified through MEDLINE (see Table 5).

Figure 2 Retention RCTs identified from one source



3.2.2. HAND SEARCH RESULTS

The reference lists of sixteen reviews relevant to the field of retention in research (Davis et al. 2002, Edwards et al. 2004, Edwards et al. 2005, Edwards et al. 2009, Fabricatore et al. 2009, Giuffrida et al. 1997, Heo et al. 2009, Jeffery et al. 2007, McDaid et al. 2006, McFarlane 2007, Nakash et al. 2006, Robinson et al. 2007, Rojas et al. 2005, Sarre et al. 2008, Schellings et al. 2006, van der Bij et al. 2002), and ten papers relevant to retention research (Bruzzese et al. 2009, Burns et al. 2008, Froelicher et al. 2003, Northouse et al. 2006, Rudy et al. 1994, Scott et al. 2006, Warner et al. 1984, Wiemann et al. 2005, Yabroff et al. 2000, Yancey et al. 2006) were searched for potentially eligible retention RCTs. Through these hand searches, four further retention RCTs (Bauer et al. 2004, Subar et al. 2001, Edwards unpublished, Svobodva unpublished), and ten duplicate retention RCTs (Cockayne et al. 2005, Dorman et al. 1997, Kenyon et al. 2005, Leigh-Brown et al. 1997,

² McCambridge (2011) (two trials in one publication)

McColl et al. 2003, Renfroe et al. 2002, Sharp et al. 2006, Sutherland et al. 1996, Tai et al. 1997)³ were identified.

The twenty four reference lists of the 38 included retention RCT papers, including the reference list of one PhD thesis (Nakash 2007), were also searched for eligible retention RCTs. Through this search a further six eligible retention RCTs were identified (Dorman et al. 1997, Kenyon et al. 2005, McColl et al. 2003, Sutherland et al. 1996, Letley unpublished)⁴. Four other RCTs identified through this method were duplicates (Couper et al. 2007, Leigh-Brown et al. 1997, Sharp et al. 2006, Tai et al. 1997).

3.2.3. ABSTRACTS AND CONFERENCE PROCEEDINGS SEARCH RESULTS

The search of the Society for Clinical Trials published abstracts from 1980-2012 identified 4829 abstracts. Among these, 50 papers and abstracts were screened and, four eligible retention RCTs were identified (Hughes 1989, Kenton et al. 2007, Renfroe et al. 2002, Sharp et al. 2006) plus two duplicates (Avenell et al. 2004, Bowen et al. 2000).

3.2.4. RCT REGISTER SEARCH RESULTS

There were no new retention RCTs identified through the searches of the three RCT registers searched i.e. Current Controlled Trials *meta*Register of Controlled Trials (*mRCT*), WHO register of trials, and the Cochrane Methodology register. Three duplicate retention RCTs already included in the review were identified through the Cochrane Methodology register (Gates et al. 2009, Renfroe et al. 2002, Sharp et al. 2006).

3.2.5. OTHER SOURCES SEARCHED

Seven retention RCTs were identified through word of mouth (Gates et al. 2009, Khadjesari et al. 2011, Severi et al. 2011, two trials by Bailey unpublished)⁵. Twenty one RCTs from the MRC GPRF database were screened for eligibility. No new eligible RCTs were identified through this source.

3.2.6. UK CLINICAL TRIALS UNITS SURVEY RESULTS

Sixty nine per cent (n=34) of the 49 UK clinical trials units responded to the survey. Twenty two (45%) units responded to the initial mail-out and 12 (24%) to a reminder.

³ McColl (2003) (Two trials in one publication)

⁴ McColl (2003) (Two trials in one publication)

⁵ Severi (2011) trials 1 and 2, Khadjesari (2011) trials 1 and 2

Sixteen potentially eligible studies at different stages of progression were identified through the survey. These included:

1. Published studies.
2. Studies in progress.
3. Studies planned.
4. Completed studies not published with no intention to publish.
5. Studies in analysis with an intention to publish.

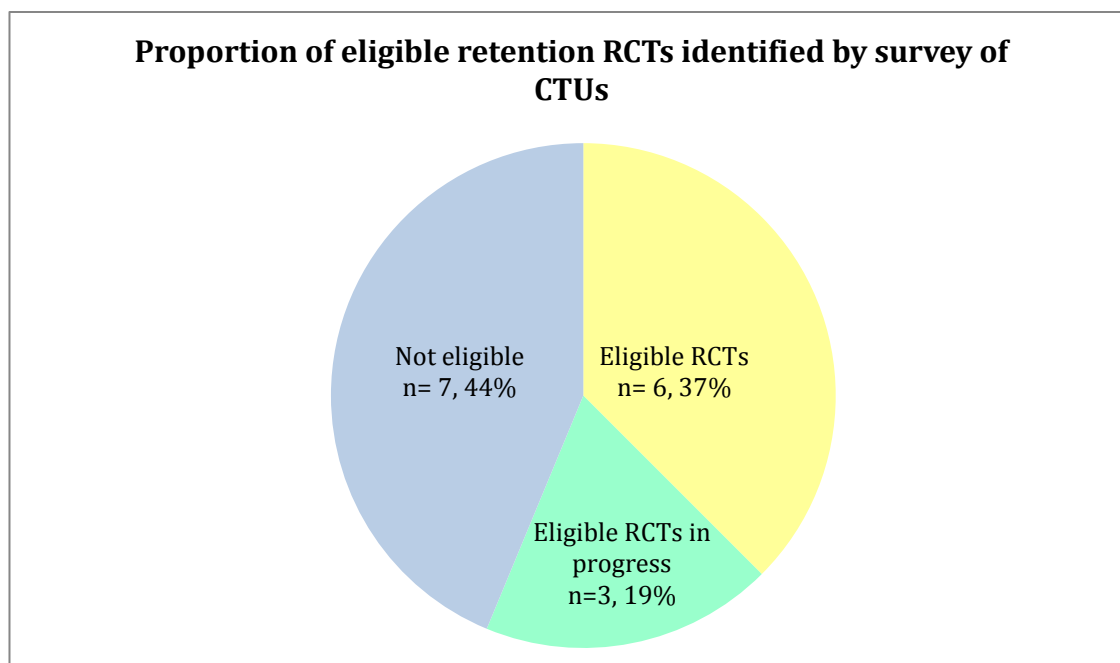
All studies identified through the survey focused on response to postal or electronic questionnaires. For published studies, full text papers were screened for eligibility. For unpublished studies the principal or chief investigator was contacted for response / retention data, details of randomisation, and outcome measures to determine if the study was a retention RCT that met the inclusion criteria for the review.

The proportion of the sixteen studies identified through the survey and considered eligible for inclusion in the systematic review is presented in Figure 3. Six retention RCTs not previously identified through other sources were eligible for inclusion from the 16 studies identified. These were: one completed unpublished RCT (MacLennan unpublished), one RCT then in press but published since (Ashby et al. 2011); one PhD thesis (Nakash 2007), one appendix to a Health Technology Assessment (HTA) report (Marson unpublished) and two published papers (Cockayne et al. 2005, Leigh-Brown et al. 1997). The hand searches of the reference lists of published reports of included RCTs identified by the survey identified two further unique retention RCTs (McColl et al. 2003)⁶. Furthermore, two other retention RCTs already identified through word of mouth were identified through the survey (Severi et al. 2011)⁷, and one on-going RCT by Mitchell which will be included in a review update.

⁶ McColl (2003) trials 1 and 2

⁷ Severi (2011) trials 1 and 2

Figure 3 Results of survey of CTUs



3.3. CHARACTERISTICS OF INCLUDED RETENTION RCTs

The 38 eligible retention RCTs evaluated six broad types of retention strategies. The most common strategies to be evaluated were incentives with 14 RCTs and 19 RCT comparisons (Bauer et al. 2004, Bowen et al. 2000, Cockayne et al. 2005, Gates et al. 2009, Hughes 1989, Kenton et al. 2007, Kenyon et al. 2005, Khadjesari et al. 2011, Leigh-Brown et al. 1997, Renfroe et al. 2002, Sharp et al. 2006, Bailey unpublished, Bailey unpublished)⁸, and communication strategies, again with 14 RCTs and 20 RCT comparisons (Ashby et al. 2011, Couper et al. 2007, Kenton et al. 2007, Man et al. 2011, Renfroe et al. 2002, Severi et al. 2011, Sharp et al. 2006, Sutherland et al. 1996, Tai et al. 1997 Nakash 2007, Land unpublished, MacLennan unpublished, Marson unpublished)⁹. Four retention RCTs used factorial designs to evaluate different combinations of both incentives and communication strategies (Kenton et al. 2007, Renfroe et al. 2002, Sharp et al. 2006, Bowen, 2000). New variations in the format of follow-up questionnaires were evaluated in eight retention RCTs (Dorman et al. 1997, McCambridge et al. 2011, McColl et al. 2003, Subar et al. 2001, Edwards unpublished, Svobodva unpublished, Letley unpublished)¹⁰. One retention RCT evaluated case management (Ford et al. 2006) and

⁸ Khadjesari (2011) trials 1 and 2

⁹ Severi (2011) trials 1 and 2

¹⁰ McColl 2003 trials 1 and 2; McCambridge (2011) trials 1 and 2.

another evaluated a methodology strategy (Avenell et al. 2004). Two further retention RCTs evaluated behavioural strategies (Chaffin et al. 2009, Cox et al. 2008).

Twenty two host RCTs included a single retention RCT each (Boyd et al. 1992, Chaffin et al. 2009, Cooke et al. 2009, Cox et al. 2008, Dennis et al. 2009, Gail et al. 1992, Hughes et al. 1984, International Stroke Trial Collaborative Group 1997, Kenyon et al. 2001a, Kenyon et al. 2001b, Lamb et al. 2007, Leigh-Brown et al. 2001, Marson et al. 2007, Omenn et al. 1996, Porthouse et al. 2005, Rothert et al. 2006, Tai S et al. 1999, The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators 1997, Tilbrook et al. 2011, TOMBOLA Group 2009a, TOMBOLA Group 2009b, UK BEAM Trial Team 2004). Host RCTs associated with retention RCTs by Ashby (2011), Land (unpublished) and Bailey were unpublished at the time this thesis was submitted.

Several host RCTs had more than one nested retention RCT. There were two embedded retention RCTs in each of the following host RCTs:

- The US based Prostate, Lung, Colorectal, Ovarian, PLCO screening trial (Buys et al. 2005) included two eligible retention RCTs that evaluated case management (Ford et al. 2006) and questionnaire format i.e. long and clear versus short and condensed questionnaires (Subar et al. 2001).
- The RECORD fracture prevention trial (The RECORD Trial Group 2007) included two retention RCTs that evaluated an additional telephone reminder (MacLennan unpublished) and a methodology strategy which compared a blind versus open trial design (Avenell et al. 2004).
- The CRASH trial (CRASH trial collaborators 2004) included two unpublished eligible retention RCTs by Edwards and Svobodva that evaluated questionnaire length.
- The “Txt2Stop” smoking cessation trial (Free et al. 2011) included two retention RCTs by Severi (2011)¹¹ that evaluated different additional telephone and fridge magnet reminders.
- The COGENT trial (Eccles et al. 2002) included two retention RCTs by McColl (McColl et al. 2003). These evaluated the effect of question order on questionnaire response.

Two further retention RCTs nested in the “Sex unzipped” website feasibility RCT (unpublished) assessed incentives (Bailey 1 unpublished, Bailey 2 unpublished).

¹¹ Severi (2001) (two trials one publication)

Of the four included retention RCTs embedded in the “Down your Drink” host RCT (Murray et al. 2007) two evaluated incentives (Khadjesari et al. 2011)¹² and a further two evaluated the length and relevance of questionnaires (McCambridge et al. 2011)¹³.

3.3.1. DESIGN OF INCLUDED RETENTION RCTS

Different RCT designs were used to evaluate strategies to improve retention. One retention RCT was a cluster RCT (Land unpublished). Four retention RCTs used factorial designs. Two of these were 2x2 factorial designed RCTs (Kenton et al. 2007) (Bowen et al. 2000), one was a 2x2x2 design (Sharp et al. 2006), and a more complex 2x2x2x2 RCT (Renfroe et al. 2002). One retention RCT was three armed (Bauer et al. 2004). Three retention RCTs were four armed (Khadjesari Z et al. 2011, McCambridge et al. 2011)^{14,15}. Five retention RCTs used quasi randomisation to allocate participants (Bowen et al. 2000, Ford et al. 2006, Gates et al. 2009, McColl et al. 2003)¹⁶. Of the quasi randomised retention RCTs, two used participant identification numbers (Ford et al. 2006, Gates et al. 2009), two allocated the first half of a simple random sample of patients to receive one version of a questionnaire McColl (2003)¹⁷, the remaining half was allocated to version two of the questionnaire, and one used the day of clinic visit to randomise participants (Bowen et al. 2000). All included retention RCTs apart from one targeted individual participants. One retention RCT targeted sites (Land unpublished).

The timing of randomisation in the host RCT versus the retention RCT was also recorded. Twenty nine retention RCTs commenced during follow-up for the host RCT (Ashby et al. 2011, Avenell et al. 2004, Bowen et al. 2000, Cockayne et al. 2005, Couper et al. 2007, Cox et al. 2008, Dorman et al. 1997, Ford et al. 2006, Gates et al. 2009, Khadjesari et al. 2011, Leigh-Brown et al. 1997, Man et al. 2011, McCambridge et al. 2011, McColl et al. 2003, Renfroe et al. 2002, Severi et al. 2011, Sharp et al. 2006, Subar et al. 2001, Tai et al. 1997, unpublished trials by Edwards, Svoboda, Marson, Bailey 1, Bailey 2, MacLennan, Nakash, Land)¹⁸. Three retention RCTs commenced after the host RCT had finished (Bauer et al.

¹² Khadjesari (2011) trials 1 and 2

¹³ McCambridge (2011) trials 1 and 2

¹⁴ Khadjesari (2011) trial 1

¹⁵ McCambridge (2011) trials 1 and 2

¹⁶ McColl (2003) trials 1 and 2

¹⁷ McColl (2003) trials 1 and 2

¹⁸ McCambridge (2011) trial 2;Khadjesari (2011) trial 2;Severi (2011) trials 1 and 2;McColl trials 1 and 2

2004, Hughes 1989, Kenyon et al. 2005). For these RCTs, the outcome in the retention RCT was related to the outcome for the host RCT. One retention RCT started before the host RCT commenced (Chaffin et al. 2009). Four retention RCTs commenced during the pilot RCT for the host RCT (Khadjesari et al. 2011, McCambridge et al. 2011, Sutherland et al. 1996, Letley unpublished)¹⁹. For one retention RCT published as an abstract, it was unclear when the retention RCT commenced in relation to the host RCT (Kenton et al. 2007).

3.3.2. PARTICIPANTS AND SETTINGS

Included retention RCTs were embedded in host RCTs conducted from a range of geographical and clinical settings (Appendix 6.1.). Twenty five retention RCTs were UK based. Of the UK based retention RCTs, ten associated host RCTs recruited participants through secondary health care facilities (Avenell et al. 2004, Dorman et al. 1997, Gates et al. 2009, Kenyon et al. 2005, Leigh-Brown et al. 1997, Sharp et al. 2006, and unpublished trials by Nakash, Edwards, Marson, MacLennan). Six RCTs recruited participants through GP practices (Cockayne et al. 2005, Man et al. 2011, McColl et al. 2003, Tai et al. 1997, Letley unpublished)²⁰. One recruited participants solely via the community through a disease specific organisation and a newsletter (Ashby et al. 2011). Two RCTs used a combination of recruitment through GP practices and the media (Severi et al. 2011)²¹. Six RCTs recruited participants via the internet (Khadjesari et al. 2011, McCambridge et al. 2011)²² (Bailey 1 unpublished, Bailey 2 unpublished).

Nine included retention RCTs were USA based (Bauer et al. 2004, Bowen et al. 2000, Chaffin et al. 2009, Couper et al. 2007, Ford et al. 2006, Hughes et al. 1984, Renfroe et al. 2002, Subar et al. 2001, Land unpublished). Of those, two associated host RCTs recruited participants directly from the community (Bauer et al. 2004, Chaffin et al. 2009). Five associated host RCTs recruited through secondary care facilities (Couper et al. 2007, Ford et al. 2006, Renfroe et al. 2002, Subar et al. 2001, Land unpublished). One associated host RCT recruited participants through a combination of state workers compensation programs, occupational medicine and physician clinics, a surveillance program and union records (Bowen et al. 2000). For one US based smoking cessation host RCT it was unclear how the participants were recruited (Hughes 1989).

¹⁹ Khadjesari et al (2011) trial 1; McCambridge et al (2011) trial 1

²⁰ McColl et al (2003) trials 1 and 2

²¹ Severi et al (2011) trials 1 and 2

²² Khadjesari et al (2011) trials 1 and 2; McCambridge et al (2011) trials 1 and 2

The associated host RCTs for two Canadian retention RCTs recruited through community public health nurses (Kenton et al. 2007) and hospital clinics (Sutherland et al. 1996). One RCT was conducted in the Czech Republic where the participants were recruited through hospital records (Svoboda unpublished). One Australian RCT recruited participants through the community (Cox et al. 2008).

The retention RCTs were embedded in host RCTs of different disease treatments. Eight included retention RCTs were embedded in host RCTs for treatment of alcohol and smoking dependency (Bauer et al. 2004, Hughes 1989, Khadjesari et al. 2011, McCambridge et al. 2011, Severi et al. 2011)²³. Four were embedded in host RCTs investigating treatments for injuries (Gates et al. 2009, unpublished trials by Nakash, Edwards, Svoboda). A further six retention RCTs were set in disease treatment RCTs for cancers, cardiovascular disease, epilepsy, and back pain (Dorman et al. 1997, Man et al. 2011, Renfroe et al. 2002, unpublished trials by Land, Marson, Letley). Four retention RCTs were embedded in screening RCTs for cancers, and post natal depression (Ford et al. 2006, Kenton et al. 2007, Sharp et al. 2006, Subar et al. 2001). Six retention RCTs were embedded in disease prevention RCTs. These included two cancer prevention RCTs for lung and breast cancer (Bowen et al. 2000, Sutherland et al. 1996), one migraine prevention RCT (Ashby et al. 2011) and three fracture prevention RCTs (Avenell et al. 2004, Cockayne et al. 2005, MacLennan unpublished). Four retention RCTs were embedded in clinical management RCTs for orthopaedics, asthma, diabetes, and angina (Leigh-Brown et al. 1997, McColl et al. 2003, Tai et al. 1997)²⁴. Six retention RCTs were conducted in other areas, these included: an exercise RCT (Cox et al. 2008), a parenting RCT (Chaffin et al. 2009), a weight management RCT (Couper et al. 2007), a neonatal outcome RCT (Kenyon et al. 2005) and an RCT evaluation of a sexual health promotion website (unpublished Bailey 1 Bailey 2).

3.3.3. TYPES OF FOLLOW-UP

The types of follow-up in included retention RCTs were:

1. Return of questionnaires
 - a. Postal (Gates 2009, Kenyon 2005, Hughes 1989, Cockayne 2005, Leigh-Brown 1997, Tai 1997, Nakash 2007, Sutherland 1996, Ashby 2011, Avenell 2004, Renfroe 2002, Sharp 2006, Kenton 2007, Subar 2001,

²³ Khadjesari et al (2011) McCambridge et al (2011) and Severi et al (2011) trials 1 and 2.

²⁴ McColl et al (2003) trials 1 and 2

Dorman 1997, McColl 2003, Couper 2007 Man 2011, unpublished trials by MacLennan, Marson, Edwards, Svoboda, Letley, Land, Bailey 1)²⁵

- b. Electronic questionnaires (Khadjesari 2011, McCambridge 2011)²⁶.
2. Return of biomedical data (Bauer et al. 2004, Bailey 2 unpublished).
3. A combination of follow-up methods including postal, telephone, and email follow-up (Severi 2011)²⁷.
4. Face-to-face follow-up measuring RCT retention (Bowen et al. 2000, Chaffin et al. 2009, Cox et al. 2008, Ford et al. 2006).

3.3.4. TIME POINTS AND PRIMARY OUTCOMES FOR RETENTION RCTs

Nine retention RCTs specified that the primary outcome was questionnaire response measured at one time point. Both RCTs by Khadjesari (2011) measured questionnaire response within 40 days of the first reminder. McCambridge (2011) (trial 1), measured questionnaire response at 1 month and at 3 months, and McCambridge (2011) (trial 2) measured response at 3 months and 12 months. For Severi (2011) (trial 1), the primary outcome was completed follow-up at 30 weeks from randomisation. For Severi (2011) (trial 2), the primary outcome was return of specimens one month after a telephone call. Avenell (2004) measured questionnaire response at one year. Cockayne (2005) and Sharp (2006) had a primary outcome of final follow-up questionnaire response at any time.

Three retention RCTs reported response or retention at one time point only without specifying a primary outcome for the RCT. Edwards and Svobodva (both unpublished) measured response at three months from a questionnaire being sent, while Ford (2006) measured retention at three years.

Three further retention RCTs recorded retention at two time points without stating which time point was the primary outcome (Cox et al. 2008, Dorman et al. 1997, Gates et al. 2009). Data for the first time point reported was used as the primary outcome for analyses. Another retention RCT reported response at three time points i.e. at 4 weeks, 12 weeks and 9 months (Nakash unpublished). All were stated as the primary outcome. Data for week 4 response was used in the main analysis.

²⁵ McColl (2003) trials 1 and 2

²⁶ Khadjesari (2011) and McCambridge (2011) trials 1 and 2.

²⁷ Severi trial 1

Five retention RCTs reported data in survival curves. For these the final analysis point was used (Ashby et al. 2011, Bowen et al. 2000, Chaffin et al. 2009, Sutherland et al. 1996, Land unpublished). The authors of those RCT papers confirmed the data when it was extracted. Fifteen RCTs reported the number of questionnaires returned with no time point specified (Bauer et al. 2004, Couper et al. 2007, Hughes 1989, Kenton et al. 2007, Kenyon et al. 2005, Leigh-Brown et al. 1997, Man et al. 2011, McColl et al. 2003, Renfroe et al. 2002, Subar et al. 2001, Tai et al. 1997, Letley, MacLennan, Marson unpublished)²⁸.

3.4. THE TYPES OF RETENTION STRATEGIES EVALUATED

3.4.1. INCENTIVES

There were 14 retention RCTs of strategies that evaluated incentives, and 19 RCT comparisons (Table 6). The different types of incentives evaluated and comparators are listed in Table 6. The incentives evaluated were: vouchers, charity donations, entry into prize draws, cheques, offer of study results, certificates of appreciation, and lapel pins. All retention RCTs apart from one in this group targeted questionnaire response. The RCT by Bowen (2000) targeted improving return for follow-up at site. The value of incentives used in UK evaluations ranged from £5-£20. These were distributed in cash or voucher format. The value of incentives used in US based retention RCTs was \$2-\$10. The value of offers of entry into prize draws was higher. These ranged from £25-£250 for UK prize draws, and \$50 for US based draws. One retention RCT evaluated giving a monetary incentive with a promise of a further incentive for return of questionnaires (Bailey trial 2 unpublished).

Table 6 Incentive strategies

| Retention RCT or comparison | Total number randomised | Incentive arms | Control arm | Outcome type | Host RCT disease/ condition |
|---|-------------------------|---|--------------|---|--|
| Addition of incentive vs. no incentive | | | | | |
| Bauer 2004 (ab) USA | 300 | a)\$10 cheque b)\$2 cheque Arms combined for main analysis to avoid double counting | No incentive | Overall DNA specimen kit return and postal questionnaire response | Smoking dependence treatment (Gail 1992) |
| Gates 2009 UK | 2144 | £5 voucher | No incentive | Postal questionnaire response | Neck injury treatment (Lamb 2007) |
| Kenyon 2005 UK | 722 | £5 voucher | No incentive | Postal questionnaire response | Pre-term labour treatment (Kenyon 2001) |
| Addition of offer of monetary incentive vs. no offer | | | | | |
| Khadjesari 2011 (1) (ac) UK web based | 1022 | a)Offer £5 voucher c)Offer entry £250 prize draw Arms combined | No incentive | Web based questionnaire response within 40 days of first email reminder | Alcohol dependence treatment (Murray 2007) |

²⁸ McColl (2003) trials 1 and 2

| Retention RCT or comparison | Total number randomised | Incentive arms | Control arm | Outcome type | Host RCT disease/ condition |
|---|-------------------------|--|--|--|--|
| Khadjesari 2011 (2) UK web based | 2591 | Offer £10 Amazon voucher | No incentive | Web based questionnaire response within 40 days of first email reminder | Alcohol dependence treatment (Murray 2007) |
| Addition of non-monetary incentive vs. no incentive | | | | | |
| Bowen 2000 (abc) USA | 4728 | a)Certificate b)Pin c)Pin and certificate Arms combined for main analysis | No incentive | Trial retention Time from randomisation to first inactivation (stop taking vits or placebo) during PRIDE 2 year follow-up. | Lung cancer prevention (Omenn 1996) |
| Renfroe 2002 (a) USA | 664 | Certificate of appreciation. Cover letter signed by physician or coordinator sent either by express or standard post, 2-3 weeks after last AVID follow-up visit or 1-4 months after last AVID follow-up visit. | No certificate of appreciation. Cover letter signed by physician or coordinator, sent either by express or standard post, 2-3 weeks after last AVID follow-up visit or 1-4 months after last AVID follow-up visit. | Overall postal questionnaire response | Treatment ventricular fibrillation ventricular tachycardia (AVID Investigators 1997) |
| Sharp 2006 (a) UK | 231 | Pen + 1st + stamped return envelope | No pen + 1st + stamped return envelope | Overall postal questionnaire response | Cervical cancer screening (TAMBOLA Group 2009) |
| Sharp 2006 (b) UK | 232 | Pen + 1st + business reply envelope | No pen + 1st + business reply envelope | Overall postal questionnaire response | Cervical cancer screening (TAMBOLA Group 2009) |
| Sharp 2006 (c) UK | 233 | Pen + 2nd + stamped reply envelope | No pen + 2nd + stamped reply envelope | Overall postal questionnaire response | Cervical cancer screening (TAMBOLA Group 2009) |
| Sharp 2006 (d) UK | 234 | Pen + 2nd + business reply envelope | No pen + 2nd + business reply envelope | Overall postal questionnaire response | Cervical cancer screening (TAMBOLA Group 2009) |
| Addition of offer of non-monetary incentive vs. no offer | | | | | |
| Cockayne 2005 UK | 1038 | Offer of study results | No offer | Overall postal questionnaire response | Fracture prevention (Porthouse 2005) |
| Hughes 1989 USA | 100 | Offer free reprint of results | No reprint | Overall postal questionnaire response | Smoking dependence treatment (Hughes 1984) |
| Addition of offer of monetary donation to charity vs. no offer | | | | | |
| Khadjesari 2011 (1) (b) UK web based | 815 | Offer £5 charity donation | No offer | Web based questionnaire response within 40 days of first email reminder after randomisation | Alcohol dependence treatment (Murray 2007) |
| Addition of monetary incentive to both arms | | | | | |
| Bailey (1) unpublished UK | 417 | Offer of £20 shopping voucher | Offer of £10 shopping voucher | Postal questionnaire response | Sexual health promotion (unpublished) |
| Bailey (2) unpublished UK | 485 | Shopping voucher: £10 in advance £10 on data return | Shopping voucher: £5 in advance and £5 on data return | Questionnaire response and chlamydia kit return | Sexual health promotion (unpublished) |
| Addition of monetary incentive vs. offer of incentive | | | | | |
| Kenton 2007 (a) Canada | 147 | \$2 coin + ordinary mail | Draw for \$50 gift voucher + ordinary mail | Postal questionnaire response | Postnatal depression screening (Dennis 2009) |

| Retention RCT or comparison | Total number randomised | Incentive arms | Control arm | Outcome type | Host RCT disease/ condition |
|---|-------------------------|---|---|--|--|
| Kenton 2007 (b) Canada | 150 | \$2 coin + priority mail | Draw for \$50 gift voucher+ priority mail | Postal questionnaire response | Postnatal depression screening (Dennis 2009) |
| Offer of prize draw vs. no offer | | | | | |
| Leigh-Brown 1997 UK | 1307 | Offer of monthly prize draw of £25 gift voucher | No offer of draw | Postal questionnaire response. No data available | Management orthopaedics Leigh-Brown 2001 |

3.4.2. COMMUNICATION STRATEGIES

The different types of communication strategies evaluated and the comparators are listed in Table 7. Methods of communication were evaluated in 14 retention RCTs with 20 RCT comparisons. The strategies evaluated were: telephone reminder (MacLennan unpublished), telephone reminders by a principal investigator (Severi 2011)²⁹, recorded delivery of questionnaires (Tai et al. 1997), calendars with reminders (Nakash 2007 unpublished), SMS text and or email reminders (Ashby et al. 2011). One retention RCT evaluated reminders to sites of upcoming assessments (Land unpublished). Another RCT used a package of postal communication strategies known as the Total Design Method (TDM) (Sutherland et al. 1996). The Total Design Method (TDM) package encompassed sending hand signed letters typed on letter headed note paper, sent in a white envelope with a hospital logo and a commemorative stamp, a reply self-addressed stamped envelope enclosed the contents. This method also included follow-up with a postcard sent after seven days, followed by two further reminder letters. The TDM method was compared to a customary method used for postal follow-up that included a return addressed stamped brown envelope folded and inserted behind the contents. Computer printed labels were attached to the outgoing envelopes. Letters were not signed, and no reminders were sent.

Table 7 Communication strategies

| Retention RCT or comparison | Total number randomised | Communication strategy | Control arm | Outcome type | Host trial disease/ condition |
|--|-------------------------|---|---|---------------------------------------|--|
| Enhanced letter vs. standard letter | | | | | |
| Renfroe 2002(c) USA | 664 | Cover letter signed by physician sent either by express or standard post, with or without a certificate of appreciation 2-3 weeks after last AVID follow-up visit or 1-4 months after last AVID follow-up visit. | Cover letter signed by coordinator sent either by express or standard post, with or without a certificate of appreciation 2-3 weeks after last AVID follow-up visit or 1-4 months after last AVID follow-up visit. | Overall postal questionnaire response | Treatment ventricular fibrillation ventricular tachycardia (AVID Investigators 1997) |

²⁹ Severi (2011) trial 2

| Retention RCT or comparison | Total number randomised | Communication strategy | Control arm | Outcome type | Host trial disease/ condition |
|--|-------------------------|---|---|---|--|
| Marson 2007 UK | 1815 | Letter explaining the approximate length of time to complete questionnaire | Standard letter | Overall postal questionnaire response | Epilepsy treatment (Marson 2007) |
| Total design method vs. customary method | | | | | |
| Sutherland 1996 Canada | 226 | Total design method for postal follow-up | Customary method for postal follow-up | Postal questionnaire response Day 70 response | Breast Cancer prevention (Boyd 1992) |
| Priority vs. regular post | | | | | |
| Sharp 2006 (e) UK | 233 | Pen + 1st class stamp + stamped reply envelope | Pen + 2nd class stamp + stamped reply envelope | Overall postal questionnaire response | Cervical cancer screening (TAMBOLA Group 2009) |
| Sharp 2006 (f) | 231 | No pen + 1st class stamp + stamped reply envelope | No pen + 2nd class stamp + stamped reply envelope | Overall postal questionnaire response | Cervical cancer (TAMBOLA Group 2009) screening (TAMBOLA Group 2009) |
| Sharp 2006 (g) | 240 | Pen + 1st class stamp + stamped reply envelope | Pen + 1st class stamp + business reply envelope | Overall postal questionnaire response | Cervical cancer screening (TAMBOLA Group 2009) |
| Sharp 2006 (h) | 223 | No pen + 1st class stamp + stamped reply envelope | No pen + 1st class stamp + business reply envelope | Overall postal questionnaire response | Cervical cancer screening (TAMBOLA Group 2009) |
| Renfroe 2002 (b) USA | 664 | Express delivery of questionnaire with cover letter signed by physician or coordinator with or without a certificate of appreciation 2-3 weeks after last AVID follow-up visit or 1-4 months after last AVID follow-up visit. | Standard delivery of questionnaire with cover letter signed by physician or coordinator with or without certificate of appreciation 2-3 weeks after last AVID follow-up visit or 1-4 months after last visit. | Overall postal questionnaire response | Treatment ventricular fibrillation ventricular tachycardia (AVID Investigators 1997) |
| Kenton 2007 (c) Canada | 149 | \$2 coin + priority mail | \$2 + standard mail | Overall postal questionnaire response | Postnatal depression screening (Dennis 2009) |
| Kenton 2007 (d) | 148 | Draw for \$50 gift voucher+ priority mail | Draw for \$50 gift voucher + standard mail | Overall postal questionnaire response | Postnatal depression screening (Dennis 2009) |
| Additional communication reminder vs. usual follow-up | | | | | |
| Ashby 2011 UK | 148 | Electronic reminder to return questionnaire i.e. email, or SMS text, or SMS text message plus email on the day the questionnaire was sent | No electronic reminder | Postal questionnaire response Response at 40 days | Migraine prevention (unpublished) |
| MacLennan unpublished UK | 753 | Telephone reminder before receiving first reminder to return questionnaires | No telephone reminder | Overall postal questionnaire response | Fracture prevention (RECORD Trial group 2005) |
| Nakash unpublished UK | 298 | Trial calendar given at recruitment with pre notification on months where participant due a questionnaire. A reminder was posted the following month. | No calendar | Postal questionnaire response at week four | Treatment ankle injury (Cooke 2009) |

| Retention RCT or comparison | Total number randomised | Communication strategy | Control arm | Outcome type | Host trial disease/ condition |
|---|-------------------------|---|---|---|--|
| Severi 2011 (1) UK | 1950 | Text message and fridge magnet both with messages emphasising social benefits of study participation. Fridge magnet sent by post 16 and 20 weeks post randomisation. Text message sent 3 days after text to stop postal follow-up questionnaire sent. | Text message sent 3 days after questionnaire sent reminding participant follow-up questionnaire was due | Postal questionnaire response at 30 weeks | Smoking dependence treatment (Free 2011) |
| Severi 2011 (2) UK | 127 | Telephone reminder from PI inviting participants six weeks over due returning their specimens to complete follow-up | Standard text to stop procedures. No phone call from PI | Return of cotinine samples | Smoking dependence treatment (Free 2011) |
| Man 2011 UK | 125 | SMS text message as follow-up questionnaire sent out | No SMS text message as follow-up questionnaire sent | Overall postal questionnaire response | Treatment Backpain (Tilbrook 2011) |
| Additional site reminder vs. usual reminder | | | | | |
| Land 2007 USA | 429 | Prospective monthly reminder of upcoming assessments to sites | No extra reminder to sites | Postal questionnaire response | Breast cancer treatment (unpublished) |
| Early vs. late administration of questionnaire | | | | | |
| Renfroe 2002 (d) USA | 664 | Questionnaire sent 2-3 weeks after last AVID follow-up visit by express or standard post with cover letter signed by physician or coordinator with or without a certificate of appreciation | Questionnaire sent 1-4 months after last AVID follow-up visit , by express or standard post with cover letter signed by physician or coordinator with or without a certificate of appreciation | Overall postal questionnaire response | Treatment ventricular fibrillation ventricular tachycardia (AVID Investigators 1997) |
| Recorded delivery vs. telephone reminder | | | | | |
| Tai 1997 UK | 192 | Recorded delivery reminder | Telephone reminder | Postal questionnaire response | Asthma / diabetes clinical management (Tai 1999) |
| Addition telephone follow-up vs. incentive | | | | | |
| Couper 2007 USA | 700 | Telephone survey by trained interviewer | Postal questionnaire and \$5 bill | Overall postal questionnaire response | Weight loss management (Rothert 2006) |

3.4.3. COMBINED COMMUNICATION AND INCENTIVE STRATEGIES

Five retention RCTs evaluated a combination of communication strategies and incentives to improve retention in RCTs (Couper et al. 2007, Kenton L et al. 2007, Renfroe et al. 2002, Severi et al. 2011, Sharp et al. 2006)³⁰. The incentives evaluated and the comparators are listed in Tables 6 and 7. The incentives evaluated in combination with communication strategies were: certificates of appreciation for study involvement (Renfroe 2002), study branded pens (Sharp 2006), cash in coin \$2 and notes/bills \$5 (Kenton 2007, Couper 2007), and fridge magnets (Severi 2011). These were combined with: 1st and 2nd class outward post (Renfroe 2002, Sharp 2006, Kenton 2007), stamped and business reply envelopes (Sharp 2006), letters signed by different study personnel

³⁰ Severi (2011) trial 1

(Renfroe 2002), letters posted at different times (Renfroe 2002), telephone data collection (Couper 2007) and text messages (Severi 2011).

3.4.4. NEW QUESTIONNAIRE STRATEGIES

New questionnaire strategies were evaluated in nine retention RCTs. The comparators are listed in Table 8. The different types evaluated were: questionnaire length and the order of questions. Two retention RCTs by McCambridge (2011) evaluated condition / disease specific questionnaires in the context of research in alcohol dependence. In these RCTs alcohol questionnaires were compared to general mental health assessment questionnaires.

Table 8 New questionnaire strategies

| Retention RCT or comparison | Total number randomised | Questionnaire strategy | Control arm | Outcome type | Host trial disease/ condition |
|---|-------------------------|--|---|--|--|
| Short vs. long | | | | | |
| Dorman 1997 UK | 2253 | Short EUROQOL | Long SF 36 questionnaire. | Postal questionnaire response after first reminder | Stroke treatment (International Stroke Trial 1997) |
| Edwards 2001 unpublished UK | 99 | 1-page, 7 question functional dependence questionnaire | 3-page, 16 question functional dependence questionnaire. | Postal questionnaire response at 3 months | Head injury treatment (Crash Trial 2004) |
| Svoboda 2001 unpublished Czech | 91 | 1-page, 7 question functional dependence questionnaire | 3-page, 16 question functional dependence questionnaire. | Postal questionnaire response at three months | Head injury treatment (Crash Trial 2004) |
| McCambridge 2011 (1b) UK web | 2835 | Audit Short (alcohol use disorders questionnaire) + LDQ (Leeds dependency questionnaire) | APQ (alcohol problems questionnaire) | Web based questionnaire response at one month | Treatment alcohol dependence (Murray 2007) |
| McCambridge 2011 (2b) UK web | 1999 | Audit Short (alcohol use disorders questionnaire) + LDQ (Leeds dependency questionnaire) | APQ (alcohol problems questionnaire) | Web based questionnaire response at 3 months | Treatment alcohol dependence (Murray 2007) |
| Long and clear vs. short and condensed | | | | | |
| Subar 2001 USA | 900 | DHQ (36-page food frequency questionnaire) | The PLCO (16-page food frequency questionnaire) | Overall postal questionnaire response and on site completion | Cancer screening (Prorok 2007) |
| Question order | | | | | |
| McColl 2003 (1) UK | 4751 | Asthma condition specific questions first followed by generic | Generic questions followed by condition specific | Overall postal questionnaire response | Clinical management Asthma (Eccles 2002) |
| McColl 2003 (2) UK | 4684 | Angina condition specific questions followed by generic | Generic questions followed by condition specific | Overall postal questionnaire response | Clinical management angina (Eccles 2002) |
| Letley Unpublished UK | Data not available | 23 page self-completion questionnaire Roland disability questionnaire at front and SF 36 at back | Vice versa. 23 page self completion questionnaire SF36 at front Roland disability questionnaire at back | Postal questionnaire response. No data available | Backpain treatment (UK BEAM Trial team 2004) |

| Retention RCT or comparison | Total number randomised | Questionnaire strategy | Control arm | Outcome type | Host trial disease/condition |
|-----------------------------------|-------------------------|--|--|--|--|
| Relevance of questionnaire | | | | | |
| McCambridge 2011 (1a) UK web | 1892 | Alcohol problem questionnaire (APQ)23 items | Core OM Mental health assessment 23/34 items | Web based questionnaire response at 1 month | Alcohol dependence treatment (Murray 2007) |
| McCambridge 2011 (2a) UK web | 2001 | Audit Short (alcohol use disorders questionnaire) + LDQ (Leeds dependency questionnaire) | Core OM Mental health assessment 10 items | Web based questionnaire response at 3 months | Alcohol dependence treatment (Murray 2007) |

3.4.5. BEHAVIOURAL STRATEGIES

Behavioural strategies to improve RCT retention were evaluated in two retention RCTs listed in Table 9 (Chaffin et al. 2009, Cox et al. 2008). These strategies aimed to change participant behaviour and to motivate participants to remain in an RCT. Cox (2008) compared giving RCT participants information with motivational workshops, and Chaffin (2009) compared self-motivation orientation with standard information in the context of a parenting program. This retention RCT was run prior to the host RCT, and only those participants who completed the orientation / retention RCT were included in the subsequent parenting RCT. The analysis for this retention RCT was based on the number of participants eligible for inclusion in the primary analyses for the host parenting RCT.

Table 9 Behavioural strategies

| Retention RCT or comparison | Total number randomised | Behavioural strategy | Control arm | Outcome type | Host trial disease/condition |
|-----------------------------|-------------------------|---|---|-----------------|--------------------------------------|
| Cox 2008 Australia | 120 | Workshops with strategies for goal setting, time management and overcoming barriers to attending program activities. Sent newsletters after 6 months. 12 work sheets with strategies for goal setting, time management and overcoming barriers. After 6 months sent newsletters | Information sheets about program and 9 newsletters | Trial retention | Exercise improvement (Cox 2008) |
| Chaffin 2009 USA | 153 | Self-motivation information group sessions. Testimonials from parents. Decision exercises. Sessions had written exercises, presentation to group and feedback | Six sessions. Standard information about role of services e.g. child welfare and the effect of mal treatment on children. | Trial retention | Parenting improvement (Chaffin 2009) |

3.4.6. CASE MANAGEMENT

One retention RCT evaluated the effectiveness of case management (Ford et al. 2006) Table 10. This strategy involved referring intervention group participants to community agencies. Liaison with each intervention group participant occurred at least once per month by telephone and more frequently if requests to be referred to a service were made by the participants.

Table 10 Case management strategy

| Retention RCT or comparison | Total number randomised | Case management strategy | Control arm | Outcome type | Host trial disease/condition |
|-----------------------------|-------------------------|---|---------------------------|-----------------|--------------------------------------|
| Ford 2006 USA | 703 | In-depth case management. This involved referring intervention group participants to community agencies and liaison with each intervention group participant at least once per month by telephone, and more frequently if service requests were made. | Regular trial procedures. | Trial retention | Cancer screening trial (Prorok 2000) |

3.4.7. METHODOLOGY STRATEGIES

One retention RCT evaluated a methodology strategy to improve questionnaire response in an open versus blind designed RCT (Avenell et al. 2004) see Table 11.

Table 11 Methodology strategy

| Retention RCT or comparison | Total number randomised | Methodology strategy | Control arm | Outcome type | Host trial disease/condition |
|-----------------------------|-------------------------|----------------------|--------------------|-------------------------------|---|
| Avenell 2004 UK | 538 | Open trial design | Blind trial design | Postal questionnaire response | Fracture prevention (RECORD Trial Group 2009) |

3.4.8. RETENTION RCT'S EXCLUDED FROM ANALYSES

Two included retention RCTs were not included in the meta-analyses (Leigh-Brown et al. 1997) (Letley unpublished). In the study by Leigh-Brown (1997) the host study participants were divided into two groups. One group was randomised and the other determined by the preference of the referring primary care practitioner. The author confirmed that participants in this retention RCT were from both randomised and non-randomised groups in the host RCT and that these could not be separated for analyses. For the retention RCT by Letley (unpublished), the authors confirmed that outcome data was not available for each RCT arm.

One recently completed unpublished retention RCT was not included in the review because data was not available at the time of writing. This RCT was identified through the CTU survey, and examined the effect of newsletters on retention (Mitchell unpublished). Data for this RCT will be included when this review is updated.

3.5. RISK OF BIAS IN INCLUDED RETENTION RCTS

3.5.1. ALLOCATION

The Cochrane Collaboration risk of bias assessment tool was used to assess the risk of bias of included retention RCTs (Higgins 2008). All included retention RCTs reported that participants were randomly allocated to groups for comparison. Twenty four of the included retention RCTs described adequate sequence generation by either computer generated numbers, block randomisation, or use of a table of random numbers (Avenell et al. 2004, Bowen et al. 2000, Chaffin et al. 2009, Cockayne et al. 2005, Cox et al. 2008, Hughes 1989, Kenyon et al. 2005, Khadjesari et al. 2011, Leigh-Brown et al. 1997, Man et al. 2011, McCambridge et al. 2011, Renfroe et al. 2002, Severi et al. 2011, Sutherland et al. 1996, unpublished trials by Letley, Land, MacLennan, Marson, Nakash, Bailey 1, Bailey 2)³¹. There was insufficient information about how the sequence was generated for ten retention RCTs (Ashby et al. 2011, Bauer et al. 2004, Couper et al. 2007, Dorman et al. 1997, Kenton et al. 2007, Sharp et al. 2006, Subar et al. 2001, Tai et al. 1997, Edwards unpublished, Svoboda unpublished). Five included retention RCTs used quasi randomisation to allocate participants (Bowen et al. 2000, Ford et al. 2006, Gates et al. 2009, McColl et al. 2003)³². Where possible, the authors of included retention RCT publications were contacted when the method of allocation or sequence generation was unclear from the publication.

Several methods were used in the included retention RCTs to avoid foreseen allocation of participants. This was achieved through different types of sequence generation by either: a trial statistician and implemented by a trial manager, an independent researcher, a central randomisation service, a nurse using a pre-programmed computer, allocation by sealed envelopes, or sequentially numbered packs. Fifteen retention RCTs report both adequate sequence generation and allocation concealment (Avenell et al. 2004, Cockayne et al. 2005, Cox et al. 2008, Hughes 1989, Kenyon et al. 2005, Khadjesari et al. 2011, Man et al. 2011,

³¹ Khadjesari et al (2011) trials 1 and 2, McCambridge et al (2011), Severi et al (2011).

³² McColl (2003) trials 1 and 2.

McCambridge et al. 2011, unpublished trials by Letley, Nakash, MacLennan, Bailey1 Bailey 2)³³.

3.5.2. BLINDING

Blinding of participants was generally not possible in the included retention RCTs. For example, it may not be possible to blind participants to the following strategies to improve retention: incentives or offer of incentives, behavioural or case management strategies such as those seen in the retention RCTs by Cox (2008) and Ford (2006), different types of communication strategies, or questionnaire format strategies. For some included retention RCTs, the authors mentioned that participants were aware of the intervention they were getting but were unaware that this was being evaluated (Bowen et al. 2000, Chaffin et al. 2009, Kenton et al. 2007, Kenyon et al. 2005, Leigh-Brown et al. 1997, McColl et al. 2003, unpublished trials by MacLennan, Marson)³⁴. For other retention RCTs blinding of participants or study personnel to the outcome or intervention was not mentioned in the RCT report. For one retention RCT a judgement about blinding was not applicable because the RCT evaluated the effect of blind versus open RCTs on retention (Avenell et al. 2004).

3.5.3. FOLLOW UP AND EXCLUSIONS

As the outcome measure for this systematic review was retention, this was well reported for the retention RCTs included in the review. Authors were contacted for clarification of any exclusions after randomisation if this was unclear from retention RCT reports.

3.5.4. SELECTIVE REPORTING

Although published protocols were not available for the included retention RCTs (to check the outcome proposed), the majority of published and unpublished reports reported all of the expected outcomes in relation to retention.

3.5.5. OTHER POTENTIAL SOURCES OF BIAS

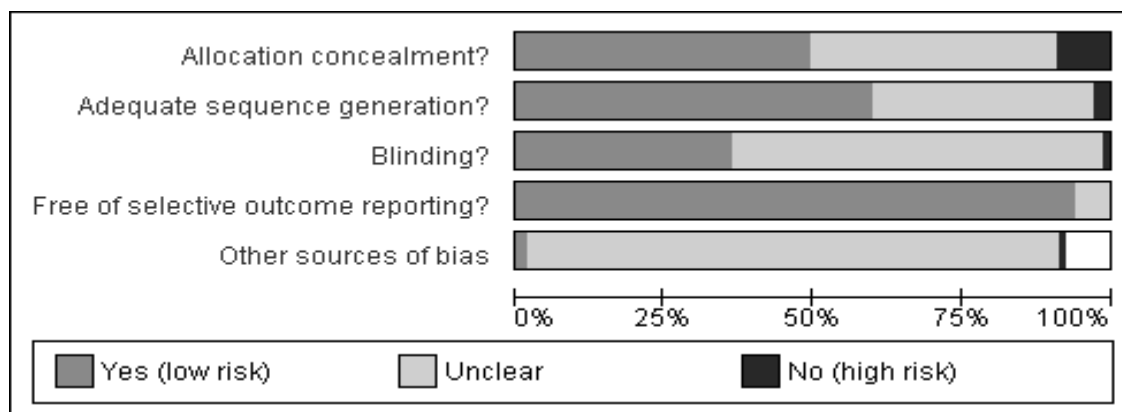
There were few other potential sources of bias identified from reports of included retention RCTs. The exception was the behavioural intervention trial by Cox (2008), where the authors mentioned that the walk and swim sessions were not separated according to the behavioural intervention and the participants were asked not to discuss written materials in the practical sessions. Therefore, potential contamination between

³³ Khadjesari (2011) trials 1 and 2; McCambridge (2011) trials 1 and 2.

³⁴ McColl (2003) trials 1 and 2.

the RCT study groups could have led to biased results. The risk of bias graph with judgements about each risk of bias item presented as percentages across all included retention RCTs is shown in Figure 4.

Figure 4 **Risk of bias graph for retention RCTs**



A summary of the risk of bias judgements made about each risk of bias item for each included retention RCT is given in Table 12.

Table 12 **Risk of bias judgements for retention RCTs**

| Risk of bias item for each included retention RCT | Yes Number of RCTs | No Number of RCTs | Unclear Number of RCTs | Total Number of RCTs |
|---|--------------------------|-------------------------|------------------------------|----------------------------|
| Allocation concealment | 21 | 6 | 11 | 38 |
| Adequate sequence generation | 24 | 2 | 12 | 38 |
| Blinding | 13 | 1 | 24 | 38 |
| Free of selective outcome reporting | 38 | 0 | 0 | 38 |
| Other sources of bias | 2 | 1 | 36 | 38 |

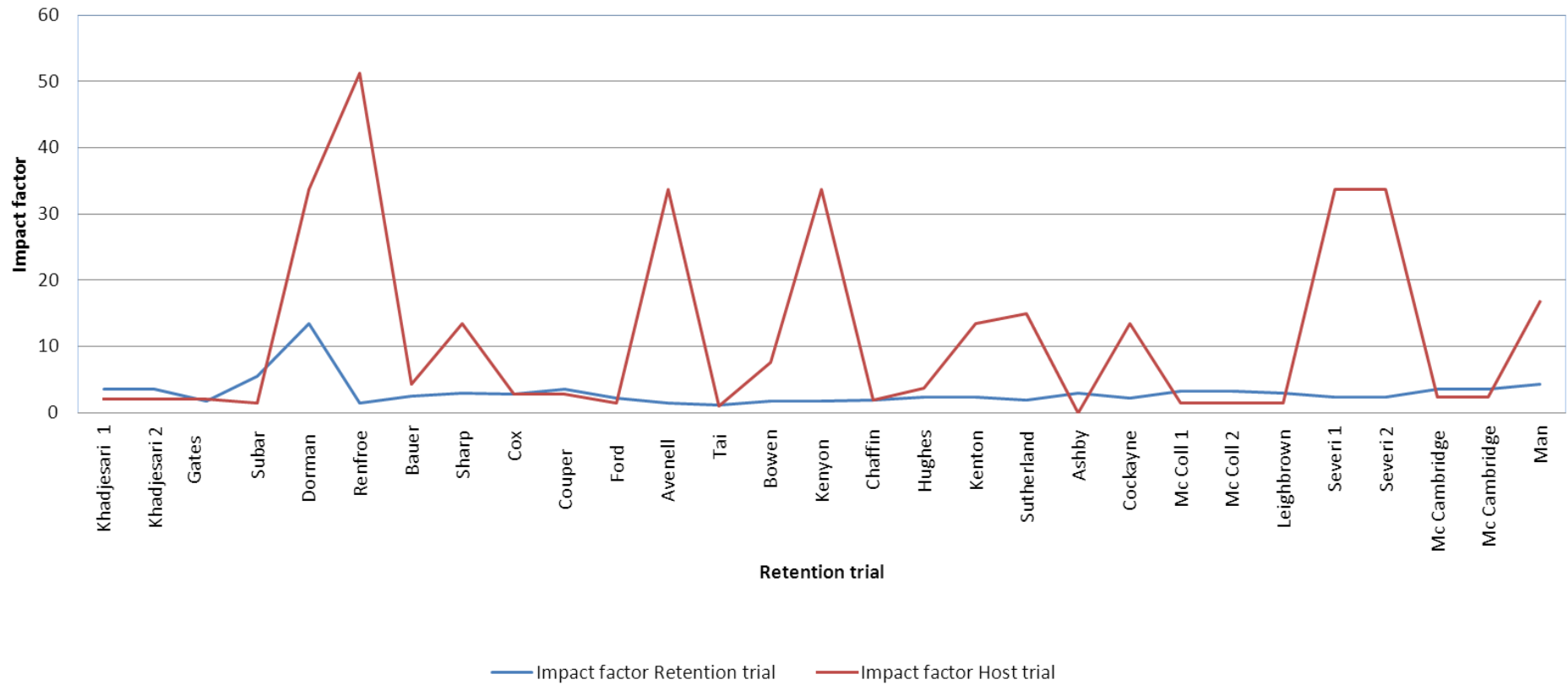
3.6. IMPACT FACTORS: HOST AND RETENTION RCT PUBLICATIONS

The impact factor of a journal is defined as the average number of citations for each article published in the journal and is an indicator of the impact and importance the journal has in a particular field of research. To find the difference between impact factors of journals that published host RCTs and those that published retention RCTs, the impact factors for each retention RCT and the corresponding host RCT was sourced in 2011. Journal impact factors for host RCT publications ranged from 1.05 for the journal entitled *Methods of Information in Medicine* to 51.29 for the *New England Journal of Medicine*. The impact factor that occurs most often i.e. the mode impact factor for this group of publications is 33.60 which is the impact factor for *Lancet*. The median impact factor value is 7.514, which is the impact factor for the journal *Cancer Research*. The 25th

percentile for host RCT publications is 2.03 which is the impact factor for BMC Public Health.

Impact factors for journals publishing retention RCTs ranged from 1.10 which is the impact factor for the Journal of Public Health Medicine to 13.47 which is the impact factor for the British Medical Journal. The mode impact factor for retention RCT publications is 3.6 Journal of Medical Internet Research, and the median is 2.35 Clinical Trials. The 25th percentile impact factor value for retention RCT publications is 1.7 BMC Trials. Published protocols for host RCTs and publications that included the combined results of host and retention RCTs had lower impact factors. For example, the impact factor of Preventive Medicine the journal that published the host and retention RCT results by Cox (2008) has an impact factor of 2.757. No published protocols for retention RCTs were found during the searches. The impact factor for each published retention and associated host RCT is illustrated in Figure 5.

Figure 5 Journal impact factors 2011: host and retention RCTs



3.7. STUDIES EXCLUDED FROM THE REVIEW

Thirty studies were excluded from the systematic review after screening potentially eligible papers (see PRISMA Appendix 6.2). Excluded studies were grouped into five categories: a) non-randomised host studies (n=9), b) non-randomised retention studies (n=9), c) studies where the primary outcome of the retention RCT was missing data (n=3), d) studies where the primary outcome of the retention RCT was treatment compliance (n=7), and e) studies where the strategy targeted baseline questionnaire response and not the number of questionnaires returned during follow-up (n=2). Excluded studies were discussed by four of the systematic review authors VB, GR, SS, and JT. Where possible, the authors of abstracts and full RCT reports were contacted about points relating to the eligibility of a study for the systematic review.

3.7.1. NON-RANDOMISED HOST STUDIES

All retention RCTs embedded in surveys were excluded, and any 2x2 factorial RCTs embedded in surveys (Hopkins et al. 1983, Puffer et al. 2004, Roberts et al. 2000). Also excluded was one RCT where the host study was part randomised and part matched (Marsh et al. 1999), and an RCT with a non-randomised pilot study (Johnson et al. 2004). Cohort studies with embedded evaluations were also excluded (Arnevik et al. 2009, Hoffman et al. 1998, Iglesias et al. 2001), one of which was a 2x2x2 factorial RCT (Eaker et al. 2004).

3.7.2. NON-RANDOMISED RETENTION STUDIES

One host RCT with a single randomisation and subsequent stratification of participants to an embedded retention study (McAuley et al. 1994) was excluded. A cluster randomised host RCT that took a random sample of participants from the intervention arm and gave the participants vouchers to improve retention (Stoner et al. 1998) was also excluded.

Studies where incentives or communication strategies were used but where it was unclear from the RCT report if these were formally evaluated were excluded after the author confirmed that there was no formal randomised or quasi randomised evaluation (Atherton et al. 2010, Edelstein et al. 2005, Hall et al. 1975, Hall et al. 1978, Katz et al. 2001, McBee et al. 2009, Tassopoulos 2007).

3.7.3. MISSING DATA

Two studies were excluded that compared different ways of ordering questions and item response score options in questionnaires (Barry et al. 1996, Wu et al. 1997). Both authors confirmed that the primary outcome measured score differences and means but not

retention. One study (abstract only) compared the order of questionnaires measuring the frequency of missing data items. Response as an outcome was not reported (Leidy et al. 2000) and several attempts were made to contact authors to ascertain if response rates were measured. Three retention RCTs that did compare questionnaire order are included in this systematic review. These were included (Letley unpublished, McColl 2003)³⁵ after the authors or the chief investigator associated with the included retention RCT confirmed that response / retention was the outcome measured.

3.7.4. TREATMENT COMPLIANCE

Six RCTs were excluded because they either evaluated treatment or diagnostic compliance only (Bednarek et al. 2008, Day et al. 1998, Grabowski et al. 1995, Poling et al. 2006, Rhoades et al. 1998, Schmitz et al. 2005). It was agreed that the primary purpose of these studies was medication / test compliance rather than follow-up compliance / retention. One other excluded study reported participant retention in an RCT measuring exercise intensity (Cox et al. 2003). In this study, exercise intensity was considered as a variation in treatment dose and not as a strategy used to improve retention.

3.7.5. BASELINE QUESTIONNAIRE RESPONSE

Another excluded RCT measured response rates at baseline in an elderly screening RCT for data collected by a study nurse versus data collected through self-completed postal questionnaires (Smeeth et al. 2001). Another RCT excluded from the review was embedded in the recruitment phase of the host RCT and was conducted prior to the host RCT randomisation (Iglesias et al. 2001).

3.8. SEARCH CHALLENGES

There were several challenges associated with the searches for eligible retention RCTs. These were: deciding which search terms, filters and data to extract to measure the effectiveness of the retention strategies used in RCTs. There were also challenges associated with database performance for some of the less established databases searched e.g. ERIC, and there were challenges associated with searches of reference lists and conference abstracts. Because of the breadth of the sources searched, and the broad search terms used, many irrelevant abstracts were generated by the initial search strategy. In the following sections these challenges are addressed individually.

³⁵ McColl (2003) trials 1 and 2

3.8.1. SEARCH TERMS

Although the search undertaken was comprehensive in terms of the breadth of sources searched for eligible retention RCTs, the search terms used in the initial search did not capture some eligible RCTs. The search term “response”, used in the context of response to postal or electronic questionnaires, was not used in our initial search strategy. The term was used by Edwards (2009) in the review of strategies to increase response to postal and electronic questionnaires. It was thought that eligible retention RCTs associated with the term “response” to questionnaires would be identified by hand searching the table of characteristics of Edwards (2009) Cochrane review (Edwards 2009). However, when this was conducted it was noted that some of the entries in the table of characteristics were not categorised as RCTs embedded in host RCTs. As a result the retention RCTs by Cochayne (2005), Leigh-Brown (2005) and McColl (2003), identified through the survey of clinical trials units were not identified through hand searches of the Edwards (2009) Cochrane review or through our original search strategy. Therefore “response” was added as a search term to the search update search strategy.

The RCTs by Gates (2009), Khadjesari (2011), Severi (2011) and Ashby (2011) were found in the updated searches. This was important for validating the updated search strategy because these retention RCTs were initially identified through the survey of clinical trials units or by word of mouth in the first instance and were since published after the initial searches were undertaken.

The initial search strategy also included “compliance” as a search term. As treatment compliance was not a focus of this review, search strategies with the terms “compliance” were removed for the 2009-2012 updates.

3.8.2. DATA EXTRACTION

The data extraction was lengthy and complex for each eligible retention RCT and the associated host RCT. A risk of bias assessment was conducted on each host RCT to ensure it was adequately randomised to avoid selection bias. Retention RCTs were often not reported in as much detail as host RCTs. For example, in some instances the intervention group was unclear for example in the retention RCTs by Couper (2007), McColl (2003) and Tai (1997). Furthermore, the primary and secondary outcomes were not well defined, and time points for analysis were unclear. Forty eight per cent of all included published retention RCTs included a CONSORT diagram (n=14/29) and Fifty five per cent of published retention RCTs reported a power calculation (n=16). Most unpublished RCTs were reported in summary form apart from the retention RCT by Nakash (2007). This

increased the need in some instances to contact RCT authors to obtain data. Data for papers published more than 10 years ago was difficult to obtain from retention RCT authors because some had since retired or moved. However, every effort was made to contact authors through co-authors whose contact details were identified through the internet.

The length of time taken to conduct this review was considerable compared with other more straight forward clinical systematic reviews. This was because the review question was broad covering all strategies to improve retention in RCTs that have been evaluated, and also because the data extraction was lengthy and complex for host and retention RCT data. An individualised approach was used when communicating with authors to obtain the data needed, therefore, a considerable amount of time was spent contacting authors for further information needed to conduct a methodologically rigorous meta-analysis.

3.8.3. DATA BASE PERFORMANCE

The initial search strategy included a search of PreMEDLINE i.e. MEDLINE (In-Process and Other Non-Indexed Citations). There is no validated search filter for running searches to retrieve reports of RCTs in this part of the MEDLINE database. For the initial search, the MEDLINE sensitivity and precision maximising filter was used. However, this was not helpful because it was not designed to retrieve 'in-process' and other records. The feedback from the peer reviewers for the review protocol suggested testing a range of truncated free text terms such as: random\$, placebo\$, trial\$, to identify the non-indexed records (Bructon et al. 2011). This search identified over 8,500 records and was then excluded from the review because any unindexed papers generated from the search would eventually be identified through MEDLINE.

The C2 Spectre and ERIC database were searched to May 2009 only. The C2-SPECTR database <http://geb9101.gse.upenn.edu/> hosted by University of Pennsylvania was not accessible on several occasions during the update process. Therefore, these searches were not updated. The search platform for ERIC changed from Datastarweb to Proquest in December 2011. The latter now limits searches to 10 lines of text. As no studies were identified from this database through the initial search it was decided to drop the updated search planned for this database.

The Clinical Trials *meta*Register was searched via the <http://www.controlled-trials.com/mrct/> platform. This register pools together data from active registers of RCTs. The eight registers active in 2009 for the original search were: MRC Medical Research Council, UK Clinical Trials Gateway, Wellcome Trust, National Institute of

Health Action Medical Research, ISRCTN Register International Standard Randomised Controlled Trial Number Register, NIHR HTA National Institute of Health Research Health Technology Assessment Programme, and the Leukaemia Research fund. The latter two registers are no longer updated. Several problems were encountered when searching this database. For example, the maximum number of records displayed on each page was 50. However, for searches returning more than 50 records, the second page of the search results could not be accessed via the website and searches had to be re-run in order to view page 2 of the search results. The search for this database also took time to build. The use of free text without Boolean terms returned a large number of records for example 9,652 records for “follow-up”, 867 records for “retention” and 3,024 for “withdraw%”. The search terms “Strateg%” AND “retention”; “Strateg%” AND “attrition” were used. The search term “Response” was added for the search updates and no new records were identified.

3.8.4. ABSTRACT AND REFERENCE LIST SEARCHES

When the abstracts for the Society for Clinical Trials meetings were searched, missing abstracts for the following years were noted: 1990 abstract P61, 1989 abstract P3, 1987 abstract 9 and P35, 1986 abstract 14 and 28, and in 2009 abstract A45. Some time was spent contacting publishers to try to find these. Eventually the publishers confirmed that these particular abstracts did not appear in their files and were possibly withdrawn prior to the conference proceeding for each given year.

To find the abstracts and papers for all of the titles in each of the reference lists searched would have been time consuming for little reward in terms of adding to the number of eligible retention RCTs identified. Therefore, a judgement was made about the abstracts and titles most likely to be a potentially eligible retention RCT. Words for example “survey” and “cohort”, while used to describe a group of participants in an RCT, could also be used in the purist sense to describe participants in a cohort study or a survey. Because of this, some eligible retention RCTs could have been missed but these could have been picked up in the other searches conducted. This problem should improve as electronic journals become more sophisticated in their ability to link to the abstracts of references listed in reference lists.

3.8.5. NUMBER OF RECORDS

The different platforms and syntax used for the various bibliographic databases searched made the searches for this review lengthy. A preliminary search in MEDLINE using the sensitivity maximising MEDLINE search filter was conducted in the early stages of the

review. The number of records generated was over 10,247 records. For disease related reviews often less than 1000 records are generated for screening (Li et al. 2012, van Zon 2012). As a result the sensitivity and precision maximizing search filters were used in MEDLINE, EMBASE, and CINAHL combined with free text search terms to identify records to screen (Lefebvre et al. 2008, Wong et al. 2006a, Wong et al. 2006b).

The number of eligible retention RCTs identified by the review was low compared to the number of records generated. To make the screening manageable the results of the search updates that were conducted in May 2012 were de-duplicated. This was achieved by removing the duplicate abstracts that appeared in the EMBASE, MEDLINE and PsycINFO search updates (2009-2012) in OVID. The commands “mesz”, “emez” and “psyh” were used to de-duplicate co-occurring records across the databases (personal communication with JT). Separate to this, duplicate records in MEDLINE and EMBASE were excluded for search updates in CENTRAL. The command ““accession number” near pubmed” and ““accession number” near2 embase” commands recommended in the Cochrane Handbook were used to achieve this (Lefebvre et al. 2008).

The lessons learned from these searches have implications for designing future search strategies for methodological systematic reviews especially in terms of which databases and grey literature to search, which experts in the field to contact, and which search terms to include. This is discussed further in the final chapter of this thesis.

3.9. SUMMARY OF RESULTS

Thirty eight eligible retention RCTs were identified from the various sources searched. The number of eligible retention RCTs identified was low compared to the number of records identified. The six broad strategies to improve retention in RCTs identified were incentives, communication strategies, new questionnaire formats, participant case management, behavioural motivational strategies and methodology strategies. The most frequently evaluated strategies to improve retention in RCTs were incentives and communication strategies followed by new questionnaire formats. Few evaluations were found for participant case management, behavioural motivational strategies and methodological strategies. The types of incentive strategies evaluated were monetary incentives or offers of monetary incentives in cash, donation or voucher format of values between £5-£20 and \$2-\$10. Offers of entry into prize draws ranged between £25-£250 for UK retention RCTs, and \$50 for the one Canadian retention RCT that used this strategy. Non-monetary incentives and offers of these were in the form of gifts: for example, pens, lapel pins, certificates of appreciation for participation in an RCT, and offers of study results. The types of new questionnaires evaluated were: shorter versions

or longer and clearer versions of existing questionnaires. Question order was also evaluated and the relevance of two different types of questionnaires in a treatment for alcohol dependency RCT. Most of the retention RCTs found were UK based and all were English language publications. None of the retention RCTs identified were from low or middle income settings. Most of the retention RCTs identified were from searches other than database searches. The successful ways to identify eligible retention RCTs were through the survey of UK clinical trials units, word of mouth, reference lists of reviews and relevant papers and through the MEDLINE and CINAHL databases.

In the next chapter the results of the meta-analyses of retention RCTs identified by the systematic review are reported.

CHAPTER 4: META-ANALYSIS RESULTS

4.1. INTRODUCTION

In the previous chapter six broad types of strategies to improve retention that have been evaluated in RCTs were identified. These strategies were: incentives, different methods of communication, new questionnaire formats, behavioural strategies, participant case management, and methodology strategies. The characteristics and comparisons of each eligible retention RCT were presented in Tables 6-11 in Chapter 3.

In the protocol for the systematic review it was planned to include retention RCTs that were targeted at treatment or follow-up compliance and to group the strategies into participant or management focused strategies (Brueton et al. 2011). As not all of the pre specified analyses were appropriate, because of the variety of retention strategies identified by the searches, revised groups and subgroups were identified for analysis. These new groups and subgroups are presented in Table 13.

In this chapter the forest plots for retention as an outcome for each retention strategy are presented. These show; the type of strategy evaluated, the comparisons, the subgroups, the number of events in the intervention and control groups, the risk ratio and 95% confidence interval for retention. A fixed effect model was used for the analysis. Heterogeneity is reported with χ^2 for differences between retention RCTs and subgroups. The forest plot for sensitivity analysis excluding quasi randomised retention RCTs, exploratory forest plots for the effect of splitting the arms of multi-armed retention RCTs combined for the main analysis, and plots for analysis of cluster RCTs prior to adjustment for clustering can be found in Appendix 5 of this thesis.

4.2. EFFECT OF INCENTIVE STRATEGIES

For the analyses of the effectiveness of incentive strategies the associated retention RCTs were grouped as follows (see Table 13):

1. The addition of an incentive versus no incentive.
2. The addition of a monetary incentive to both study arms.
3. The addition of a monetary incentive versus an offer of an alternative monetary incentive e.g. entry into a prize draw.

Table 13 Number of retention RCTs, comparisons and participants

| Groups and subgroups | Number of RCTs | Number of comparisons | Number of participants randomised |
|--|----------------|-----------------------|-----------------------------------|
| Addition of an incentive vs none | | | |
| Addition of monetary incentive vs none | 3 | 3 | 3166 |
| Addition of offer of monetary incentive vs none | 2 | 2 | 3613 |
| Addition of non-monetary incentive vs none | 3 | 6 | 6322 |
| Addition of offer of non-monetary incentive vs none | 2 | 2 | 1138 |
| Addition of offer of a monetary donation to charity vs none | 1 | 1 | 815 |
| Addition of monetary incentive to both study arms | | | |
| Addition of £10 with offer £10 vs addition of £5 with offer £5 | 1 | 1 | 485 |
| Addition of offer of £20 vs addition of offer of £10 | 1 | 1 | 417 |
| Addition of monetary incentive vs alternative monetary incentive | | | |
| Addition of money vs offer of entry into prize draw | 1 | 2 | 297 |
| Communication strategies | | | |
| Enhanced letter vs standard letter | 2 | 2 | 2479 |
| Total design method for postal questionnaire vs customary method | 1 | 1 | 226 |
| Priority vs regular post | 3 | 7 | 1888 |
| Additional reminder vs usual follow-up | 6 | 6 | 3401 |
| Additional monthly reminders to sites of assessments vs usual reminders (Cluster randomised) | 1 | 1 | |
| Early vs late post of questionnaire | 1 | 1 | 664 |
| Recorded delivery vs telephone reminder | 1 | 1 | 192 |
| Telephone survey vs monetary incentive plus questionnaire | 1 | 1 | 700 |
| New questionnaire format strategies | | | |
| Short vs long questionnaire | 5 | 5 | 7277 |
| Long and clear vs short and condensed questionnaires | 1 | 1 | 900 |
| Condition questions first vs generic questionnaires first | 2 | 2 | 9435 |
| Questionnaire relevant to condition vs less relevant to the condition | 1 | 1 | 3893 |
| Behavioural strategy | | | |
| Motivation vs information | 1 | 1 | 273 |
| Case management strategy | | | |
| Case management vs usual follow-up | 1 | 1 | 703 |
| Methodology strategy | | | |
| Open vs blind trial design | 1 | 1 | 538 |

There were 14 retention RCTs of incentives giving 19 RCT comparisons with 16,253 participants. Data were not available for one retention RCT in this group by Leigh-Brown (1997) which compared an offer of entry into a prize-draw versus no offer.

Across the incentive versus none retention RCTs there was considerable heterogeneity ($p < 0.00001$) Figure 6. So it was thought not to be appropriate to pool the results for incentives.

4.2.1. ADDITION OF AN INCENTIVE VERSUS NONE

The three RCTs (3166 participants) that evaluated the effect of giving monetary incentives to participants in return for completed postal questionnaires showed that this strategy is more effective than no incentive (RR 1.18;1.09-1.28, $p < 0.0001$) (Figure 6). There is no significant heterogeneity ($p = 0.21$).

The value of the incentives evaluated was £5 for UK based RCTs (Gates 2009, Kenyon 2005) given in voucher or cheque format. In one US base retention RCT, Bauer (2004) evaluated cheques valued at \$2 and \$10. In exploratory analysis the different incentive arms that were combined for the main analysis do not appear to show differential effects on questionnaire response; there is no significant heterogeneity ($p = 0.27$) $I^2 = 23\%$ and the effect remains the same (RR 1.18; 1.09- 1.27, $p < 0.0001$) (Figure 1a, Appendix 5.1.).

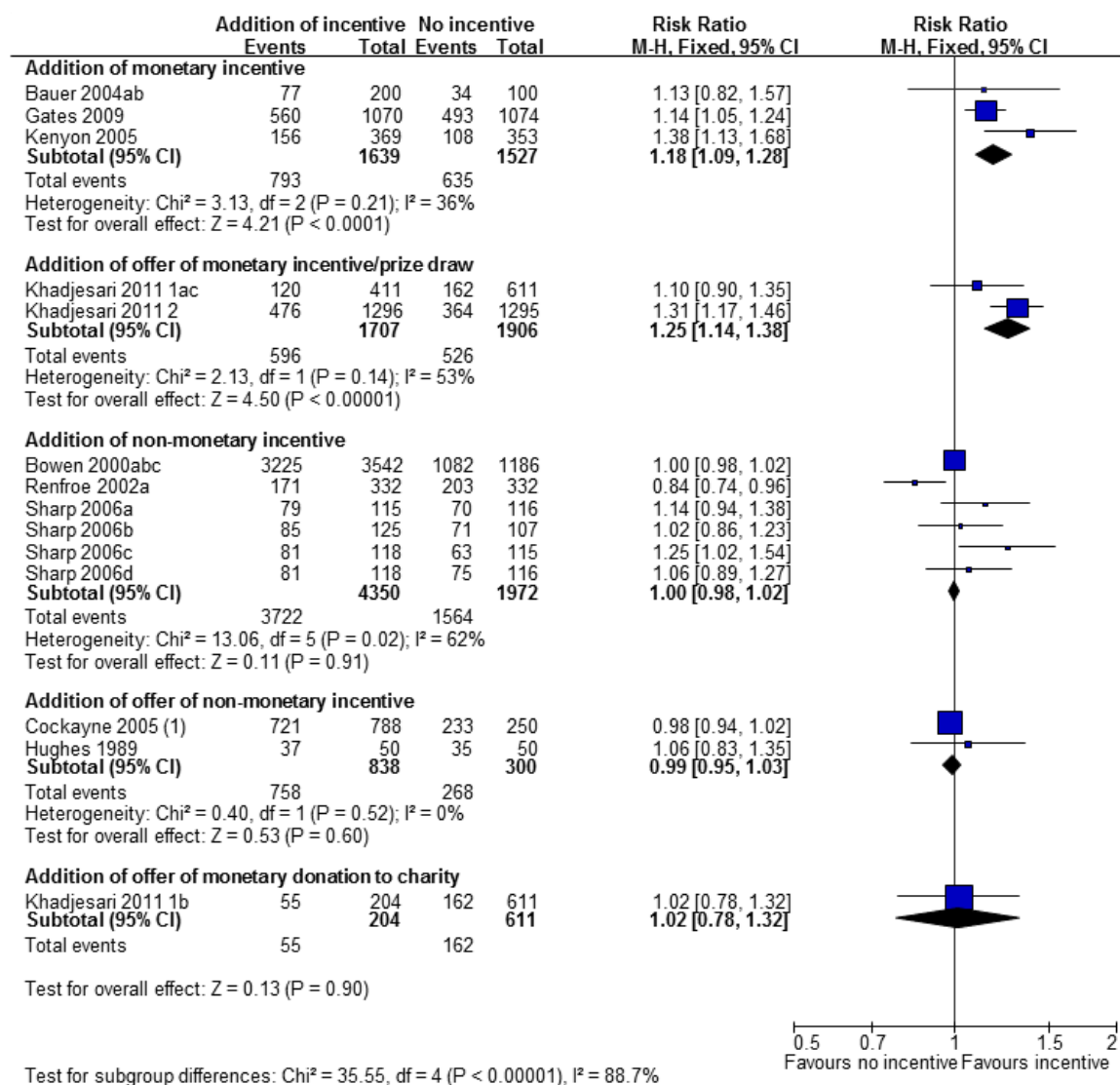
A sensitivity analysis, excluding the quasi RCT by Gates (2009), still shows that the addition of a monetary incentive remains more effective than giving no incentive (RR 1.31; 1.11-1.55; $p = 0.002$) (Figure 1b, Appendix 5.2.). Heterogeneity remains low ($p = 0.30$).

Based on the relevant arms of two web based retention RCTs (3613 participants), an offer of a monetary incentive promotes greater return of electronic questionnaires than no offer (RR 1.25; 1.14-1.38, $p < 0.00001$) (Figure 6) but there is some heterogeneity ($p = 0.14$) which might be explained by the value and type of incentive offered which varied for example £5 and £10 Amazon vouchers were used, and entry into a £250 prize draw. One single RCT comparison suggests that an offer of a monetary donation to charity does not increase response to electronic questionnaires (RR 1.02; 0.78-1.32; $p = 0.90$) (Figure 6). In exploratory analyses the different incentive arms that were combined for the main analysis of an offer of a monetary incentive do not appear to show differential effects when separated (Figure 1a, Appendix 5.1).

Based on three RCTs (6322 participants) there is no clear evidence that the addition of non-monetary incentives e.g. gifts, improved questionnaire response (RR 1.00; 0.98-1.02, $p = 0.91$), but there is some heterogeneity ($p = 0.02$) Figure 6. The types of non-monetary incentives evaluated were: a promise of a free reprint of the RCT results, pens, a certificate of appreciation, and lapel pins illustrating the name of the RCT. A sensitivity analysis excluding the quasi RCT by Bowen (2000) showed a similar effect (RR 1.00; 0.93-1.08, $p = 0.99$) (Figure 1b, Appendix 5.2) and heterogeneity ($p = 0.01$).

Figure 6 Incentive strategies: addition of incentive versus none - main analysis

Review: Strategies to improve retention in RCTs
Comparison: Incentive vs none
Outcomes: Trial retention



Two RCTs with 1,138 participants evaluated offers of non-monetary incentives. The results suggest that there is no good evidence that an offer of a non-monetary incentive is better than no offer (RR 0.99; 0.95-1.03, p=0.60) at improving questionnaire response (Figure 6).

4.2.2. ADDITION OF MONETARY INCENTIVE TO BOTH RCT ARMS

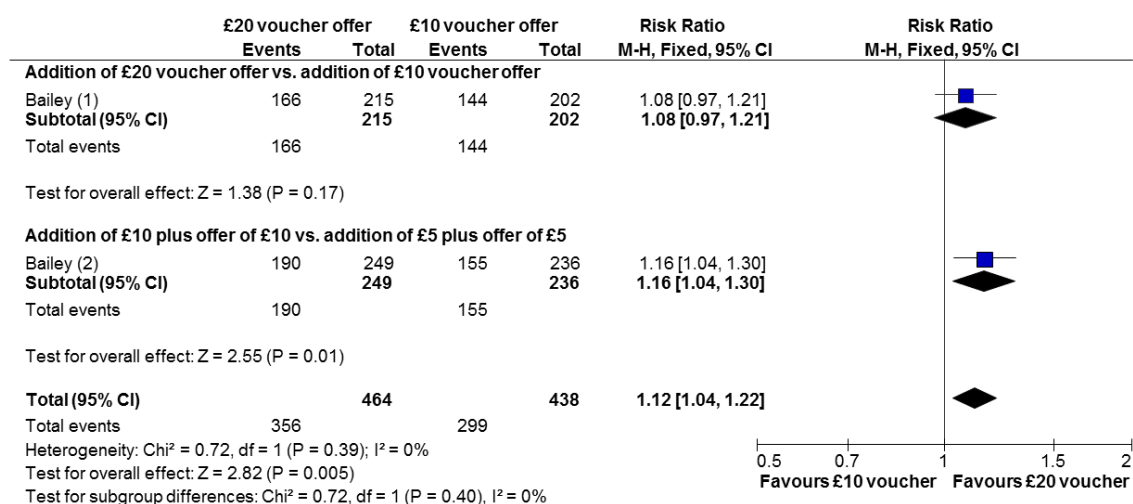
The addition of a monetary incentive to both RCT arms category was divided into two subgroups for analyses:

1. The addition of an offer of a monetary incentive (higher value) versus offer of a monetary incentive (lower value).
2. The addition of a monetary incentive plus an offer of money for data return (higher value) versus the addition of a monetary incentive plus an offer of money for data return (lower value).

Two RCTs (902 participants) show that higher value incentives (i.e. £20) are better at increasing response to postal questionnaires than lower value incentives irrespective of how they are given i.e. offered or split into an upfront voucher plus an offer of a voucher (i.e. £10) (RR 1.12; 1.04-1.22, p=0.005). Heterogeneity was not significant (p=0.39) (Figure 7). One RCT (485 participants) found that the addition of a £10 voucher with the offer of a further £10 voucher for return of a postal questionnaire with a chlamydia test kit was more effective than a £5 voucher with an offer of a further £5 voucher for return of data (RR 1.16; 1.04 -1.30 p=0.01). Based on one RCT with 417 participants, there was no clear evidence that the addition of an offer of a £20 voucher in return for a postal questionnaire was better than the addition of an offer of a £10 voucher (RR 1.08; 0.97 - 1.21, p=0.17) (Figure 7).

Figure 7 Incentive strategies: addition of monetary incentive to both RCT arms

Review: Strategies to improve retention in RCTs
Comparison: Monetary incentive vs an alternative monetary incentive
Outcomes: Trial retention

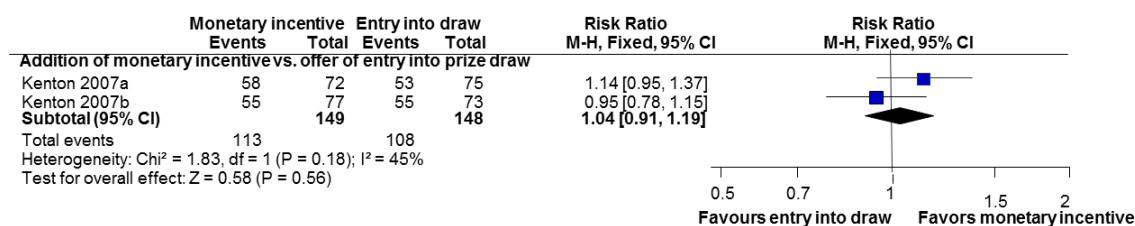


4.2.3. ADDITION OF MONETARY INCENTIVE VERSUS OFFER OF AN ALTERNATIVE MONETARY INCENTIVE

Two RCT comparisons (297 participants) provide no clear evidence that giving a \$2 monetary incentive is better than an offer of an entry into a prize draw for a \$50 gift certificate on response to postal questionnaires. (RR 1.04; 0.91- 1.19, p=0.56) (Figure 8).

Figure 8 Incentive strategies: addition of monetary incentive versus offer of incentive

Review: Strategies to improve retention in RCTs
Comparison: Incentive vs offer of incentive
Outcomes: Trial retention



4.3. EFFECT OF COMMUNICATION STRATEGIES

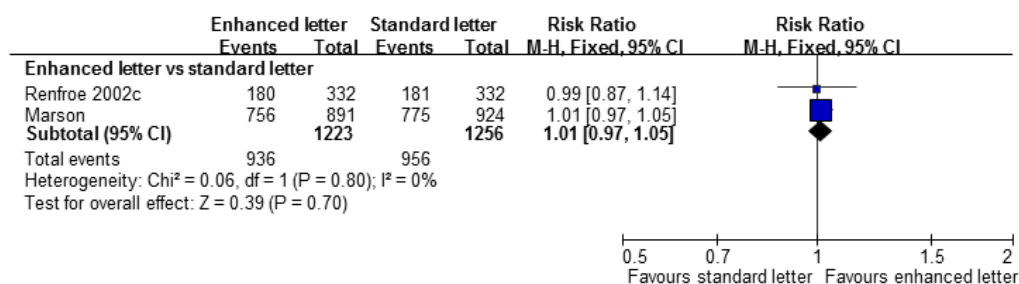
There were 14 RCTs of communication strategies and 20 RCT comparisons. The results relating to the effect of these strategies on RCT retention are presented below.

4.3.1. ENHANCED VERSUS STANDARD LETTER

The results from two RCTs (2479 participants) show that there is no good evidence that an enhanced letter i.e. a letter signed by study personnel (Renfroe 2002) or a letter with a statement about the length of time it should take to complete a questionnaire (Marson unpublished), is more effective than a standard letter for increasing response to postal questionnaires (RR 1.01; 0.97-1.05, p=0.70) (Figure 9) and there is minimal heterogeneity (p=0.80).

Figure 9 Communication strategies: enhanced letter versus standard letter

Review: Strategies to improve retention in RCTs
Comparison: Enhanced letter vs standard letter
Outcomes: Trial retention

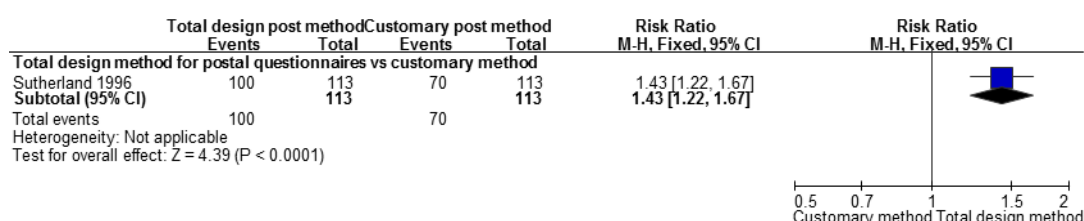


4.3.2. TOTAL DESIGN METHOD (TDM) VERSUS CUSTOMARY METHOD

Based on the results of one retention RCT, the TDM, a package of postal communication strategies (226 participants) seems much more effective than a customary postal communication method for improving questionnaire return (RR 1.43;22-1.67, $p < 0.0001$) (Figure 10).

Figure 10 Communication strategies: total design versus customary method

Review: Strategies to improve retention in RCTs
Comparison: Total design method for postal questionnaires vs customary method
Outcomes: Trial retention

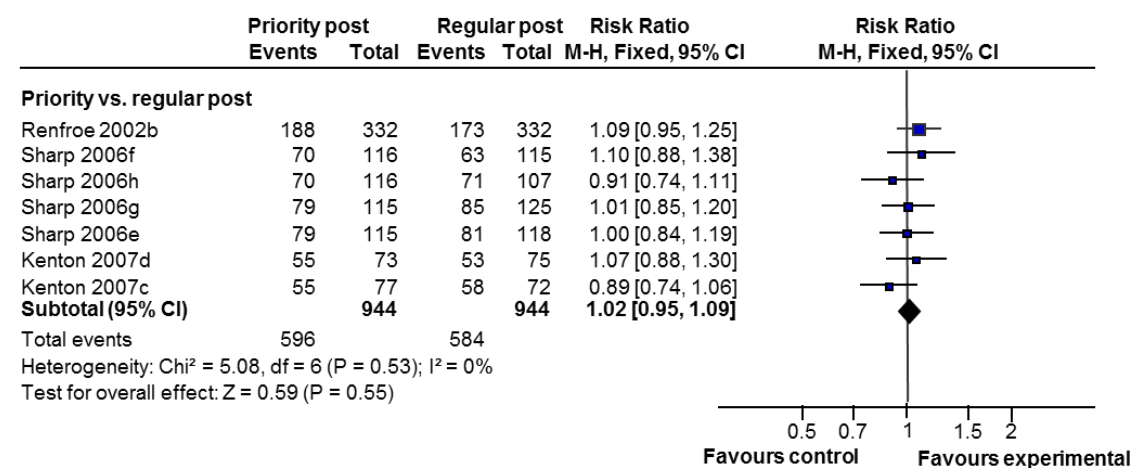


4.3.3. PRIORITY VERSUS REGULAR POST

Based on the relevant arms of three RCTs (1888 participants) there is no clear evidence that priority post is more effective than regular post for increasing questionnaire return (RR 1.02; 0.95-1.09, $p = 0.55$), and there was no clear heterogeneity ($p = 0.53$) (Figure 11).

Figure 11 Communication strategies: priority versus regular post

Review: Strategies to improve retention in RCTs
Comparison: Priority vs regular post
Outcomes: Trial retention

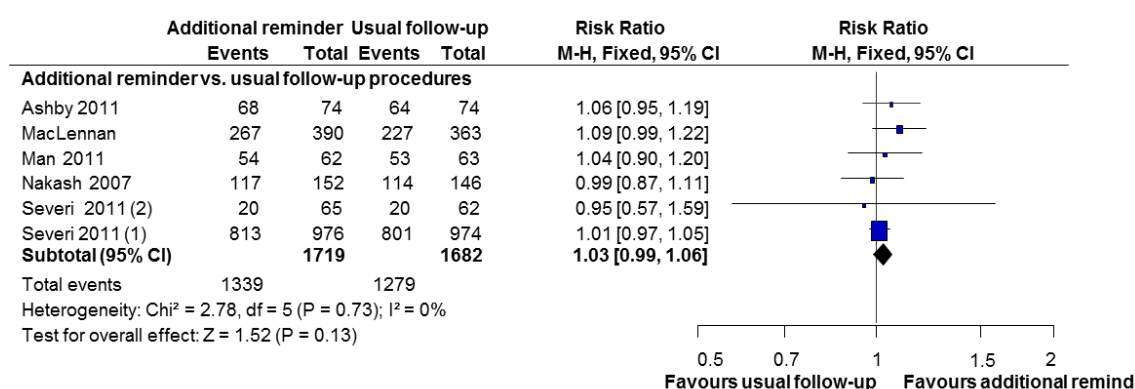


4.3.4. ADDITIONAL REMINDER VERSUS USUAL FOLLOW-UP PROCEDURES

Six RCTs (3401 participants) evaluated the effect of different types of reminders to participants on questionnaire response. There is no clear evidence that a reminder is more effective than no reminder (RR 1.03; 0.99-1.06, p=0.13) at improving response and there is no clear heterogeneity in results (p=0.73) (Figure 12).

Figure 12 Communication strategies: additional reminder versus usual follow-up

Review: Strategies to improve retention in RCTs
Comparison: Additional reminders vs usual follow-up
Outcomes: Trial retention

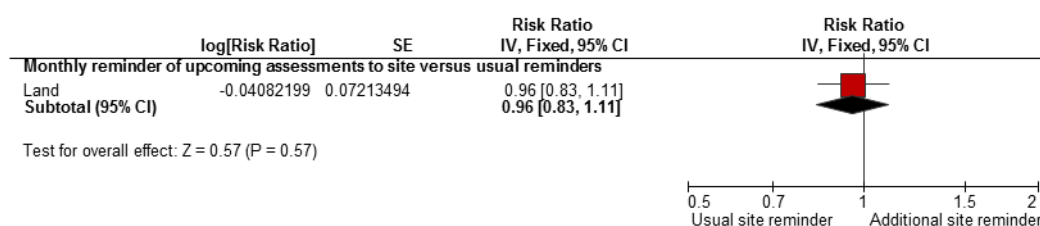


4.3.5. ADDITIONAL REMINDER TO SITE VERSUS USUAL REMINDER

Based on one cluster RCT (272 participants), there is no clear evidence that an additional monthly reminder to sites from the coordinating centre about upcoming assessment was more effective than usual follow-up reminders sent to sites at increasing the return of postal questionnaires (RR 0.96; 0.83-1.11, p=0.57) (Figure 13).

Figure 13 Communication strategies: additional reminder to sites versus usual reminders

Review: Strategies to improve retention in RCTs
Comparison: Additional monthly reminder to site vs usual reminder
Outcomes: Trial retention

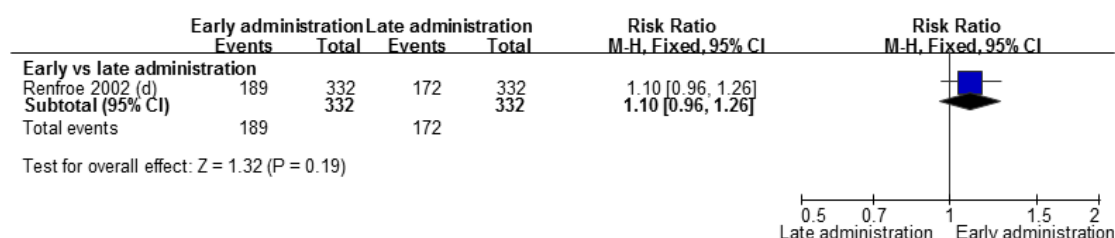


4.3.6. QUESTIONNAIRES SENT EARLY VERSUS LATER

Based on the relevant arm of one RCT (664 participants), there is no clear evidence that sending questionnaires within two weeks of the last study visit was better than sending these after study closure for improving response to postal questionnaires (RR 1.10; 0.96-1.26, P=0.19) (Figure 14).

Figure 14 Communication strategies: questionnaire sent early versus later

Review: Strategies to improve retention in RCTs
Comparison: Questionnaire sent early vs late
Outcomes: Trial retention

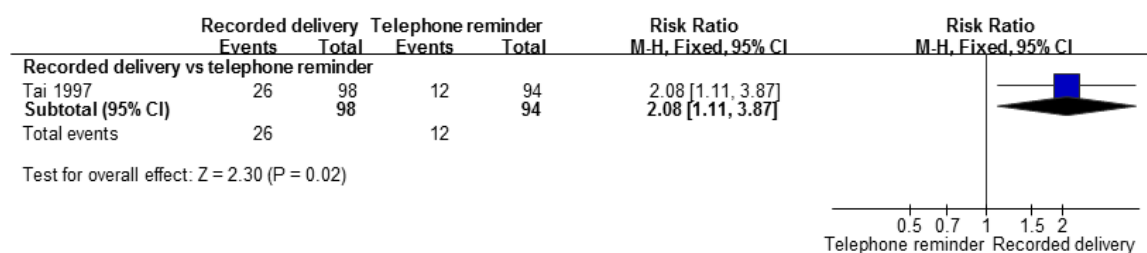


4.3.7. RECORDED DELIVERY VERSUS A TELEPHONE REMINDER

The results of one small RCT (192 participants) suggest that recorded delivery is more effective than a telephone reminder for improving postal questionnaire response (RR 2.08; 1.11-3.87, p=0.02) (Figure 15).

Figure 15 Communication strategies: recorded delivery versus telephone reminder

Review: Strategies to improve retention in RCTs
Comparison: Recorded delivery vs telephone reminder
Outcomes: Trial retention

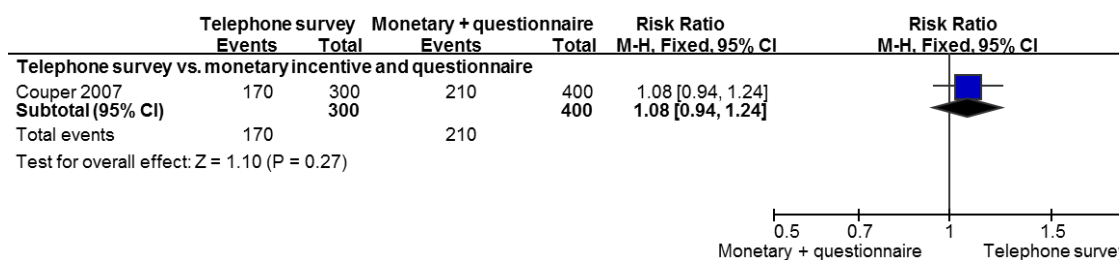


4.3.8. ADDITION OF TELEPHONE SURVEY VERSUS MONETARY INCENTIVE PLUS QUESTIONNAIRE

One RCT (700 participants) compared the addition of telephone follow-up with a monetary incentive plus a questionnaire on postal questionnaire response. There is no clear evidence that a telephone survey is more effective than a monetary incentive sent with a questionnaire (RR 1.08; 0.94-1.24, p=0.27) (Figure 16).

Figure 16 Communication strategies: telephone survey versus monetary incentive and questionnaire

Review: Strategies to improve retention in RCTs
Comparison: Telephone survey vs monetary incentive and questionnaire
Outcomes: Trial retention



4.4. EFFECT OF NEW QUESTIONNAIRE FORMAT STRATEGIES

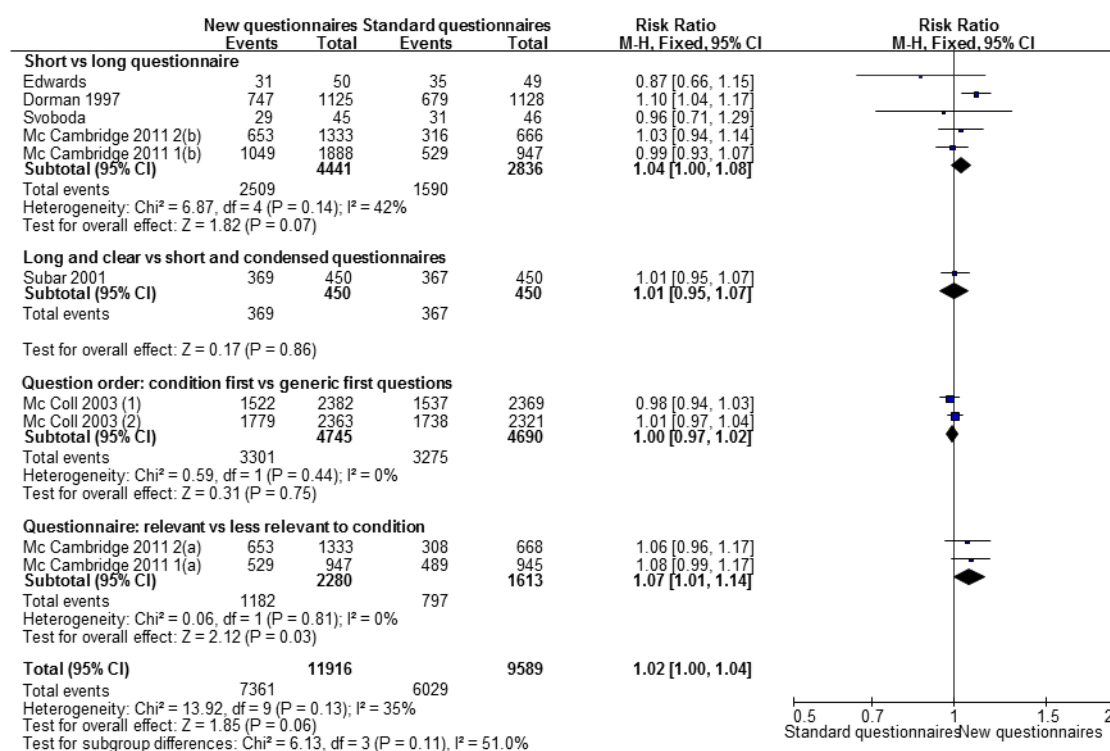
Nine RCTs (21,505 participants) evaluated the effect of a new questionnaire format on questionnaire response. In this group, data for one RCT by Letley (unpublished) which compared the different order of questionnaire questions was not available. Although there is only some heterogeneity between the new questionnaire format subgroups p=0.11, it did not seem helpful to pool the results based on such different questionnaire format interventions (Figure 17).

Five RCTs (7277 participants) compared the effect of short questionnaires versus long on postal questionnaire response. There is some slight suggestion that short questionnaires may be better (RR 1.04;1.00-1.08, p=0.07) with no clear heterogeneity (p=0.14) between trials (Figure 17). Based on one RCT (900 participants), there is no clear evidence that long and clear questionnaires are more effective than shorter condensed questionnaires (RR 1.01;0.95-1.07, p=0.86) (Figure 17).

Two RCTs (9435 participants) show no good evidence that placing disease / condition questions before generic questions is more effective than vice versa at increasing questionnaire response (RR 1.00;0.97-1.02, p=0.75). There is no apparent heterogeneity (p=0.44) between these RCTs (Figure 17). The RCTs by McColl were quasi RCTs and when they were removed in a sensitivity analysis the overall effect of new questionnaires is RR 1.04;1.01-1.08, p=.007 (Appendix 5.5 Figure 13a).

Figure 17 Questionnaire strategies: new versus standard questionnaire

Review: Strategies to improve retention in RCTs
Comparison: New vs standard questionnaires
Outcomes: Trial retention



In the context of research on reducing alcohol consumption there is also evidence that more relevant questionnaires i.e. those relating to alcohol use, increase questionnaire response rates (RR 1.07;1.01-1.14, p= 0.03) (Figure 17).

4.5. EFFECT OF BEHAVIOURAL / MOTIVATIONAL STRATEGIES

Two community based RCTs (273 participants) show no clear evidence that behavioural / motivational strategies are more effective than standard information for retaining

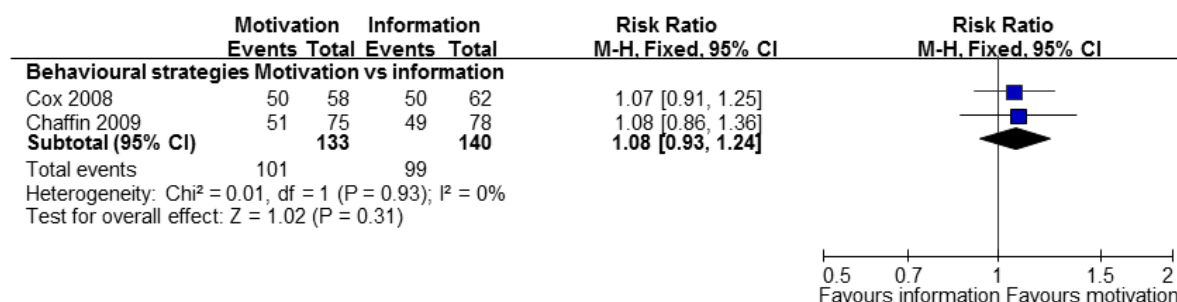
participants (RR 1.08; 0.93-1.24, p=0.31), and heterogeneity is minimal (p=0.93) (Figure 18).

Figure 18 Behavioural strategies: motivation versus information

Review: Strategies to improve retention in RCTs

Comparison: Behavioural / motivational vs standard information

Outcomes: Trial retention



4.6. EFFECT OF CASE MANAGEMENT

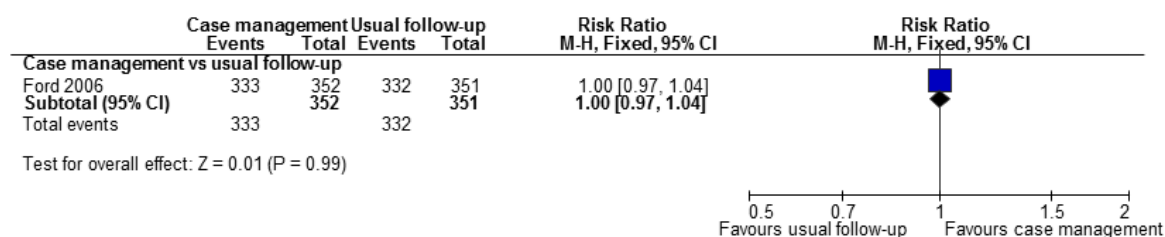
One RCT (703 participants) evaluated the effect of intensive case management procedures on retention of African American male participants aged 55+ years in a cancer screening RCT (Ford 2006). There is no evidence that this is more effective than usual follow-up in the population examined (RR 1.00; 0.97-1.04, p=0.99) (Figure 19).

Figure 19 Case management versus usual follow-up

Review: Strategies to improve retention in RCTs

Comparison: Case management vs usual follow-up

Outcomes: Trial retention



4.7. EFFECT OF METHODOLOGY STRATEGIES

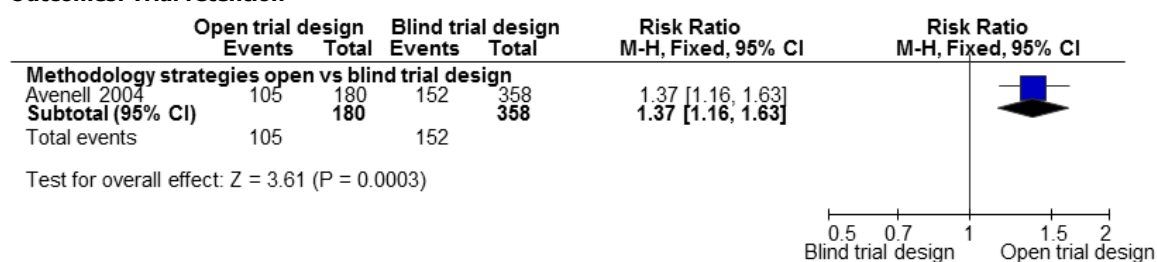
One fracture prevention RCT (538 participants) evaluated the effect of participants knowing their treatment allocation (an open RCT) compared to participants who were unaware (blinded RCT) of their allocation on questionnaire response. There is evidence that the open design improved questionnaire response rates (RR 1.37; 1.16 -1.63, p=0.0003) (Figure 20).

Figure 20 Methodology strategies: open versus blind trial design

Review: Strategies to improve retention in RCTs

Comparison: Open vs blind trial design

Outcomes: Trial retention



4.8. ABSOLUTE BENEFITS OF STRATEGIES TO IMPROVE RETENTION

The absolute benefits of effective strategies on questionnaire response are illustrated in Table 14. Based on a 40% baseline response rate for postal questionnaires, the addition of a monetary incentive is estimated to increase response by 92 questionnaires per 1000 sent (95% CI; 4.98 -13.12). With a baseline response rate of 30% in online RCTs, the addition of an offer of a monetary incentive may increase the number of electronic questionnaires returned by 140 per 1000 questionnaires sent (95% CI: 8.61-19.32). With a baseline response rate of 70% for postal questionnaires sent with a chlamydia test kit, the addition of a monetary incentive is estimated to increase the number of questionnaires returned by post by 33 per 1000 when £20 rather than £10 was offered (95% CI 1.15 - 5.41). With a baseline response rate of 50%, using a shorter questionnaire is estimated to increase response by 20 per 1000 quality of life, alcohol dependence, mental health assessment and functional dependence questionnaires sent (95% CI; 1.0 – 0.92).

Table 14 **Gain in number of questionnaires returned per 1000 sent**

| Example of proportion of questionnaires returned in control arm (assumed control risk ACR) | | | 30% | 40% | 50% | 60% | 70% | 80% | 90% |
|--|-----------|-------------|-----|-----|-----|-----|-----|-----|-----|
| Retention strategy | RR | 1/RR | | | | | | | |
| Addition of monetary incentive | 1.18 | 0.847 | 107 | 92 | 76 | 61 | 45 | 30 | 15 |
| Addition of offer of monetary incentive | 1.25 | 0.800 | 140 | 120 | 100 | 80 | 60 | 40 | 20 |
| Greater value of monetary incentive | 1.12 | 0.890 | 77 | 66 | 55 | 44 | 33 | 22 | 11 |
| Short questionnaire | 1.04 | 0.960 | 28 | 24 | 20 | 16 | 12 | 08 | 04 |

4.9. REPORTING BIAS

There were too few retention RCTs in the different retention strategy groups to allow formal testing to investigate potential reporting bias. However, considerable data from

unpublished RCTs and those published with limited information was obtained from retention RCT authors, reducing the risk of reporting bias.

4.10. META-ANALYSIS CHALLENGES

There were numerous challenges associated with conducting this meta-analysis. Several less common RCT designs were used to evaluate strategies to improve retention. These were: factorial designs (Kenton L et al. 2007, Renfroe et al. 2002, Sharp et al. 2006), multi armed RCTs (Bauer et al. 2004, Bowen et al. 2000, Khadjesari et al. 2011, McCambridge et al. 2011)³⁶, and a cluster RCT (Land unpublished). For one included RCT the retention RCT was conducted prior to the host RCT (Chaffin et al. 2009). To include these in the meta-analysis appropriate methods had to be found to avoid incorrect variance estimates and bias (Higgins et al. 2008b).

4.10.1. DIFFERENT RETENTION RCT DESIGNS

Generally factorial RCTs have two factors 2x2, however this review had only one conventional 2x2 factorial RCT (Kenton et al. 2007) and two RCTs with more than two factors: 2x2x2 (Renfroe et al. 2002), 2x2x2x2 (Sharp et al. 2006). All the comparisons in these RCTs were relevant for the review. To overcome double counting the groups were split into independent comparisons (Higgins et al. 2008b). This approach was achievable for Sharp (2006) and Kenton (2007), however, for Renfroe (2002) the numbers randomised to the independent groups were not available so all the relevant experimental intervention groups were collapsed into larger groups and then all relevant control groups were combined into a larger groups for the meta-analysis (Higgins et al. 2008b).

For the data extraction for the relevance of questionnaire comparison for both four armed trials by McCambridge (2011), confounding was controlled for by length of questionnaire. For McCambridge (2011) trial 1, an Alcohol Problems Questionnaire with 23 items (APQ), was compared with a mental health assessment questionnaire (Core 23) with 23 items. For McCambridge (2011) trial 2, a short alcohol questionnaire, the Alcohol use disorders identification test which has 10 items (Audit 10), and the Leeds Dependency Questionnaire again with 10 items (LDQ) were compared with the Mental health assessment questionnaire which also has 10 items (Core 10). This gave a clean comparison not confounded by length. The Alcohol related questionnaire was treated as the intervention questionnaire and the mental health questionnaire as the control because it could be considered a more general type of questionnaire when measuring alcohol

³⁶ Khadjesari (2011) trial ; McCambridge (2011) trials 1 and 2

associated outcomes. For the comparison of questionnaire length, the problem of confounding was relevance of questionnaire and therefore the only unbiased comparisons that could be made were for the alcohol questionnaire comparisons. For both McCambridge (2011) RCTs the comparisons used were alcohol use disorders identification test 10 item questionnaire (AUDIT 10) plus the Leeds Dependency Questionnaire (LDQ 10) versus Alcohol Problems Questionnaire with 23 items (APQ 23).

For trial 1 by Khadjesari (2011) included in the incentive meta-analysis, the three intervention groups were relevant to two different meta-analysis, therefore the relevant experimental groups were combined and compared with the control group as described in the Cochrane Handbook for systematic reviews (Higgins et al. 2008b). This was done to avoid incorrect variance estimates due to double counting of controls. So, for example for Khadjesari's (2011) trial 1, an offer of an Amazon gift voucher was labelled arm a, and an offer of entry into a £250 prize draw was labelled arm c, these arms were combined because the interventions were considered as offers of an incentive to the participant. The offer of a donation to charity was labelled arm b, and was compared with no incentive in a separate subgroup because this intervention was considered as an offer of a donation to a third party rather than to an RCT participant. For the RCTs by Bowen (2000) and Bauer (2004) the separate arms in each RCT were combined because they were relevant to a particular meta-analysis, in the case of Bauer (2004) this was the addition of a monetary incentive group and for Bowen this was the addition of a non-monetary incentive group (Figure 6). Combining the intervention arms in meta-analysis is not ideal but is at present the Cochrane recommended approach to include RCTs with more than one intervention arm in order to obtain appropriate variance estimates to which each patient contributes only once to the analyses. To supplement these analyses, estimation of the individual interventions versus control was examined in exploratory analyses.

The trial by Chaffin (2009) in the behavioural motivational meta-analysis group (Figure 18) used sequential double-randomisation. The first sequence was randomisation to a motivational orientation intervention versus standard information at entry into the first segment of a parenting program. After this part was completed, participants were randomised a second time to a parenting condition which was either the Parent Child Interaction Therapy (PCIT) or a standard didactic parent training group. This produced four RCT arms and two factors similar to a 2x2 design. These were:

1. Motivation orientation then standard parenting.
2. Motivation orientation then parent child interaction therapy (PCIT).

3. Standard orientation then standard didactic parent training.
4. Standard orientation then PCIT.

Nineteen participants withdrew from the RCT at some point after the second randomisation. All were part of the 153 eligible participants for the primary analysis i.e. who had a second randomisation. The author confirmed that 17 of these 19 withdrawals were withdrawn after the intervention was completed and the retention outcome assessed, therefore, these were not censored observations. There were two withdrawals between the first and second randomisation; these were censored in the primary survival analysis of retention.

For the one cluster RCT by Land (unpublished) the cluster rather than simply the individual was taken account of to avoid unit of analysis error. If clustering had been ignored in the analysis this would have led to small p values and false positive conclusions as a consequence of applying more weight than appropriate for analysis (Higgins et al. 2008b). External estimates for the intracluster correlation coefficient (ICC), an estimate of the relative variability within and between clusters had to be found and applied for this approximate analysis. Considerable time was spent searching for such estimates from similar studies. An ICC for the outcome retention i.e. return of quality of life questionnaires from breast cancer patients was needed. Because the RCT by Land (unpublished) is based on quality of life data from a cancer treatment RCT, the mean of two ICCs for completion of Euroqol questionnaires from the list of ICCs hosted by Aberdeen University was used.

4.10.1. AMBIGUOUS RETENTION RCT REPORTING

In cases where it was unclear from the retention RCT publication which arm was the control and which the intervention, for example in the RCTs by Couper (2007) and Tai (1997), authors were contacted. For the RCT by Tai (1997), the PI confirmed that recorded delivery was the intervention. It remained unclear from the authors reply for the RCT by Couper (2007) which arm was the intervention. Therefore, the project group decided that the investigators might have expected the telephone interview to be more expensive, even after giving \$5 with the postal questionnaire, but that the telephone interview would have also been more effective in terms of receiving a response. Therefore, the telephone interview was treated as the intervention in this instance.

Notwithstanding the numerous challenges associated with conducting this meta-analysis, a robust meta-analysis was conducted by dealing appropriately with different trial designs.

4.11. SUMMARY OF RESULTS

Six broad types of strategies to improve retention in RCTs were included in the meta-analysis. These were: incentives, communication strategies, new questionnaire format, participant case management, behavioural, and methodological interventions. In thirty four RCTs the outcome was based on the return of postal questionnaires. For four RCTs the outcome was based on retention of RCT participants (Bowen et al. 2000, Chaffin et al. 2009, Cox et al. 2008, Ford et al. 2006). The variety of strategies used to improve retention made it inappropriate to pool data.

Strategies with the clearest impact on retention were: the addition of a monetary incentive compared to no incentive for return of postal questionnaires, the addition of an offer of monetary incentive when compared to no offer for return of electronic questionnaires, and the addition of a £20 voucher when compared to a £10 voucher given in different formats for return of postal questionnaires and biomedical test kits. There was some evidence of better questionnaire response based on single RCTs for: recorded postal delivery, using an open RCT design, and a “package” of postal communication strategies known as the total design method (TDM). This review also found that an offer of a monetary incentive can potentially increase the number of questionnaires returned per 1000 sent by at least as much as the addition of a monetary incentive or increasing the amount of the incentive. There is no clear evidence that, when compared to usual follow-up procedures, questionnaire response / retention is improved by: more disease-relevant questionnaires, shorter, or long and clear questionnaires, sending questionnaires early, offering charity donations, giving or offering gifts, "enhanced" letters, priority post, sending additional reminders, changing the questionnaire order, sending reminders to sites, behavioural or case management strategies. There was also no clear effect for monetary incentives when compared to offering entry into a prize draw, or telephone surveys when compared to a monetary incentive with a questionnaire.

In the next chapter, the methods used to explore both the use of strategies to improve retention and the factors that contribute to retention and loss to follow-up in primary care RCTs are described. The results of the in-depth interviews with primary care researchers are presented in Chapter 6.

CHAPTER 5: QUALITATIVE STUDY METHODS

5.1. INTRODUCTION

In Chapter 1 we saw that strategies to improve retention in RCTs are designed to generate optimal data return or compliance to RCT follow-up procedures. Retention strategies can target either participants directly or clinicians at clinical sites responsible for participant follow-up (Senturia et al. 1998). The choice of retention strategy used can depend upon the population group and how data for the primary outcome is to be collected e.g. electronically, by post, face to face interviews, clinical specimens, or via the telephone.

In primary care RCTs, retention of relatively healthy participants is potentially more challenging for research teams because the participants enrolled may not be able to commit to regular follow-up. In contrast, RCTs conducted in secondary care where participants are treated for more acute or terminal illnesses may experience less loss to follow-up. In the feasibility study (see Chapter 1 section 1.7) it was clear that loss to follow-up in cancer RCTs is generally low because participants return for treatment and measurement of their disease progression. However, loss to follow up rates for primary care RCTs can be high e.g. in a smoking cessation RCT by Hall (2007) loss to follow-up was 39%. The strategies used to improve retention specifically in the context of primary care RCTs where loss to follow-up can be more difficult to control are not well documented and many of the retention strategies used in this context could have broad applicability to RCTs conducted in other health care contexts.

In Chapter 3 (section 3.3.2.) we saw that the evaluations of strategies to improve RCT retention were conducted in RCTs from different research contexts and disease areas. Of the 38 retention RCTs included in the systematic review, six were conducted in UK primary care settings (Cockayne et al. 2005, Man et al. 2011, McColl et al. 2003, Tai et al. 1997, Letley unpublished)³⁷. These retention RCTs were embedded in RCTs for the treatment and prevention of different diseases / conditions for example; asthma and diabetes (Tai et al. 1999), angina (Eccles et al. 2002), back pain (Tilbrook et al. 2011) and fractures (Porthouse et al. 2005). Postal questionnaires were used to collect primary outcome data for each of these RCTs and the strategies evaluated were:

1. An offer of the study results (Cockayne et al. 2005).
2. Recorded delivery of questionnaires used for follow-up (Tai et al. 1997).
3. SMS text message reminders (Man et al. 2011).

³⁷ Mc Coll(2003) trials 1 and 2

4. A change in questionnaire question order (McColl et al. 2003, Letley unpublished).

Apart from using postal questionnaires to collect follow-up data other methods, for example face to face interviews, biomedical tests, and/or clinical measurement, are used to collect primary outcome data in RCTs conducted in primary care settings. These methods often require participants to return to clinical sites for follow-up. Williamson (2009) for example required tympanometric measurements to be carried out at GP practice sites in an RCT evaluating topical intranasal corticosteroids in children. Dangour (2010), in an RCT which evaluated the effect of omega-3 on cognition, required elderly participants to return to GP practice sites for cognitive function tests. To improve participant follow-up in RCTs conducted through primary care, retention strategies may be used by the RCT team i.e. research nurses (RNs), primary care clinicians (both principal and chief investigators PIs/CIs), and trial managers (TMs). For example, flexible appointment times may be used for working mothers to bring a child for an RCT follow-up visit (Bruzzese et al. 2009) or transport may need to be provided for an elderly participant who cannot get to the clinical site for a follow-up visit as described by Areal (2003) in the PEPUP USA based RCT, of psychotherapy effectiveness for underserved primary care patients.

Some research has been conducted in the area of retention in UK primary care RCTs. Leathem (2009) describes communication strategies used to motivate the recruitment and retention of participants and sites in a heart disease prevention RCT, and Graffy (2008) identified factors important to researchers for successful recruitment and retention. However, both of these studies group recruitment and retention strategies together. Apart from these two studies, there is a dearth of literature on the spectrum of retention strategies used in UK primary care RCTs. Further exploration is needed to understand the issues surrounding the use of retention strategies in the context of primary care and may explain the results of the systematic review.

This qualitative study was therefore designed to identify the different strategies used to improve retention in UK primary care RCTs and the factors thought to lead to retention and loss to follow-up. Because the systematic review demonstrated that incentives increase questionnaire response, and the UK primary care RCTs included in the review used questionnaires to collect primary outcome data (Cockayne et al. 2005, Man et al. 2011, McColl et al. 2003, Tai et al. 1997, Letley unpublished) more information is needed about the experiences of primary care researchers who use monetary incentives and the impact of applying for ethics approval on the use of incentives. This is important because

payment to participants may raise ethical concerns about the potential for participant exploitation and coercion (Draper et al. 2009).

A qualitative study design was considered to be the most appropriate methodology for a topic that had not been explored in detail previously. Qualitative research can provide access to opinions and explanations not otherwise gained from quantitative methods (Britten et al. 1995). Qualitative in-depth interviews were chosen to explore the retention strategies used and possible explanations for the findings of the systematic review. It was thought that the in-depth interviews would help to give a more detailed picture of the complexity of retaining participants in primary care RCTs than would be achieved by using more structured interviews (Denzin et al. 1994).

Focus groups were considered for the data collection. These are known to yield rich data because they facilitate conversation and debate and allow participants to interact with each other. However, the dynamics within focus groups can affect individual expression and contribution to discussions. Nevertheless, if facilitated effectively, individual expression should not be compromised. In this study, if focus groups were used, there could have been confidentiality issues given the limited range of UK primary care RCTs and the limited size of the UK primary care research community. Furthermore, organising focus groups at convenient times and locations was not practical given that primary care researchers were dispersed throughout the UK and had varying clinical and other commitments. Therefore, an in-depth interview was planned with each primary care researcher recruited to the study at a time and place convenient to them.

5.2. AIM

The aim of the qualitative study was to identify and explore the spectrum of strategies used to improve retention in RCTs conducted in UK primary care settings, and to build on the results of the systematic review.

5.2.1. OBJECTIVES

1. To determine if the strategies identified by the systematic review of retention strategies were used to improve retention in primary care RCTs.
2. To establish barriers to the use of strategies to improve retention in primary care RCTs.
3. To identify retention strategies for further evaluation.

The methods used for the qualitative study are described in the remainder of this chapter.

5.3. STUDY DESIGN

In-depth one to one interviews with members of primary care research teams were used to collect data.

5.3.1. PARTICIPANTS

To meet the study objectives, experts from UK primary care RCTs were identified and interviewed. Participants were TMs, PI/CIs, and RNs (collectively known as primary care researchers) who had worked on published RCTs conducted through UK GP practices. Specifically, participants / interviewees had to have worked on a published RCT conducted through UK GP practices. The interviewees had expertise in the design, coordination, and collection of data for primary care RCTs.

5.3.2. SAMPLING FRAME

A list of potentially eligible RCTs conducted in UK primary care settings published from 2000-2010 was compiled to provide a matrix for purposive sampling of potential interviewees. The time frame was chosen to include the more recently published primary care RCTs and to identify primary care researchers involved in RCT conduct who were working on RCTs. Also, the CONSORT guidelines on reporting RCTs were first published in 1996 (Begg 1996) and it was thought that the RCTs conducted and reported after the publication of these guidelines were more likely to have considered reporting loss to follow-up.

5.3.3. SAMPLING FRAME INCLUSION CRITERIA

RCTs included in the sampling frame represented a spectrum of the diseases and conditions seen in primary care. This broad representation of diseases was important for unbiased sampling because loss to follow-up may vary with different diseases, and the strategies used to improve retention may vary with the type of disease.

In consideration of the requirements set out above for an unbiased sample, published RCTs fulfilling the following criteria were included in the sampling frame:

1. RCTs conducted in UK primary care with results published between 2000-2010.
2. RCTs that used primary care for recruitment and/or follow-up of participants.
3. RCTs where the primary outcome required interaction with participants (i.e. where data for the primary outcome could not be obtained from a central registry data).
4. RCTs involving participants of different age groups.

5. RCTs of treatments for different diseases / conditions.
6. RCTs with loss to follow-up rates above and below 20%.

5.3.4. EXCLUSIONS

1. RCTs for which loss to follow-up rates had not been published.
2. RCTs where loss to follow-up rates could not be calculated e.g. RCTs reporting survival rates or cluster RCTs with unclear denominators because of an indeterminate cluster size.
3. RCTs where the primary outcome data was sourced from death registers or hospital record data (e.g. survival data).

5.3.5. SEARCHES FOR ELIGIBLE RCTS TO INCLUDE IN THE SAMPLING FRAME

Several methods were used to identify RCTs for the sampling frame. These were:

1. A search of databases of published primary care research.
2. A hand search of relevant journals known to publish primary care RCTs.
3. A mail out to the Trial Managers Network (TMN).
4. Snowball sampling.

Each method used is described in further detail below.

5.3.5.1. Database searches

Although UK clinical RCTs can be identified through the controlled clinical RCTs *meta*-Register available at URL:<http://www.controlled-trials.com/mrct/>, RCTs conducted specifically in primary care are not readily identifiable through the website. Therefore, RCTs that met the inclusion criteria were identified through several independent databases. In the first instance, the GPRF database of RCTs conducted through the GPRF and published from 2000-2010 was searched.

Through discussions with GPRF colleagues, other UK based primary care research organisations were identified as potential sources for published primary care RCTs to include in the sampling frame. The eight websites searched are listed in Table 15. The searches took longer than anticipated as the website layout differed between research units. For example, publications were classified by author, disease area or year of publication, making a search of all publications for every UK primary care research unit unfeasible within the time frame. Therefore, an in-depth web based search for RCT publications from primary care units was undertaken. This process was lengthy, with few RCTs identified to add to the sampling frame over and above the RCTs identified through the GPRF database.

Table 15 Qualitative study sampling frame: websites searched

| Primary Care research network /unit | Website |
|--|---|
| MidReC The Midlands Research Practice Consortium | http://www.haps.bham.ac.uk/primarycare/pc-crtu/funding/index.shtml |
| Birmingham Primary Care and Clinical Sciences Unit | http://www.haps.bham.ac.uk/primarycare/index.shtml |
| Primary Care Research Network (PCRN) | http://www.crnc.nihr.ac.uk/about_us/pcrn/ |
| National Institute for Health Research (NIHR) National School for Primary Care Research website. | http://www.nihr.ac.uk/research/Pages/programmes_primary_care_research.aspx |
| Mental Health Research Network (MHRN) | http://www.mhrn.info/ |
| Cambridge General Practice and Primary Care Research Unit | http://www.medschl.cam.ac.uk/gppcru/ |
| Pragmatic Clinical Trials Unit | http://www.icms.qmul.ac.uk/chs/pctu/ |
| East of England Primary Care Research Network | http://www.pcrn-eoe.org/default.asp?id=115 |

5.3.5.2. Journal hand searches

To increase the number of RCTs to include in the sampling frame, high impact and subject focused journals thought likely to publish primary care RCTs were searched for RCTs published during 2009 and 2010 (Table 16). These journals were chosen because they are known to publish the results of scientifically rigorous RCTs conducted in primary care. The search was limited to publications for two years for primary care researchers who had recently conducted RCTs to be invited to participate.

Table 16 Qualitative study sampling frame: RCTs from journal hand searches

| Journal | Impact factor 2011 | Number of potentially eligible RCTs identified | Number excluded | Number included in sampling frame |
|-------------------------------------|--------------------|--|---|-----------------------------------|
| British Medical Journal | 12.8 | 7 | 4 GPRF RCTs already included. | 3 |
| British Journal of General Practice | 2.4 | 6 | 1 GPRF RCT 1 Primary outcome data collected through registry data. 3 Insufficient data to calculate loss to follow-up | 1 |
| Lancet | 28.4 | 4 | 1 GPRF RCT 1 CI linked with another GPRF RCT | 2 |
| Family Practice | 1.5 | 0 | None | 0 |

5.3.5.3. Trial Managers Network (TMN) mail out

The TMN was approached to help recruit TMs that may have changed employment since the RCT they had worked on was completed. All current TMN members were emailed and invited to participate. A reminder email was sent at three weeks (Appendix 4.3). The RCTs associated with TMs who expressed an interest in participation were screened for eligibility for the sampling frame. These eligible RCTs were added to the sampling frame

when the PI for the RCT gave permission. The TMs were subsequently contacted through email.

5.3.5.4. Snowball sampling

Snowball sampling was used to identify CIs/PIs to invite for interview. Suggestions made by the management group and other interviewees for potential interviewees to contact were followed up when the RCT linked to the proposed PI / CI met the inclusion criteria for the sampling frame.

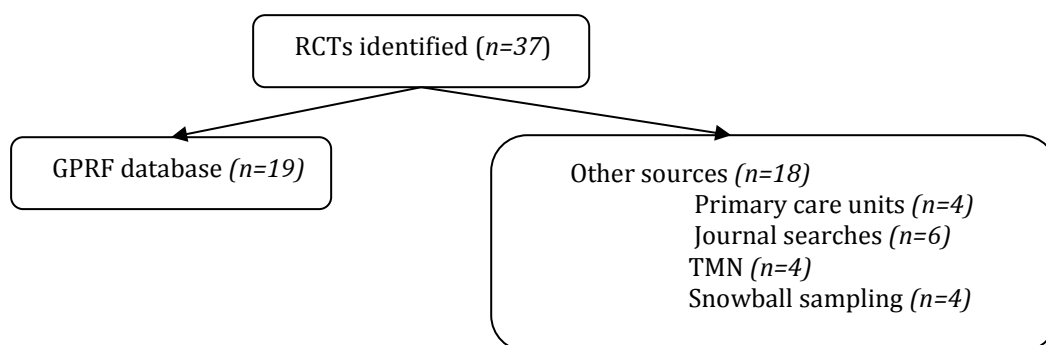
5.3.6. THE SAMPLING GRID

RCTs with loss to follow-up equal to, above or below 20% were included in the sampling grid. Twenty per cent was used as the cut off because loss to follow-up above this level can threaten RCT validity. Such RCTs were included in the sampling grid to examine the complexities of keeping participants in RCTs with high levels of loss to follow-up.

Loss to follow-up was calculated for the primary outcome of each published RCT included in the sampling frame. Data for these calculations was extracted from consort diagrams, tables, and the text of the included RCT publication. Where loss to follow-up could not be calculated, RCTs were excluded from the sampling frame, for example for RCTs reporting overall survival (Meade et al. 2002).

Thirty seven RCTs were identified for inclusion in the sampling grid (Figure 21). Of these, 24 RCTs had loss to follow-up rates of <20%, and 13 RCTs had loss to follow-up rates of >20%. Seven RCTs were published between 2000-2004. Thirty RCTs were published between 2005 and 2010. The RCTs represented 10 broad disease areas and conditions: management of major and minor conditions ($n=5$), endocrine conditions (for example diabetes) ($n=5$), musculoskeletal conditions ($n=5$), mental health ($n=4$), respiratory ($n=4$), elderly care ($n=3$), gynaecological ($n=3$), neurological ($n=2$), dependency treatment ($n=2$) and other groups ($n=4$) which were: ear nose and throat, cardiovascular, nutrition and health promotion.

Figure 21 Qualitative study: source of sampling RCTs



The RCTs identified for the sampling frame were mapped to a sampling grid (Table 17) and categorised by year published and level of loss to follow-up. This was to identify gaps in the grid and to ensure an even distribution when sampling across the different levels of the grid.

Table 17 Qualitative study sampling grid

| RCT publication date | Level of loss to follow-up | Disease area | Principal investigator | Research manager | Research nurse |
|--------------------------|----------------------------|--------------|------------------------|------------------|----------------|
| MRC GPRF RCTs | | | | | |
| Jan 2000- Dec 2004 | >20% <20% | | | | |
| Jan 2005- Dec 2010 | >20% <20% | | | | |
| Non MRC GPRF RCTs | | | | | |
| Jan 2000- Dec 2004 | >20% <20% | | | | |
| Jan 2005- Dec 2010 | >20% <20% | | | | |

5.4. SAMPLING

Names and contact details were identified for potential interviewees linked to RCTs in each cell of the sampling grid. The plan was to recruit 10 PI/CIs, 10 TMs and 10 RNs from the 37 RCTs identified (see Appendix 10). Potential interviewees were invited to participate. The RNs were sampled from a group of experienced RNs from published RCTs run through the MRC GPRF. RNs were not linked to any of the non GPRF trials.

5.5. RECRUITMENT

The recruitment process used is illustrated in Figure 22. As the sampling frame included fewer primary care RCTs published between 2000-2005 and also because TMs positions are usually limited by funding, two slightly different approaches were used to recruit interviewees from RCTs published pre and post 2005. For the RCTs published pre 2005, the PI and an RN were invited to participate. It was assumed that the TM had moved. The RN was contacted through the MRC GPRF. For RCTs published during 2005-10, the PI was initially emailed to: a) obtain permission to include the RCT in the sampling frame, and b) to obtain contact details for the TM. Again, the RN was contacted through the MRC GPRF. All recruitment for the qualitative study was conducted via email.

Invitations sent to PIs included a personalised covering letter, a two page summary of the qualitative study proposal, a participant information sheet, and a reply slip for permission to include the RCT in the sampling frame (Appendix 4.1). TMs nominated by a CI / PI and the RN linked to the RCT were subsequently invited to participate (Appendix 4.2.). A standard recruitment pack was sent to each invitee by email. This included a participant information sheet (Appendix 3.2), a reply slip and a personalised letter. Non-responders were sent one reminder email (Fig 22).

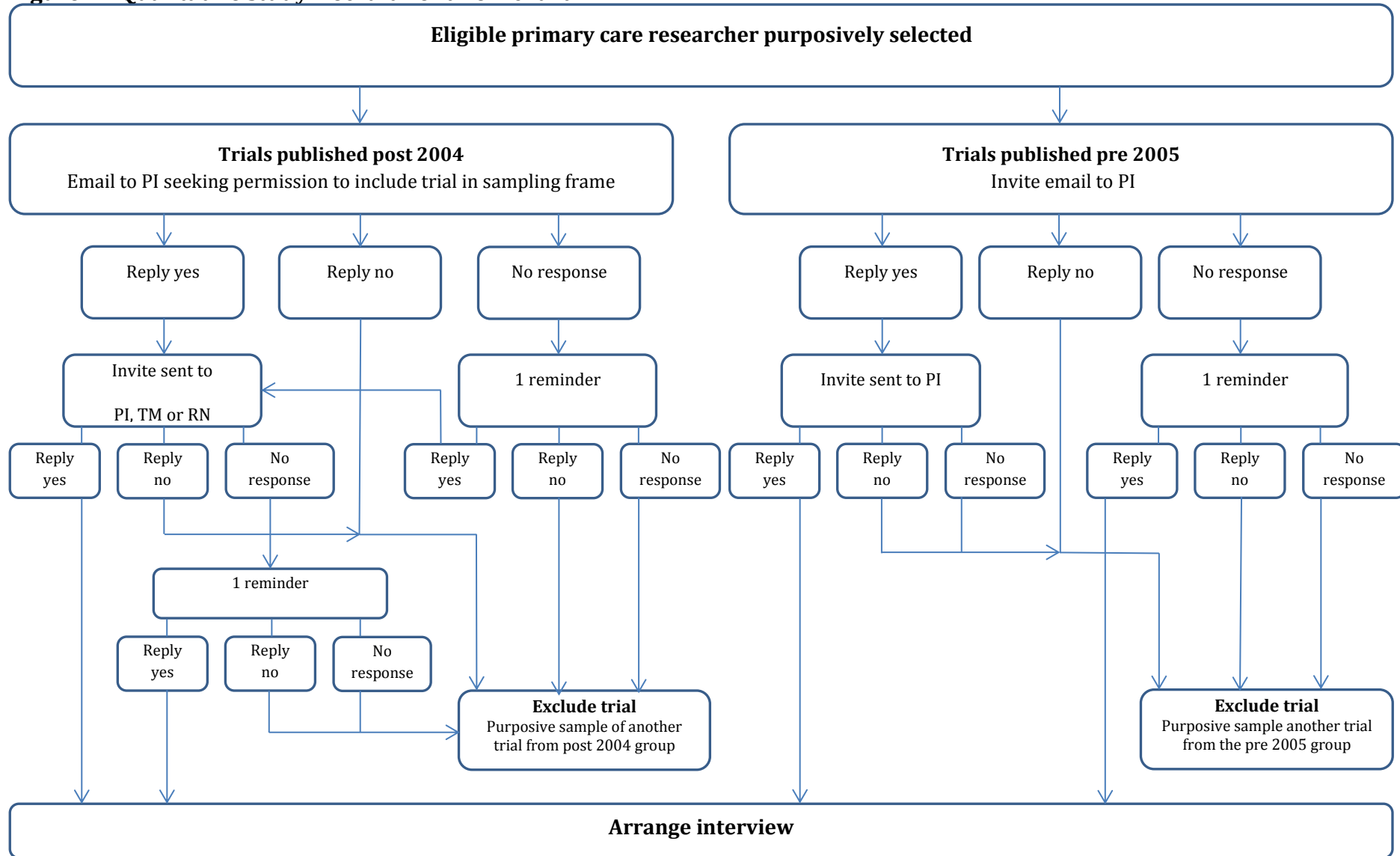
For RCTs published between 2000-04, PIs, and RNs were sent a standard recruitment pack as outlined above.

5.5.1. ETHICS APPROVAL

Ethics approval was sought originally to conduct in-depth interviews with PI/CIs, TMs and RNs who had worked on MRC GPRF RCTs published from 2000-2010. This was granted on the 19.04.10 by UCL Research Ethics Committee: Ethics application 2342/002 (Appendix 3.1). A minor amendment was granted for three changes to the recruitment and interview process on the 7.02.11 (Appendix 3.1). The changes proposed were:

1. To extend the sampling frame to include PIs and TMs from other UK clinical trials units.
2. To seek permission to contact the Trial Managers Network.
3. To add another question to the reply slip sent to PIs. The additional question invited the PI/CI for an interview.

Figure 22 Qualitative study: recruitment flow chart



5.6. DATA COLLECTION

Those recruited were invited for an in-depth interview at a time and place convenient to them. A study explanation was given before each interview. This included:

1. An explanation of attrition from RCTs, and other terms used to describe attrition for example “drop out”, “withdrawal”, “loss to follow-up”.
2. A statement about data confidentiality and anonymity.
3. An explanation about probing to explore in greater depth the retention strategies used in RCTs.
4. A statement of reassurance that there were no right or wrong answers to the questions asked.

Potential participants were asked to sign a consent form (Appendix 3.3). This included consent to record the interview. A signed copy was then given to each participant and another copy was kept for records at MRC GPRF.

To put the interview in context, participants were asked to focus on loss to follow-up in the RCT/s they were currently working on or have worked on in the past (Bowling 2002). The interview was opened with a broad question inviting the interviewee to talk about RCTs they had worked on in order to get them to think about RCTs (Pope et al. 2000). More specific, yet open questions, about retention and loss to follow-up in RCTs based on their reply were then asked to further explore what was said (Pope et al. 2000). Probing for depth was introduced during the interview when rapport was established with the interviewee.

During the interview, detailed written notes were kept on any contextual observations made (Bailey 2008). These were referred to during the interview in order to further explore topics and to keep the interviewee and interviewer focused on the topic of loss to follow-up in RCTs and retention. Notes were used to: formulate summaries of the discussion before moving to the next part of the interview, to also seek clarification of points raised, and to support the data analysis. Participants in each of the three groups were interviewed until saturation was reached and no new themes or retention strategies emerged from the interviews (Bowling 2002).

5.6.1. TOPIC GUIDE

Questions in the interview topic guide drew on the findings of the Cochrane literature review and also on the objectives of the qualitative study set out in section 5.2.1. of this chapter (Appendix 3.4). The topic guide was developed by myself and further refined through discussion with the research management group which included two primary care researchers. One pilot interview with a trainee GP was conducted in order to test the interview schedule. Development of the interview schedule was iterative; after the first five interviews the topic guide was reviewed by the transcript review group (see section 5.8.1. of this Chapter) and further refined.

The first section of the topic guide was designed to ask open questions. The questions at the end of the topic guide were specifically about the retention strategies identified by the systematic review. The interview topics addressed:

1. The interviewees experience of loss to follow-up in RCTs.
2. The factors they thought contributed to retention in RCTs.
3. The factors they thought contributed to loss to follow-up in RCTs.
4. Decision making around which strategies to use to prevent or control loss to follow-up, and how these decisions are made.
5. The impact of ethics committee approval on the use of incentive strategies to increase follow-up.
6. The advantages and disadvantages of using strategies to improve retention identified by the Cochrane systematic review.

At the end of each interview, the interviewee was given a list of all of the retention strategies identified by the systematic review. They were asked about the advantages and disadvantages associated with using each retention strategy. The conduct of this stage of the interview was changed after the first three interview transcripts were reviewed. It was unclear from those three transcripts which strategy was being discussed because the participants did not follow the order of the list of the retention strategies given to them. A card system, with one strategy per card plus a succinct explanation of that strategy, was subsequently developed and used for all subsequent interviews. This change was piloted among colleagues at the MRC GPRF. It was clearer from the subsequent interview transcripts which strategy was being referred to making it easier to code textual data for analysis related to the different RCT retention strategies.

5.7. DATA MANAGEMENT

5.7.1. TRANSCRIPTS

The interviews were digitally recorded with an Olympus WS-300M voice recorder. The interview date, number, and role of the interviewee e.g. D/M/Y/ Number/ TM/PI/RN were used as file identifiers. Digital voice recordings were uploaded to a secure password protected computer. These were checked for sound quality, and sent via an internet secure delivery system YouSendIt™ to an MRC contracted transcription service. Interview recordings were transcribed verbatim. Transcripts were checked for accuracy against the recording and corrected and anonymised by removing place and person names, RCT identifiers and acronyms. Misinterpretations in the transcripts were corrected by reference to the field notes and digital recordings for each interview. These errors were minimal across all transcripts. A short anonymised biography referring to the role of each interviewee in primary care clinical RCTs was added to each transcript.

5.7.2. DATA STORAGE IN ATLAS TI

The interview transcripts were stored in a text bank folder in Atlas ti. This software facilitates the labelling of textual data with appropriate codes for subsequent retrieval and analyses. Transcripts and codes can be stored in group folders. For example all transcripts from the interviews with PIs were grouped in one folder labelled “PI”. Transcripts for interviews with TMs and RNs were stored in similar folders. Atlas ti. allows data queries to be applied to transcript groups. The results can be exported, saved and printed for subsequent reference and data analyses. For instance textual data coded “communication” and “text messaging” can be retrieved from one or more of the different groups of transcripts stored.

5.8. DATA ANALYSIS

A thematic analysis was conducted. The interview schedule was used as a framework guide for the analysis. The analysis involved reading, rereading, and coding transcripts, and comparing coded content across transcripts and groups of interviewees for emerging themes around the following:

1. The spectrum of strategies used to improve retention.
2. Factors associated with RCT retention.
3. Decision making about which strategy to use.
4. The impact of ethics approval on the use of incentives in RCTs.

5.8.1. TRANSCRIPT REVIEW GROUP

Following transcription, the transcripts were read and anonymised. A four member transcript review group was convened with CV, FS, GR, VB as members. The purpose of the group was to discuss each transcript, agree the coding framework, and to identify the emerging themes. The group was heterogeneous in terms of each members' professional background and previous experience of qualitative research. This allowed for the different perspectives of working on RCTs. The group included a systematic reviewer (CV), a medical sociologist (FS), a primary care general practitioner (GR) and myself, the PhD student (VB). The first six transcripts were critiqued by the group for interview technique to ensure that:

1. The interviewees understood and were able to answer the questions asked during the interview.
2. Leading questions were avoided by the interviewer.
3. Appropriate probes were used to allow interviewees to expand on issues around the use of retention strategies identified by the systematic review and any other strategies used.

Each subsequent transcript was reviewed independently by at least two of the group members who documented the emerging major themes in the transcript. These themes were subsequently discussed by the group in pre-planned monthly meetings as the data were collected. There was a high degree of convergence in the themes identified by the group members. The transcripts were analysed iteratively, and the early results incorporated and probed in later interviews to increase the depth of the findings.

5.8.2. DATA CODING

The codes developed for the textual data were both deductive and inductive. Deductive codes were based on the retention strategies identified by the systematic review. Broad codes for the six strategies identified i.e. "communication", "incentives", "questionnaires", "methodology", "case management" and "behavioural" were decided upon a priori. Codes for "spontaneous" and "prompted" mentions of the use of strategies to improve retention were also agreed. As the transcripts were read and re read, inductive codes were agreed. For example, for the broad code "Communication" sub codes e.g. "letter", "emails", "telephone", "text messaging" were used (See Appendix 4.4.). Inductive codes were also decided upon for other strategies other than those identified by the Cochrane review, and for factors associated with retention and loss to follow-up. All inductive and deductive

codes were discussed and agreed between the PhD student (VB) and one PhD supervisor (FS) prior to coding the transcripts.

As the transcripts and contemporaneous written notes were read and re read, the identified codes were used to label the textual data in each transcript in Atlas ti for data retrieval and analyses. All transcripts were coded by myself, the PhD student (VB), and the first two coded transcripts were checked by the PhD supervisor (FS). A key consideration in the coding and the analyses was to ensure the distinction between data produced spontaneously and that which was specifically asked about. Therefore, data were coded to take account of the response and the question that prompted that response in order to apply appropriate emphasis on responses. Where interviewees spontaneously mentioned a strategy that they had used in the open section of the interview schedule (see Appendix 3.4. and section 5.6.1. topic guide) e.g. a spontaneous mention by the interviewee of reminder letters used for follow-up, the interviewer probed the interviewee to talk more about the use of that strategy. This text was then labelled with the codes “spontaneous”, “communication”, “letter”. Textual data in the open section of the interview was also labelled with inductive codes. For example, factors thought to impact upon retention were labelled e.g. “altruism”, “staff flexibility”, “appointment schedules”, “staff personalities” where this was considered to be appropriate (see Appendix 4.4). This coding process was applied across all of the transcripts.

5.8.3. DATA RETRIEVAL AND INTERPRETATION

The transcripts of the TM interviews were analysed first because of the TMs central role in coordinating RCTs. The transcripts of the PIs / CIs were then analysed in order to understand the leadership, methodological, and decision making processes associated with RCT retention. Finally, the RN transcripts were analysed to understand the challenges of retention with face to face follow-up in RCTs conducted in primary care GP practice sites.

To explore the use and the barriers to the use of the six strategies to improve retention identified by the Cochrane review - the labelled textual data, i.e. quotes from across the groups of interviewees about the use of retention strategies were retrieved from the coded transcripts stored in the Atlas ti. database. Similarly, textual data were also retrieved on: the advantages and disadvantages of using each retention strategy, the decision making process around choosing which retention strategy to use when loss to follow-up occurs, and the barriers to getting ethics approval for the use of incentives. Textual data about the factors thought to lead to loss to follow-up and other retention strategies used but not yet formally evaluated were also retrieved for content analysis.

The output from each Atlas ti. database query was downloaded into a Microsoft word file. The coded text retrieved, was summarised, and then interpreted grounded in the original transcript from which it was extracted. The emerging themes and content were verified and confirmed by constant comparison across the three groups of trial personnel (i.e. PIs, TMs, RNs). Deviant cases were identified and recorded, e.g. where interviewees did not use strategies identified by the review, or they had used a different retention strategy or disagreed with the majority view. This was in order to show the spectrum of points of view about the use of retention strategies and factors associated with retention in primary care RCTs. The themes identified were grouped and described to answer the objectives of the qualitative study. The findings are reported in Chapter 6. Relevant quotes, representing the interviewee's views, were selected to illustrate the findings.

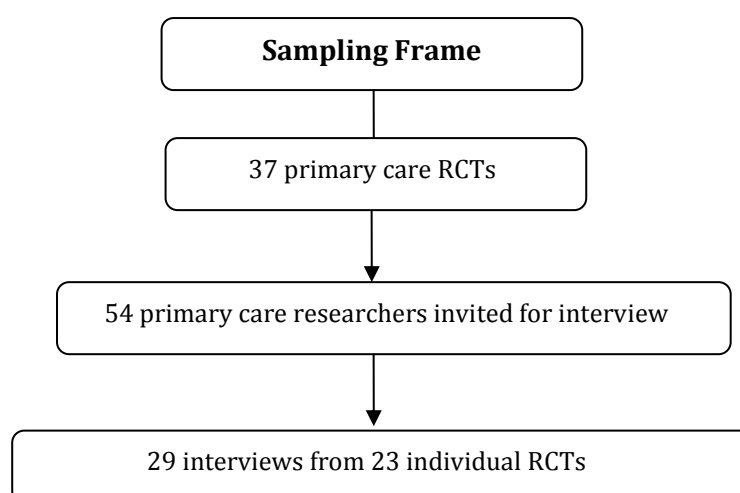
CHAPTER 6: QUALITATIVE STUDY RESULTS

6.1. INTRODUCTION

In this chapter the results of the qualitative study are presented. First a description of the sample of interviewees and how they made decisions about the strategies they used to improve retention is reported. The interviewee's experiences and their perspectives on the use of the six types of retention strategies identified by the systematic review are also reported. The impact of seeking ethics approval on the use of incentives is also recorded, and new strategies for future evaluation are identified. Verbatim quotes from the transcripts are provided to support the interpretation of the data.

From the 37 UK primary care RCTs included in the sampling frame (Fig 23), 54 potential interviewees across the three groups (i.e. PIs, TMs and RNs) were invited for an in-depth interview. Interviews were declined by 11 researchers, seven of whom identified a replacement researcher to approach from the RCT that they were sampled from. Fourteen invitees did not respond after one reminder. Overall, 29 of the 54 invitees agreed to an in-depth interview. They were from 23 different RCTs. In-depth interviews were conducted with 10 TM, 10 PIs/CIs, and nine RNs between the 10.08.10 and 10.05.11. At the time of interview, all of the interviewees were working on research conducted in UK primary care settings.

Figure 23 **Qualitative study sampling frame: number of interviewees**



Thirty (81%) of the 37 RCTs included in the sampling frame were published after 2004, and had loss to follow-up rates of between 6% - 39%. Twenty-three interviewees were from this group of RCTs. Six interviewees were from RCTs that were published before 2005, four of these interviewees were RNs and two were TMs (see Tables 18 and 19 for the characteristics of interviewees).

Table 18 Qualitative study: characteristics of interviewees

| Interviewee characteristics | Number of interviewees |
|--|------------------------|
| Gender | |
| Male | 10 |
| Female | 19 |
| Role | |
| Research nurse | 9 |
| Principal investigator | 10 |
| Trial manager | 10 |
| Location | |
| London | 8 |
| Midlands | 8 |
| Northeast England | 3 |
| Southwest England | 3 |
| East of England | 5 |
| Scotland | 2 |
| Unit | |
| University/Research organisation based | 23 |
| General practice site based | 6 |

Seventeen interviewees were from RCTs with loss to follow-up rates below 20%. These RCTs were from the fields of nutrition, musculoskeletal, ear nose and throat (ENT), neurology, respiratory medicine, mental health, endocrine, and health promotion. Thirteen of the RCTs from this group used face to face methods for follow-up either at home or at a general practice clinic site. Postal questionnaires were used to measure primary and secondary outcomes in the remaining four RCTs.

Table 19 Qualitative study: other sample characteristics

| Other characteristics | Number of interviewees |
|---|------------------------|
| Number of interviewees from RCTs published between 2000-2004 | 6 |
| Number of interviewees from RCTs published between 2005-2010 | 23 |
| Number of interviewees from RCTs conducted through the MRC GPRF | 19 |
| Number of interviewees from RCTs conducted through other research units | 10 |
| Number of interviewees recruited from RCTs with loss-to-follow-up levels* | |
| >20% | 10 |
| <20% | 17 |

* Two nurses were not linked to a sampling frame RCT

Ten interviewees were recruited from RCTs with loss to follow-up rates above 20%. These RCTs were conducted in the areas of elderly care, musculoskeletal medicine, gynaecology, and minor medical conditions. Six of these RCTs used postal questionnaires to collect data for the primary outcome, the remainder used clinic or home visits.

6.2. CHARACTERISTICS OF INTERVIEWEES

6.2.1. PRINCIPAL INVESTIGATORS (PIs)

Nine PIs were registered GPs involved in clinical practice, and each had an academic role. One PI was a senior academic in the field of primary and community care research. The PIs worked through primary care academic research units. All were responsible for the overall design and implementation of RCTs, including applying for research governance and ethics approval. Some PIs were also the CI for the RCT sampled. The 10 PIs were equally spread between RCTs with above and below 20% loss to follow-up. Seventy per cent of PIs were male.

6.2.2. TRIAL MANAGERS (TMs)

The TMs had experience coordinating research, collecting data via telephone, post, email and text message. They were based in academic research units that conducted research through GP practice clinics. None of the TMs were GP practice site based. All apart from one TM had experience managing more than one RCT. Eight TMs were recruited from RCTs with loss to follow-up rates of <20%. Two TMs were recruited from RCTs with over 20% loss to follow-up. Seventy per cent of TMs were female.

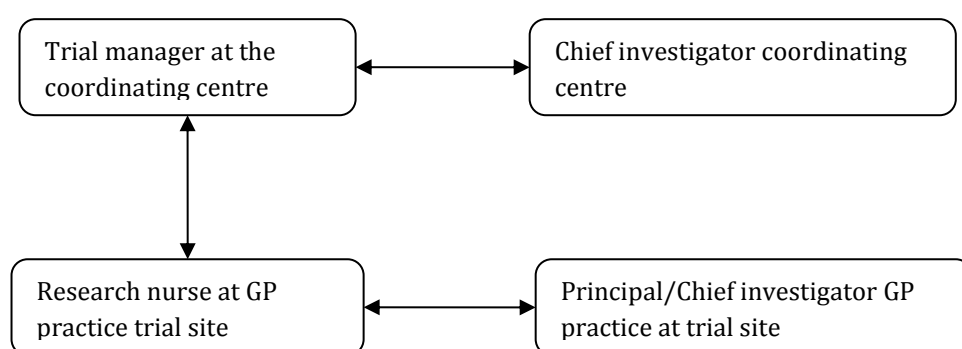
6.2.3. RESEARCH NURSES (RNs)

Six of the RNs were based at GP practice sites and a further three were based at a national primary care research coordinating centre. The site based RNs were responsible for managing RCTs at site level. This included data collection by telephone interview, face to face interview, postal questionnaire, and collection of biomedical specimens. Their role also included communicating both with the coordinating centre and clinicians at the site about recruitment and follow-up. These RNs were also responsible for conducting site quality control visits on behalf of the national primary care research coordinating centre and for supporting other RNs at regional level to manage data collection at GP practice sites. Furthermore, they were also involved in piloting RCT processes. All of the RNs were female.

The role of the three RNs based at the national primary care coordinating centre differed from the site based nurses in that they had input into RCT design. They also coordinated the monitoring of data quality for a portfolio of primary care research that included RCTs. These RNs occasionally conducted data quality control visits at sites and had previously held positions as GP practice site RNs.

Four of the RNs interviewed were from RCTs with loss to follow-up rates of <20%, three were from RCTs with loss to follow-up rates of >20%. Two RNs were working on RCTs yet to be published and had not worked on any RCTs in the sampling frame. One of these RNs had experience working in RCTs conducted for the pharmaceutical industry. The transcripts from these two interviews were included in this analysis as it was felt that they would contribute to the richness and breadth of the data collected. The communication flow between PI/CI, TM and RNs in primary care RCTs is presented in Figure 24.

Figure 24 Flow of communication within RCT teams



The researchers interviewed were very experienced in the field of primary care research. Although they were sampled from RCTs with different rates of loss to follow-up (Table 19), they were asked at the beginning of each interview to think of loss to follow-up from RCTs in general rather than the RCT that they were currently working on, or were sampled from. Therefore, the results reported in this chapter are drawn on the researchers experiences of RCTs from both within and outside the RCTs identified for the sampling frame. Other interviewee characteristics are outlined in Table 18.

6.3. MONITORING AND DECISION MAKING ABOUT LOSS TO FOLLOW-UP

Interviewees were asked about when and how they identified and monitored loss to follow-up in RCTs, and what they did about this when it presented.

6.3.1. MONITORING LOSS TO FOLLOW-UP

The TMs and RNs said that they began to think about loss to follow up when participants either did not return for a follow-up interview or failed to return a questionnaire. This process was overseen by PIs / CIs and monitored centrally by TMs, and locally at the RCT site by RNs. For larger RCTs, data managers and research assistants also monitored follow-up.

TMs, RNs and PIs mentioned that systems were put in place for monitoring follow-up and loss to follow-up centrally at the coordinating centre for each RCT. Problems were escalated to the steering group if loss to follow-up was unresolved. The approach used by TMs to monitor loss to follow-up appeared systematic. All participant events were logged in follow-up databases. The details of the dates that letters and questionnaires were sent, the number of reminders to be sent, the number of questionnaires returned and the number expected were recorded in these databases.

The calculation of standardised follow-up rates at time points accounting for participants in the process of returning questionnaires was considered a particular problem by PIs and TMs when reporting losses to follow-up. A seventy per cent follow-up rate was considered poor retention by some PIs. Data management programs were sometimes used to calculate follow-up rates which were then discussed at coordinating centre team meetings. The content of these team meetings were described by this TM:

“every fortnight we run through each site how many [participants] [are] booked for this week, how many have you seen, what’s happened to the ones that you’ve not seen, how many of those are you trying to book, how many have you given up on? So……., every two weeks it gets reviewed and I think probably reviewing it more often is good.”

Trial manager interview 17, RCT loss to follow-up <20%

The RNs monitored follow-up and loss to follow-up at RCT general practice (GP) site level. Monitoring of follow-up was documented and communicated to the coordinating centre. The form of reporting depended upon the systems set up for the RCT. Some RNs said that they acted early on loss to follow-up when participants failed to attend a follow-up visit

after two or three missed appointments. Other RNs identified loss to follow-up as a problem when three or four participants did not attend for their follow-up visit. Some RNs reported that they kept the site PI / CI informed of their RCT monitoring activities through formal and informal discussions at the site. Other RNs used a flagging system on the EMIS GP practice site computer system which they felt enabled them to target non-attenders when they returned for non-RCT related routine visits at the GP practice. This RN describes how this process worked:

"If the phone call and the calls and the letters hadn't worked ... I have put an alert on there [EMIS].... just to sort of flag up so that while the patient's there [at the clinic]. Because at least it gives them the opportunity to say, yeah, I'm really sorry but I don't want to take part any more..., and have some sort of end point rather than just wavering away into the ether and not knowing ...".

Research nurse interview 2, RCT loss to follow-up >20%

The TMs communicated with RNs at site level when RCT participants did not respond to communication from the coordinating centre. The RN then tried to determine the barriers to follow-up and appropriate solutions for this so that the participant could continue to participate in the RCT as described by this RN:

"... people don't have to give a reason why ... they drop out, but if you can find the reason why then it may be that you can address whatever the issue is, and actually not lose them..."

Research nurse interview 5, RCT loss to follow-up <20%

6.3.2. DECISION MAKING ABOUT WAYS TO DEAL WITH LOSS TO FOLLOW-UP

Across the interviews it was clear that decisions about which strategy to use to deal with loss to follow-up are made on an RCT-by-RCT basis. Some PIs said that problems with follow-up were not easy to predict at the beginning of an RCT and that there was no standard way of dealing with loss to follow-up once it arose:

"You wouldn't necessarily in your original ethics approval have put down everything you might possibly want to do at a later date. And what is practical and it depends what your outcome for the trial is.... So it's a take it on a case by case basis, it's nothing, there isn't a systematic way of saying "well if this doesn't work we'll do that".

Principal investigator interview 19, RCT loss to follow-up <20%

For PIs, the trigger for using strategies to improve retention was when loss to follow-up affected the power of the RCT and the collection of data for the primary outcome, or when loss to follow-up led to an imbalance between the study arms. Where there was convergence between the target and the actual numbers retained then loss to follow-up was not considered a problem as described by this PI.

“If the line for..., follow-up achieved against follow-up target is falling away so there is a divergence then we would perceive it [loss to follow-up] is a problem. If there is a convergence then we don’t see it as such a problem so... it’s close, careful monitoring and change[s] over time and it is set... against a target line based on what we think we ought to be able to get”.

Principal investigator interview 19, RCT loss to follow-up <20%

Some PIs and TMs talked about how decisions were made about which strategy to use to improve retention. This PI describes their concern about loss to follow-up, how it is dealt with and how individual solutions to fit the problem are sought:

“I worry about it [loss to follow-up] right away, yeah, and treat a lack of follow-up as a critical incident of the study management group meeting where we would say, “This guy hasn’t come for his follow-up visit you know, can we work out why, is this a one off..., the man’s moved ...there’s no way we can get him, or is there a problem?”, and really try and focus on that...”

Principal investigator interview 4, RCT loss to follow-up <20%

Some PIs and TMs sought the opinion of other experienced researchers who had dealt with loss to follow-up. They said that, at team meetings for key follow-up time points, a lot of time was spent thinking about how to optimise contact with RCT participants and about the different ways to minimise loss to follow-up. Decisions about the strategies to use were made collectively by the team at the RCT coordinating centre and occasionally service users and collaborators were involved in this process. The decision made was based on consensus regarding the best approach to use for a specific loss to follow-up circumstance. These strategies were then communicated to RNs (if data was being collected at site level) or implemented from the coordinating centre (if data was being collected centrally). Some PIs felt that all members of the team had “to buy into” the follow-up strategy, particularly those who would have to implement it at either the RCT site or at the coordinating centre. The TMs experience of dealing with long-term follow-up played an important role in informing the decisions made to reduce loss to follow-up, as expressed by this TM:

“...it’s mostly a team decision. We’re very lucky in that a couple of the PIs are, ... very hot on this topic [it] is so much easier than when you’re dealing with PIs who maybe don’t think quite like that. And so it would be up to... the trial team to suggest... It’s all done... very open and it’s always well received but it’s just obviously something that PIs who maybe haven’t had experience of a long-term follow-up study don’t necessarily think about at the start so that’s kind of where we see our roles coming in”.

Trial manager interview 26, RCT loss to follow-up <20%

When follow-up appointments were missed by the RCT participants, attempts were made by RNs to make an alternative appointment. RNs also tried to determine the barriers to follow-up for the participant and to find appropriate solutions to resolve this. For example, in some instances a home visit was arranged to collect data if the participant was unable to return to the clinic for follow-up. This usually happened in small towns and rural areas where the RN was known to the participant. Other RNs described collecting follow-up data by telephone. It is unclear from the interviews whether this was a spontaneous action by the RN or an action conducted in response to a request from the RCT coordinating centre.

Some RNs mentioned consulting the RCT protocol / or a pre specified RCT procedures manual for guidance on which strategies to use when loss to follow-up occurred. If the retention strategies were perceived by the RN not to work, then they would try another strategy, for example, a home visit. Sometimes the coordinating centre was informed of this, at other times it was clear that the RNs acted alone.

6.4. STRATEGIES USED TO IMPROVE RETENTION

In the following sections the use of the retention strategies identified by the Cochrane systematic review in primary care RCTs is presented. The interviewees’ thoughts on the effect of these retention strategies and their perceptions of the advantages and disadvantages of using the retention strategies are also reported. Consideration is given as to whether the retention strategies were mentioned spontaneously as this could indicate how routinely the strategy was used.

6.4.1. COMMUNICATION

Communication strategies for example contact with participants by telephone, letter and email were routinely used by researchers to improve RCT retention. Most interviewees spontaneously mentioned communication strategies when they were asked specifically

about the factors that lead to retention in RCTs. They also said that either knowing the participant or having a good rapport with the RCT participant also improved retention.

Several methods of communication were used to encourage or remind RCT participants to return for follow-up visits or to return questionnaires. These were:

1. Sending letters or cards by post.
2. Contact through telephone, text message and email.
3. Home visits.

6.4.1.1. Letters and cards

Letters

Many different types of letters were sent to RCT participants to try to improve follow-up. The types of letters and dispatch used were:

1. Reminder letters sent before follow-up appointments.
2. Letters to confirm a new appointment time.
3. Letters accompanying follow-up questionnaires.
4. Reminder letters to return follow-up questionnaires.

Letters were sent by RNs from the clinical site only if this was pre-specified in the study protocol / RCT procedures manual for participants who had not returned for an RCT follow-up visit. These letters were usually short. For some RNs a telephone reminder was preferable to sending a reminder letter because they considered it easy to engage in dialogue with the participant and to invite them to return a questionnaire or to return to the clinic for a follow-up appointment. Some RNs openly said that they did “*not like letters*”. They speculated that the participants might not open a letter if it did not look interesting, or that the letter could get lost in the post, or be opened by another person.

TMs regularly used letters to communicate with RCT participants and they felt that these were useful for retention. Some used standardised letters to send with a questionnaire that also contained a statement about how much the participant was valued by the RCT team. The letters sent to participants were usually signed by the TM if the letter was sent from the coordinating centre. There was uncertainty among TMs whether the signatory had an impact on retention. The TMs thought that consistency in the person signing the letter was more important than the status of the signatory. This was thought to be particularly so once participants were recruited to the RCT. Some TMs thought that

including the name of the chief investigator in a letter was important because some participants might respond to a figure of authority.

The interviewees described the many different ways that they used to prepare the letters that were sent to participants in the hope of improving retention. Some TMs used electronic coloured signatures, while others signed letters by hand. Some thought that the participants may take more notice of the institution sending the letter rather than who signed it and therefore, envelopes were franked with an institution logo, however there was uncertainty about the impact of this on questionnaire response and RCT retention.

Some TMs mentioned that brown envelopes were the cheapest to use. Some said that they "*hated*" these and thought that participants may think they contained either "*bills*", a "*letter from the tax office*", "*junk mail*" or correspondence "*from charities*" and that they could remain unopened as a result. One TM said that there was "*no evidence*" that envelope colour impacted response. The TMs were ambiguous about the effect on response of handwritten envelopes over pre-addressed labels.

Different ways were used by the TMs to send letters. First class post was routinely used to send letters because it was felt that this gave the impression that the team cared. The TMs also felt that the letter was more likely to be opened by the addressee if a first class stamp was used. Second class post was used to save money for prepaid reply envelopes sent with questionnaires. It was thought that postal delivery was affected by extreme weather conditions in winter, and that the geographical location of the participant could affect whether responses are returned on time, particularly from RCT participants living in rural areas. Some TMs and RNs demonstrated altruism, flexibility, and commitment to the RCT by delivering letters by hand to participants who were otherwise difficult to contact.

Recorded delivery was used by TMs however they had mixed attitudes toward this. This was sometimes used for delivery of a second copy of a questionnaire to ensure it reached the participant. If the letter was undelivered this was sometimes the only confirmation for the TM that a participant had moved away. One TM and one RN who had used recorded delivery thought that it could be inconvenient for participants if they had to go to the post office to pick up the letter / package. They felt that it would be best to forewarn the participant before hand to expect a recorded delivery package / letter.

Few PIs commented on the usefulness of letters for retaining participants in RCTs. One PI mentioned that they did not get involved in reviewing letters written by TMs because they did not want to interfere with the management of the RCT. Those who did comment on

the usefulness of letters referred to the tone and the language used, and whether the letter was personalised or generic. One PI gave an example of a generic letter that was considered off-putting and upsetting by the RCT participants where they were addressed by their disease / condition, for example; “*dear stroke suffer*”. One PI thought that it could be beneficial to get participant representatives to review letters before they were posted out to participants. Some PIs mentioned that, for large RCTs, mail-outs were a boring task for TMs to undertake and a great burden for the administration team.

Cards

Different types of cards were also sent to participants on behalf of the RCT team. These were sent in order to show appreciation of the participants’ involvement and to maintain a connection with participants. The types of cards used were: Christmas, birthday, and new home greeting cards. The interviewees were divided in their opinion about the usefulness of these in terms of retention. Christmas cards were sent to RCT sites and were considered a useful reminder to GP practice site staff about the RCT. Some TMs thought that sending Christmas cards directly to participants could be considered “*naff*” by the RCT participants. Others thought that these were costly to send. But others thought that if RCT participants were being sent packs, for example with questionnaire/s, in December that this could be a good time to send a Christmas card to show the teams appreciation for the participants’ time as well as being a reminder of the RCT. The RNs and PIs tended to agree with this.

Birthday cards were thought by one TM to be useful for children to keep them interested in an RCT. However, this was not thought to be the case for adults. Some interviewees across all three groups interviewed thought that sending birthday cards to participants from the RCT team may come across as being over familiar with participants and could even be disturbing for some participants. A more personalised approach to sending cards with the aim of retention and maintaining communication with RCT participants was if a card was sent in response to a life event that a participant shared with an RCT team member during a follow-up visit. One TM described such an event as follows:

“If a participant rings us up and say[s], oh by the way, I’ve moved, here’s my new address. Then we’ll put a good luck in your new home card in the post.Or if somebody has had a particularly difficult time and they’ve shared it with us and there has been say a long illness of a spouse or a family member and then they’ve died, then we might pop a sympathy card in the post. So we always take the lead from the participant as to how much they’ve chosen to share with us about their lives and if they’ve been very open and forthcoming about things then we try and reciprocate on the

same level but we always take our cues from them. We don't go round blindly doing the same thing for everybody on that level, other than the Christmas cards because we feel it's very important that you try and keep the line in a place that's comfortable with the participant, you never want to cross it with them so we always take our lead from them".

Trial manager interview 26, RCT loss to follow-up <20%

Some RNs thought that cards, if used, should be hand written where possible. One RN reported that some participants were annoyed at receiving greeting cards from the RCT team in an RCT that she had worked on.

6.4.1.2. Telephone calls and short message texting (SMS)

Communication by post was sometimes used as a standalone method to communicate with RCT participants. However, it was more often used by TMs and RNs with a follow-up telephone call to connect with or to collect data from participants.

For the RNs, a telephone call to the participant was seen as a successful retention strategy for participants who had missed a follow-up appointment. They felt that often the reasons for non-attendance were disclosed during the conversation. Some TMs recognised that RNs used telephone calls as a useful mode of communication with RCT participants. TMs thought that reminder calls to participants prior to follow-up appointments might increase attendance as described by this TM:

"I imagine if [nurses] can phone them it would really help retention, just to keep them interested in the trial because I think just getting a slip of paper through the door with a time and date on doesn't necessarily mean as much as also getting a phone call a day or two before saying, did you receive it, can you make it?"

Trial manager interview 10, RCT loss to follow-up <20%

The TMs also thought that a reminder telephone call to the site to remind the RN that a participant was due to attend for a follow-up appointment could improve participant follow-up.

TMs and RNs described how they obtain participant contact details and alternative contact details during the RCT recruitment visit in order to improve follow-up. The ground rules for contact through other family members during RCT follow-up were usually identified and set out during the recruitment visit. Some RNs gave their personal mobile number or office number to the RCT participant to facilitate ease of communication during follow-up.

This RN describes the efforts made to ensure telephone contact details and any alternative contact details were recorded:

"I try and make sure ... right at the beginning ... that I've got all the patients' telephone numbers so I have their home number, their mobile and if they're prepared to give it, I have their work number as well. And one of the other things I always check and record is whether or not they're happy for us to leave messages on all of those phones so, you know, if their wife picks up the phone or whatever, they've given permission for us to say to them, "you know, John's due for an appointment next Tuesday". And quite often I find that, ... if you're allowed to include relatives, it's a real bonus."

Research nurse interview 8, RCT loss to follow-up <20%

The PIs did not mention using telephone contact with participants. One PI thought that it would be "*daunting*" for a participant to receive a call from the RCT PI. Nevertheless, PIs were involved in decision making around when to use telephone contact, specifically where loss to follow-up was thought to be due to participant fatigue from data collection through diaries or repeat questionnaires. PIs also felt that telephone contact should be conversational to build up a rapport with participants especially when used to collect outcome data in the context poor questionnaire response.

The advantages of using telephone contact to improve retention identified by the interviewees were; that questionnaires can be administered over the telephone, a rapport can be built up with participants, the participants have an opportunity to explain their circumstances and negotiate a change of appointment. A disadvantage to the use of telephone contact with participants mentioned by one TM was that the participants may not answer calls between 9am and 5pm because of an unwillingness to engage with telephone marketing calls. One PI also speculated that young people may change their mobile phone service provider and number more frequently than other groups of participants and that this could make young people more difficult to contact. RNs mentioned that telephone calls can be frustrating and time consuming for them if the participants do not answer. The RNs were also reluctant to leave messages on answerphones because of the risk of breaching confidentiality. One RN thought that an unplanned phone call was more intrusive for participants than receiving a letter.

SMS texting was used by very few interviewees to improve follow-up in RCTs. The interviewee's views on the effect of SMS texting on retention in RCTs were mixed. Most thought that SMS texting would be useful for communicating with young people in RCTs. Use of an automated system for texting RCT appointment reminders similar to that used in

the NHS for clinic appointments was mentioned by many of the interviewees. This was thought to be a potentially useful strategy to improve retention of young people in RCTs. One RN used SMS texting at the site for follow-up clinical appointments, but reported that this did not improve clinic attendance. However, it was felt SMS texting was useful for reminding patients about appointments and for giving them the option to make another appointment.

Some TMs thought that SMS texting could be used as a last resort when all other methods of contact with participants failed. However, as telephone numbers change, unrecognised telephone numbers were thought to be off putting for RCT participants. SMS texting was also thought to be limited to those with mobile phones who can text. The PIs made few comments on the use of SMS texting but said that they would like to see more evidence for the use of this as a way to improve retention in RCTs.

6.4.1.3. Email

Some TMs and RNs included email communication in the battery of methods they used for contacting RCT participants during follow-up. Others had not used emails because participants had not given their email address for follow-up contact. Email was considered by most interviewees to be useful for communicating with RCT participants who lead busy lives and could be used by most groups as described by this TM:

“...the type of ..study, dictates whether we use things like email. Certainly with studies where we have an older population of participants, we... always offer it, we always advertise an email address and phone number and all the rest of it but if it's a younger study population we tend to encourage them more to use email and web based communication because that's the way that that age generation does things. So we sort of adapt how we do it depending on the study group”.

Trial manager interview 26, RCT loss to follow-up <20%

Barriers to using email for data collection identified by the TMs were that participants may not have a secure email address, and TMs may not have a system to manage the email data received from participants. Only a few PIs commented on the use of emails. They said that every mode of communication needed to be considered to improve follow-up in RCTs.

6.4.1.4. Reminders and calendars

The interviewees often described using a package of reminders to remind participants to return their questionnaire. Different communication strategies were used at different stages during RCT follow-up to deal with non-response as described by this TM:

"We send out the questionnaire..., if we don't hear back ...we will ring up to sayCould you possibly send it back to us?" If we still don't hearwe'll send .. another copy ... if we don't have a response from that copy then we'll ring them againif we still don't hear we've telephoned ...again to collect a set of core outcomes to get a response....."

Trial Manager interview 14, RCT loss to follow-up <20%

The interviewees from all three groups mentioned the importance of getting the balance right between the participants having enough reminders about follow-up procedures, and the participants' perception of being harassed by the number of reminders sent to them.

Trial calendars were rarely mentioned as a strategy to improve RCT retention and follow-up. However, these were used by one TM to provide reminders with prompts and information for participants about when to expect and when to return their questionnaire during a particular month.

6.4.1.5. Home visits

Home visits were used by some RNs and TMs to improve retention when people were difficult to reach. These were considered costly, time consuming and frustrating if the participant was out when the TM or RN called. All groups of interviewees thought that home visits were effective and useful for participants who could not make it to the clinic for follow-up. They thought that this was particularly useful for mothers with young children, poor and or elderly participants, nursing and residential care home residents, participants who were too unwell to come to the clinic for RCT follow-up, and participants with mental illnesses.

6.4.1.6. Blanket communication methods

Interviewees used several ways to keep participants informed about the RCT in which they were taking part. Some thought that these methods may improve RCT retention. The methods used were: information given via RCT websites, and newsletters. Some PIs mentioned that having RCT information and answers to frequently asked questions about the RCT as a resource on RCT websites could benefit RCT retention. They felt that the participants might feel part of something important if they were associated with an RCT publicised on the internet and that this may encourage them to return for follow-up. The potential use of mass media, for example TV and newspaper advertising, to raise awareness of RCTs across a broad social mix, was only very briefly mentioned by some TMs and PIs.

6.4.1.7. Newsletters

Interviewees varied in their opinion about the value and usefulness of the newsletters sent to RCT participants. Most interviewees thought that newsletters were useful for keeping participants and site clinicians informed about recruitment, retention, and general news about the RCT. Others thought that newsletters were less useful and could bias RCT results by contaminating and confounding the results of the treatment as usual group.

Newsletters were used by TMs and PIs to keep in contact with staff at sites, and to show how the participants were valued by the RCT team especially during long-term follow-up. Advice from patient representatives was sometimes sought to make newsletters more participant focused and engaging. The frequency with which newsletters were sent to participants varied from fortnightly to annually. One PI described using newsletters to coincide with follow-up time points specifically to increase retention.

Some TMs and RNs thought that newsletters could be perceived as a waste of resources by some RCT participants if these were sent too frequently. This could also be annoying for participants. Some TMs felt that there was a mismatch between what they themselves think is useful for RCT participants to know about the RCT and the response they seem to get from participants. This TM described the satisfaction felt by the team creating the newsletter which was not mirrored by the RCT participants who received it.

“Newsletters are another thing that we all love to do... we recently sent out a newsletter and we were all pleased with ourselves ... and then I’ll say to them [participants] “oh did you get the newsletter?” And... a good proportion go “ah, um, I think so...”. And I think.. when people receive so much stuff through the post it’s just another bit of, ...junk mail”.

Trial manager interview 7, RCT loss to follow-up <20%

Some TMs and PIs did not use newsletters to keep in contact with participants for methodological and economic reasons. Some TMs felt newsletters were labour intensive and not worth the additional cost. One TM did not use newsletters if these were not part of an intervention after RCT closure. Some PIs also thought that the information in the newsletter may contaminate and confound the treatment as usual group. This was thought to be the case particularly for behavioural interventions when compared to usual treatment as described by this TM:

“I know a lot of trials use newsletters to keep people informed, we tried not to do that because ...we were trying to find out, if the NHSwere going to provide the support for people at home, we wouldn’t be sending

newsletters, the NHS wouldn't do that.because we'd got a treatment as usual group, we didn't really want to be sending information out that might give them some essence of what the other two therapies were delivering".

Trial manager interview 17, RCT loss to follow-up <20%

In the next section the interviewees' use of incentive strategies is reported.

6.4.2. INCENTIVES

Incentives were sometimes used to increase questionnaire response in RCTs. Opinions differed about the effect of incentives on retention. When asked about successful retention strategies, the use of incentives to increase questionnaire return was mentioned spontaneously by most PIs and some of the TMs. The different types of incentives used were: monetary incentives, offers of monetary incentives for return of questionnaires, gifts, otherwise known as non-monetary incentives and offers of non-monetary incentives. Additional medical care given as part of participation in an RCT was thought to be seen by some RCT participants as a benefit or an incentive to participate and to return for RCT follow-up appointments.

Some of the interviewees across the three groups were unsure of the effect of monetary incentives and non-monetary incentives (gifts) as strategies to improve retention. They felt that response / retention in some instances could be dependent upon the RCT participant's personal circumstances.

6.4.2.1. Monetary incentives

Giving monetary incentives to participants was a sensitive issue for some interviewees and opinions varied about the use of these. It is clear from the interviews that the attitude toward giving small incentives to participants is changing from one of disapproval to approval as the attitudes and expectations of people toward time and work has changed. This was expressed by this PI and TM:

And you mentioned that there's a shift, [for example] 10 years ago you would have thought differently about using incentives?

"Yes, I think I would have seen it as a potential bribe, whereas now I see it as more... how society is going really, people don't expect to do anything for nothing".

Principal investigator interview 16, RCT loss to follow-up >20%

“I know that the evidence is mixed as to whether incentives to participants work and the nature and the value of those incentives. I personally don’t have a problem with it. I think a token of appreciation is always better; it’s easier to defend than it is to say that we pay people to stay in our RCTs”.

Trial manager interview 27, RCT loss to follow-up >20%

Monetary incentives were thought to be useful in RCTs depending on the social and economic circumstances of the participants, the disease / condition being investigated, and the type of follow-up. However, the interviewees generally thought that most participants became involved in primary care RCTs for altruistic reasons. For participants from affluent areas, monetary incentives were thought to be unnecessary. However, for RCTs conducted in poorer areas, monetary incentives were thought to be potentially beneficial for the participants as well as for RCT retention. The interviewees generally thought that younger people were attracted to participate in RCTs when a monetary incentive was offered, and that older people had altruistic motivations for participating in RCTs. One PI, who had never used incentives, felt strongly that these would not motivate older people to participate in RCTs.

Some of the TMs and PIs thought that it was reasonable to “pay” RCT participants to complete questionnaires because researchers are paid for their research time. One TM preferred using the term “*honorarium*” to describe the incentives given to participants for the time they spend involved in RCTs. However, other RNs, TMs and PIs said that they thought that giving incentives to participants could be perceived as bribery and coercion if the amount given was excessive. One PI thought that the risks to the participants associated with early phase pharmaceutical RCTs made the higher valued payments to participants in such RCTs ethically acceptable. However, not all PI’s agreed with this. One PI suggested that higher value payments for participation in pharmaceutical company RCTs had the potential to bias the RCT results, in particular where participants are offered a rate per visit, plus payment for travel, and compensation for work time missed as a results of participation in the RCT. One PI had experience of a patient taking part in several pharmaceutical RCTs as a form of income.

“I saw [someone] in surgery yesterday who’d recently been in four studies of investigational drugs and it seemed to be one of the main ways of.... supplementing .. incapacity benefit, so money comes in to it for some people”.

Principal investigator interview 4, RCT loss to follow-up <20%

Nevertheless, most interviewees from each group thought that giving incentives was an acceptable practice for retaining RCT participants especially for increasing questionnaire response. There was some uncertainty among TMs about when to administer incentives during follow-up. Some TMs had split the incentive i.e. they gave participants e.g. £5 at randomisation and £5 at RCT completion. Sometimes the incentive was sent with the questionnaire, on other occasions the incentive was sent on receipt of the questionnaire. One PI suggested increasing the value of the incentive for each questionnaire returned.

6.4.2.2. The monetary value of incentives used

The range of values of the incentives used was from between £5-£20 for cash or voucher incentives. These were similar to those identified in the systematic review. These amounts were considered reasonable for incentivising both adults and children. Some of the interviewees thought that these amounts may not be considered large enough by some participants, but considered plenty by others who are concerned about the use of public money. PIs thought that higher amounts of money offered i.e. offers of £50, £100, £500 and £1000 constituted coercion / bribery. The PIs thought that these higher amounts may not be approved by an ethics committee.

Clear and effective communication at recruitment about the purpose of the incentives given, as well as getting the value of an incentive “right”, was felt to be important to manage participants’ expectations about the value and function of the incentive. For example, some interviewees thought that if the amount was thought by the RCT participant to be too small that the incentive might be perceived as disrespectful by the participant. If the value was too high, this could lead to suspicions about the RCT. The PIs thought that it was important to get the balance right between giving a token of appreciation, meeting the participants expenses associated with RCT participation, valuing the participants time, and creating realistic expectations about the incentive. The importance of getting this right from the beginning of an RCT was described by these PIs:

“I think people shouldn’t be out of pocket and that should be clear, but you probably can’t pay a realistic amount to get people to come along to do something ,... if you have a senior Lawyer in the study you can’t pay him for his time at a different rate than an unemployed retired person, so it’s really a token if anything we give beyond offering to meet their expenses, so communication is probably I think the main thing, making sure that people are on board before the study starts”.

Principal investigator interview 4, RCT loss to follow-up <20%

"I think you need to be quite careful with the value of the monetary incentives because if it doesn't correspond with what people think is the value of their time...[it]...can.... misfire because people get a bit suspicious and think, hang on, they're giving me a hundred pounds for this and it's actually only taking me fifteen minutes, what's the hidden agenda here?"

Principal investigator interview 28, RCT loss to follow-up >20%

The use of prize draws as a strategy to improve retention was mentioned by one TM and one PI. Prize draws were thought to be cost effective and to be more acceptable to ethics committees as a way of expressing thanks to the participants for their time. Furthermore, a larger amount of money could be offered for the prize draw than that given to the participants individually.

6.4.2.3. Reimbursement of expenses

Most interviewees across the groups thought that it was important to reimburse the participants' travel and parking expenses associated with follow-up so that they were not "out of pocket". They differentiated between this and giving incentives to participants to improve follow-up. Some RNs and TMs reported that some RCT participants were happy to pay for transport to their RCT follow-up visit. Cases were recounted where participants did not want to be reimbursed. However, the interviewees thought that the offer of covering transport expenses could make the participants feel valued, as described by this RN:

"We actually gave them ten pounds for their travel costs, once at the beginning and once at the end, although they had to come in three monthly... And a lot of them didn't want it, you know, they'd say, oh... And I'd say, well just pop it in your local charity. But again, that made them feel valued."

Research nurse interview no 2 RCT, loss to follow-up >20%

One RN reported that some ethics committees now request that participants are reimbursed for any RCT related expenses. Some RNs and TMs reported that processing travel expense claims can be a burden for sites and coordinating centres. Some however suggested that this burden could be overcome by administering a flat fee to each participant as a contribution to their expenses at randomisation and on RCT completion.

The TMs and PIs from RCTs with loss to follow-up of <20% had tried more ways to reduce the financial burden of RCT participation on participants. They had looked for evidence of how to reduce loss to follow-up from RCTs compared to TMs and PIs from RCTs with

>20% loss to follow-up. For example, they gave incentives at different time points in an RCT to try to keep the participants motivated. The RCT managers in this group also used telephone calls to contact participants. Although the TMs and PIs recruited from RCTs with >20% loss to follow-up had used incentives they were cautious that the participants may feel coerced by the use of monetary incentives in RCTs.

6.4.2.4. Vouchers

Some RNs and PIs thought that giving a voucher was valued more by the participants than the monetary value of the voucher itself. The interviewees from across all groups thought that vouchers might be useful to improve retention of participants from low income groups or healthy volunteers. However, some PIs who had used cash to improve questionnaire follow-up felt that “*cash in the hand*” was a more useful motivator. This was felt to be more flexible than giving the participants vouchers. However, money given in voucher format appeared to be used more often than cash.

For those that had used vouchers to improve follow-up, the types of vouchers used were for high street stores (M&S, ASDA, and Tesco), online gift tokens (Amazon, Waterstones and WHS) or fresh fruit vouchers. Some of the interviewees had tailored the type of voucher to the participants request, for example one TM used B&Q home improvement vouchers. Mobile phone top up vouchers were used in one RCT by a TM who thought that these were useful for retaining young people. Some TMs and PIs felt that generic vouchers for use at different retail outlets were the most appropriate for universal use.

Vouchers were generally sent by TMs from the coordinating centre with questionnaires or with a promissory element that on completion of a questionnaire that the participant would receive a voucher. Administratively, vouchers were thought by TMs to be less open to corruption, but they were thought to be a burden to bulk buy. They were seldom administered at RCT sites by RNs. Where vouchers were used as a recognition or thank you for the participant’s time, the RNs were unsure that this was enough to motivate participants to remain in an RCT. One TM and one PI had never used vouchers as incentives and were not clear if these were successful for RCT retention. One PI and one RN thought that RCT participants should have a means to donate the value of the voucher they receive rather than receive a voucher that they would not use.

6.4.2.5. Use of gifts (non-monetary incentives)

The TMs and RNs said that they had administered gifts on behalf of the RCT team to retain people in RCTs, however this was seldom mentioned spontaneously. Gifts were used more as reminders for site clinicians about an RCT and for participant recruitment.

The gifts used were RCT branded:

1. Pens.
2. Key rings.
3. Mugs.
4. Mouse mats.
5. Pedicure kits.
6. Bags.
7. Umbrellas.
8. Pedometers.
9. Certificates of appreciation.
10. Stationary.

Most RNs said that in their experience gifts were administered on behalf of the RCT team to increase recruitment rather than retention. They felt that gifts such as those listed above would not retain participants in an RCT. They thought that building a rapport with the participant and the time given to the participant when they returned for follow-up were more effective (see section 6.4.1. communication). They also felt that gifts, offered or given, should be useful, appropriate, not patronising and tailored toward the participant group. Some TMs thought that for participants taking part in an RCT for altruistic reasons, gifts could be perceived as “*insulting*” or “*uninteresting*” and poor use of public funding.

TMs used gifts as reminders to keep the RCT at the forefront of participants’ and clinicians’ minds or as a thank you to the participants for their time. They were uncertain about the effectiveness of these. They used pens with a study logo as reminders and these were thought to be useful to improve responses to questionnaires. However, some TMs and PIs thought that pens could be associated with charities and fundraising. One RN thought that pens in particular could be considered as “*incidentals*” rather than as gifts.

The types of gifts given to clinicians at sites to remind them about an RCT depended on the RCT funding available. Examples given of these types of gifts were: Post-it® Notes,

branded bags, and mouse mats. TMs felt that it was difficult to assess the impact of these gifts on retention in RCTs.

Some TMs and RNs thought that targeted gifts for children worked well, for example one TM described using sticker badges for children in a paediatric RCT which were given at each follow-up visit. Some interviewees reported that children collected the stickers and that this was a motivator for participants in paediatric RCTs to return for follow-up visits.

Some TMs and PIs thought that some RCT participants could be suspicious about the use of public sector money on gifts. They thought that this could be interpreted as wasteful or extravagant by some participants especially if their motivation for participation in the RCT was purely altruistic as expressed by this TM:

“I think people are very sensitive about money especially in the public sector, ...if they see something that could be considered wasteful or extravagant, I don't think it would go down too well. Because..... if you get involved in a study that's being funded from public funds and from charity, you know, it's quite an altruistic thing to do, I don't think people are looking to be rewarded for itthen they see you wasting money on pens and mugs ...”.

Trial manager interview 7, RCT loss to follow-up <20%

Other interviewees thought that offering participants something that facilitated their return for a follow-up visit, for example travel expenses, could be more effective than an unwanted gift.

Although gifts were not administered by PIs to participants directly on behalf of the study team, they were interested to know what participants thought about using gifts as a strategy to improve retention. Some PIs felt that gifts were patronising to participants, a waste of money and that pens in particular could be associated with charity fundraising. Some thought that the participants would prefer monetary alternatives for example cash or shopping vouchers. Others believed that the participants needed to be motivated, altruistic, interested in the RCT, and in the health benefits they might receive from participation in the RCT to remain involved in the RCT. These factors were considered to be more motivational than gifts.

6.4.3. THE IMPACT OF ETHICS APPROVAL ON THE USE OF INCENTIVES

The interviewees were asked whether they thought the ethics approval process impacted their use of incentives to improve retention in RCTs. RNs were generally not involved in

seeking ethics approval however, they thought it was important that ethics committees questioned the use of incentives in RCTs to prevent bribery or coercion of participants. TMs and PIs felt that ethics committees varied in their opinion about the use of incentives to improve retention especially for smaller RCTs. This PI describes the variety of opinion among ethics committees on the use of incentives and the consequences of this for ethics approval applications:

"I think..... some Ethics Committees really like incentives and they say, "Of course it's important to incentive[i]s[e] patients, we don't ask questions about the incentivising of Clinicians so why should we treat patients any different?", whereas others, it's a moral hazard and they say, "Under no circumstances should you try to inveigle your way in to the patient's affections by offering them any more than their bus fare to the study centre", so it is a bit difficult to judge and so one of the questions that the grant writing team have got are, "Well, who are we submitting, which Ethics Committee is this going to, who's the Chair, who are the outspoken members of the Committee who may approve or not approve it?", obviously for big national studies that's less important, they expect things to be more open and better regulated, but certainly at a local level these things are considerations".

Principal investigator interview 4, RCT loss to follow-up <20%

The TMs and PIs thought that it was beneficial to discuss the ethics application with an ethics committee member prior to submitting an application. The experience of the ethics committee members, their personal biases and their level of knowledge about the use of incentives and RCT conduct were thought by some PIs to complicate the ethics approval process. The PIs nevertheless thought that it was important that ethics committees asked questions about the use of incentives. PIs, with experience of using incentives in RCTs, thought that approval to use incentives was granted by ethics committees when a clear justification and robust evidence of the expected effect of incentives on follow-up was given as described by this PI:

" If ...you've got evidence to show that you're not getting good follow-up and you think it can improve with giving incentives or you can produce randomised control trial evidence to show that in this situation it improves outcomes then you need to make that argument to the ethics committee. Because my experience of ethics committees is if you make them a good argument for why you want to do something, even if it is the sort of thing that people would not initially think an ethics committee would accept, they will accept it because you've explained why and on the whole I don't have too much trouble with ethics committees accepting what it is we want to do".

Principal investigator interview 19, RCT loss to follow-up <20%

One PI mentioned that an application for ethics approval to use incentives for follow-up was likely to be approved if the financial incentive involved paying the travel expenses of the participants.

There were other PIs who did not use incentives because they thought that either an ethics committee may not approve, or they had no previous experience of having used incentives, or they felt that the incentive could interfere with participants' personal financial arrangements. One PI could not see how adding an incentive could either benefit the participant or RCT retention and felt that giving monetary incentives in voucher format might not be an appropriate way to motivate a particular patient group as described by this PI:

"No, we decided early on that we wouldn't even go down that path mostly because ethics committees don't really like that [incentives], they're opposed to it but there are jolly good reasons why they should be as well, practically. You know if you give people money, retired people money it interferes with their tax status and yes, you can give Marks and Spencer's vouchers or whatever you like but that's not always appropriate, not what people want very much".

And has an ethics committees approach to payments ever affected any trials that you've worked on in the past?

I've never been involved in trials paying people at all. I don't see that it's going to be enormously useful, in the things I'm interested in doing you wouldn't. What would a £10 voucher make you do differently?"

Principal investigator interview no 21, RCT loss to follow-up >20%

6.4.4. QUESTIONNAIRES

Some retention strategies were mentioned spontaneously as ways to increase response to postal questionnaires. These were; giving an incentive, using pre-paid reply envelopes, and sending reminders to participants to return a questionnaire.

Opinions differed among the interviewees about the effect of using different questionnaire formats to improve questionnaire response. When the interviewees were asked specifically about the effect of questionnaire length on RCT retention, most of the interviewees thought that shorter questionnaires improved questionnaire response. However, one PI with academic expertise in questionnaire design thought that the balance between length, readability, the content of the questionnaire, and the acceptability of the

topic to the RCT participant were all important factors for improving questionnaire response.

6.4.4.1. Length of questionnaires

Questionnaires of 30 - 50 pages long were considered by TMs and RNs to be off putting for participants to complete no matter how engaged they were with an RCT. These interviewees thought that most standardised questionnaires used to measure participant quality of life and other patient reported outcomes were very long. They also thought that the addition of extra questions to questionnaires was another barrier to completion that resulted in non-response. Having several short questionnaires administered at different time points rather than one longer questionnaire was thought by RNs and TMs to encourage questionnaire response. However, they thought these should not be so short that RCT participants did not see the point of completing them. Some PIs and TMs reported that they used a shorter follow-up questionnaire when they sent a second reminder in order to encourage response from non-responders.

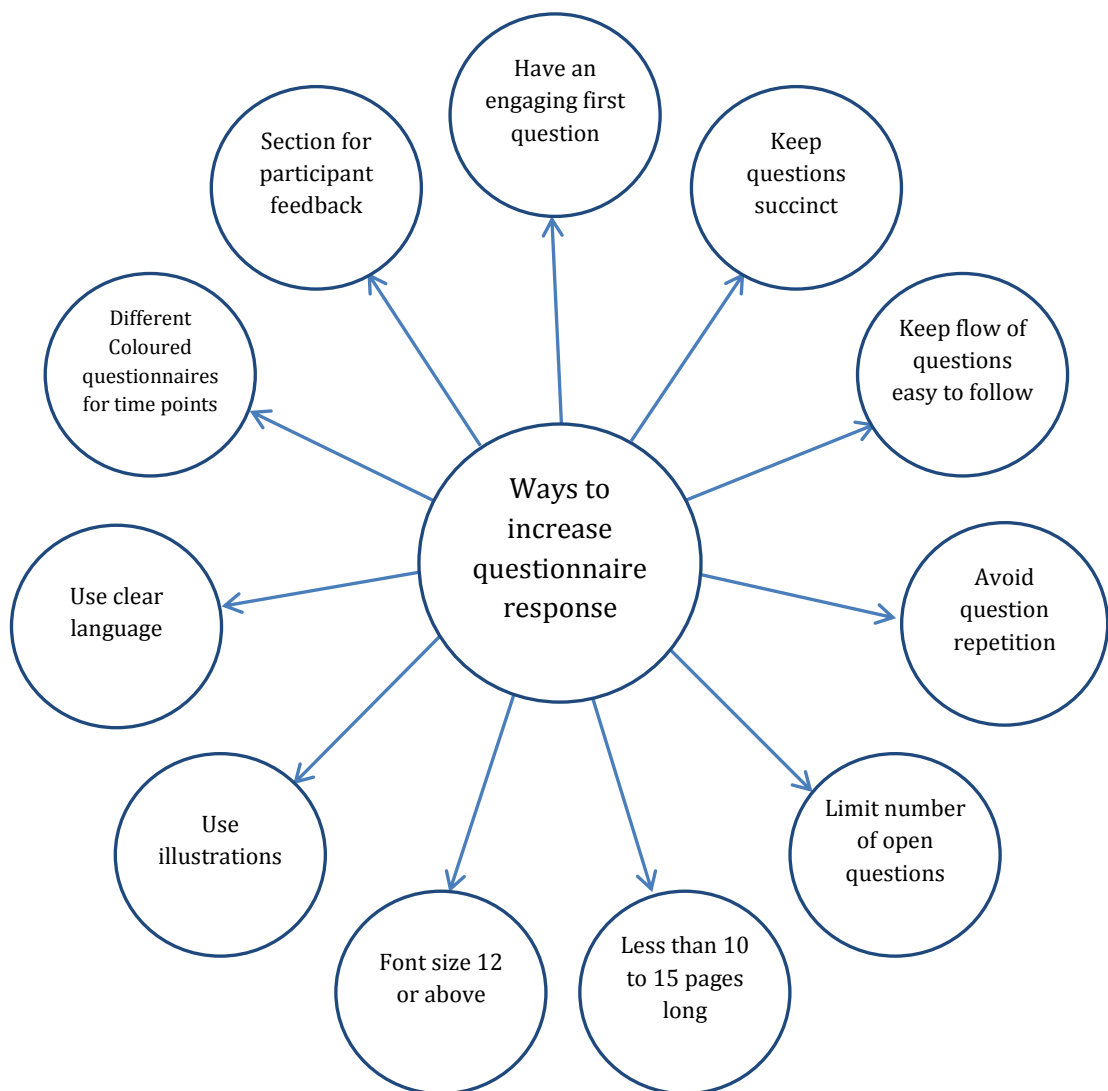
6.4.4.2. Suggestions to improve questionnaire design

The interviewees also made many spontaneous suggestions to improve questionnaire design with the aim of increasing response. The suggestions made are illustrated in Figure 25.

6.4.4.3. Questionnaire administration

How the questionnaire was administered and by whom was thought to impact on RCT retention. A prepaid envelope supplied to participants with a questionnaire for the return of postal questionnaires was thought to improve the number of questionnaires returned. This was sent to reduce the cost to the participants and to avoid any inconvenience associated with not having a postage stamp.

Figure 25 Questionnaire design: ways to improve questionnaire response



From their experience, the TMs and PIs thought that long questionnaires administered frequently lead to “*questionnaire fatigue*”, because the participants had to answer similar questions on a regular basis. The burden of questionnaire completion in terms of time was thought to impact on questionnaire response. Some PIs and TMs thought that if the questionnaire was administered at the clinic by a nurse rather than sent by post that this could increase response regardless of the length of the questionnaire as described by this PI:

“Once [participants are] in a clinic and [they]’re sat with the nurse you can make them do any length of questionnaire you like within reason but once they’re free living and out in the community it’s harder”.

Principal investigator interview 24, RCT loss to follow-up <20%

TMs had noticed that when the questionnaires were sent to participants affected response rates. For instance, it was thought that questionnaires sent before a clinic visit enabled the participant to complete the questionnaire before the clinic visit. A questionnaire posted on a Thursday to arrive on a Saturday was thought to enable participants to complete the questionnaire at the weekend when they were at home for return to the coordinating centre at the beginning of the following week.

6.4.4.4. Other factors associated with questionnaire response

TMs and PIs mentioned involving patient representatives in the design and pre-testing of questionnaires to make these more user friendly for participants. The TMs thought that to minimise respondent burden, clear instructions on what to do with the questionnaire once it was completed may contribute to questionnaire return. Some TMs felt that if the participants perceived there to be a benefit from participating in the RCT that they would be more likely to complete and return their follow-up questionnaires. However, if no benefit was perceived, then the participant might wish to feed that back via their questionnaire for consideration at the RCT coordinating centre.

The use of other strategies to improve retention

Other strategies identified by the systematic review were not used or mentioned spontaneously by the interviewees in the qualitative study. These were: the behavioural strategy, where participants are given information about goal setting and time management to facilitate successful RCT completion; and the methodological strategy where a blind RCT design was compared to an open / unblind RCT design. Case management, i.e. having RCT assistants manage participant follow-up by arranging services to enable participants to keep RCT follow-up appointments, was used by one TM. Opinions were mixed about the usefulness of these strategies for retention in primary care RCTs.

6.4.5. BEHAVIOURAL/MOTIVATIONAL STRATEGIES

The interviewees were asked what they thought about the use of behavioural motivational strategies to improve retention. This strategy was described to each interviewee as: arranging workshops to give participants information about goal setting and time management. If the interviewee was still unfamiliar with this concept as a strategy to improve retention, an example illustrating the use of a behavioural / motivational strategy in the retention RCTs by Cox (2008) and Chaffin (2009) that were identified by the systematic review were used (see Chapter 3 section 3.4.5. behavioural strategies).

The interviewees had not heard of using behavioural strategies to improve retention in RCTs and most interviewees were negative about using this strategy. Words used to describe what they thought were: “strange”, “preachy”, “condescending”, “a load of bollocks”, “never came across it”, “would never think of doing it”, “I don’t like that one very much. I’d be surprised if it worked” and “would need evidence that it worked”.

It was felt that behavioural / motivational strategies could be counterproductive to RCT retention in some RCTs because it might take the participants longer to attend behavioural workshops than it would to complete the follow-up task required. This PI describes why this type of strategy would not work for some RCTs:

“I could imagine some studies where helping participants with goal setting and time management in a very tight closed environment where someone’s got a big commitment to what they’re doing ...and having [a] much closer interaction with the team it’s worthwhile, but in the sort of large, fairly simple studies that I would do ... if we started telling them [participants] we were going to help them with their time management if anything I should see it as a barrier to completion...”

Principal investigator interview 19, RCT loss to follow-up <20%

Some interviewees were familiar with motivational behavioural strategies being used as part of an intervention rather than as a strategy to improve retention in RCTs. Some of the TMs were unsure that this type of strategy would have an impact on retention. Some felt that it would contaminate the intervention and could affect the generalisability of the results to clinical practice. This is summarised by this PI:

“I can see why people might want to do that, the problem ... is that if you contaminate what you’re doing is how generalisab(le) is it in the real world afterward..., that then becomes part of the intervention, so you can’t say you’ve tested the intervention separately from that ... you would have to then include that in what you’re recommending if the results were positive, otherwise it’s not fair, it’s a false result really”.

Principal investigator interview 16, RCT loss to follow-up >20%

Other interviewees thought that the logistics of introducing behavioural strategies would not work in rural areas with poor transport networks. The regular meetings required could become a burden for participants in terms of the time they would have to commit to attend workshops. However, some interviewees felt that this strategy might be useful to retain participants in RCTs for treatment of chronic conditions for example cardiovascular conditions, or for elderly participants in an RCT to get together socially.

Other disadvantages of using behavioural strategies was that this strategy could be costly and burdensome to coordinate.

6.4.6. METHODOLOGY STRATEGIES

The methodology retention strategies identified by the Cochrane review were discussed by the interviewees only when they were prompted to do so. The concept of comparing a blind RCT to an open / un blind RCT as a strategy to improve retention in RCTs had to be explained to each interviewee. The example given was the RCT by Avenell (2004) identified by the systematic review where the effect on retention of an open versus a blind RCT design was evaluated within the RECORD trial. The RCT designs compared in that evaluation were identical apart from blinding (see Chapter 3 section 3.4.7 methodology strategies).

Methodology strategies were not used or considered for use to improve retention by the interviewees. Some PIs mentioned that they did not use blinding in their RCTs because participants could not be blinded to the intervention e.g. in therapist lead interventions. Many interviewees felt that they did not know enough about the application of a blind versus open RCT as a strategy to improve retention. Most felt that blinding participants to an intervention would lead to retention, especially if the participant had a treatment preference. Other interviewees felt that participants could drop out if they were in an open label RCT and did not get their preferred treatment. This is explained by this RN:

"... although you might have explained that ... the reason you're doing the study is because it's not clear what ...would be useful and what wouldn't ... if then they get an open label... allocation to something that they didn't want ...they may be more likely to pull out..."

Research nurse interview 9, RCT loss to follow-up >20%

Some PIs felt that using a blind or an open RCT design as a methodology strategy to improve retention was not the intended aim of these RCT designs. They felt that blinding participants should be done where possible to avoid the bias associated with open RCTs as described by this PI:

"I think you should always blind if you can because we know, don't we, that the weaker the methodology, the more likely the result is to come out the way the trialists want it to. And you see that, don't you, in small, un-blinded, single-centre [trial], and then somebody comes and does a humdinger of a proper study and doesn't show anything, so I think to use it a strategy would be dishonest. If it happens to be the way the study has to be because you can't blind, then fair enough, then it's not a strategy, if you're doing it

in order to improve retention, I think that would be a big error and I don't like that idea at all".

Principal investigator interview 23, RCT loss to follow-up <20%

6.4.7. CASE MANAGEMENT

Case management was evaluated in one RCT in the systematic review by Ford (2006) (Chapter 3 section 3.4.6. case management strategies) but was not a strategy mentioned spontaneously in any of the interviews conducted in the qualitative study. When the interviewees were asked if they had used this as a strategy to improve retention, case management was described as: having RCT assistants manage participant follow-up, for example arranging transport and services to enable participants to keep their RCT follow-up appointments.

The PIs were either not familiar with case management, or had not used this as a strategy to improve retention. Most RNs were familiar with the concept of case management and felt that they performed elements of this strategy at site level to improve follow-up. They were also aware of the use of case management in an RCT conducted through the MRC GPRF.

The interviewees had mixed views about the use of case management and thought it should be considered on an RCT by RCT basis if it were to be implemented. Most thought that case management would be a useful strategy for some patient groups for example elderly, disabled, and economically deprived participants, or participants with young children, and elderly participants who do not drive. Some interviewees felt that the use of case management should be restricted because participants could become dependent on the service provided. Others thought case management would not be helpful for some groups, for example with healthy elderly volunteers. Other interviewees thought that case management could remove the burden of attending follow-up visits for healthy volunteers in RCTs where there is little benefit to the participant from participation. Some interviewees also thought that case management may need to be considered as part of the intervention as described by this PI:

"Case management .. I would ..use it where there isn't very much in it for the participant, so if they're doing a genetic study where it means giving blood tests and there's nothing in it for them, then I think that's perfectly reasonable, but if it's something where you're going to then want to reproduce what's being done you have to think quite carefully about the impact of your strategies really".

Principal investigator interview 18, RCT loss to follow-up >20%

For case management to be a successful retention strategy, the interviewees felt that the full commitment of the case manager was required. Some interviewees thought that the personality of the case manager was an important factor for the strategy to succeed. Being “organised”, “flexible” and “personable” were traits thought to contribute to the success of case management. One TM thought that case management was not a substitute for good RCT management or for communication between team members as described here:

“I’m not sure how important it would be to have the same person involved in doing [case management]. I think it’s really good to have...any strategies that your trial can afford to facilitate people getting to clinic appointments or whatever it might be for their participation in the study...really well organised, I think that’s the most important point... .. if you have a number of people working within one study centre... and there’s a central sort of logging of what has been arranged for somebody or if that falls through what things have been put in place so that anybody can know at any point in time what the situation is, I think that’s far more important than it necessarily being the same person every time because you’ve very rarely got the luxury to do that”.

Trial manager interview no 22, RCT loss to follow-up >20%

There were several disadvantages associated with using case management in RCTs. It was thought to be costly to implement in terms of time and human resources and it needed to be included in a grant application if it were to be used. Some interviewees felt that the cost could be justified if the RCT were to succeed. Others thought that case management could be frustrating to coordinate if participants were not compliant. Some interviewees thought that the boundaries could become blurred between the case manager and the RCT participant if the case manager was asked to do tasks outside of the role.

6.5. FACTORS THOUGHT TO IMPROVE RETENTION

Factors thought to improve retention were also described by the interviewees. These were: the time participants have available to participate in the RCT, effective communication with participants, and the perceived benefit to the participant of taking part in the RCT.

6.5.1. TIME

The time the participants spend getting to, from, and at follow-up visits was thought to impact on retention by the interviewees. They felt that it was important for RCT clinicians to keep to appointment schedules so that the participants did not have to wait to be seen for their follow-up appointment. Some TMs tried to synchronise RCT time points with

disease treatment follow-up appointments so that the participants did not have to make separate visits to the clinical site for follow-up.

6.5.2. COMMUNICATION

Most interviewees mentioned that establishing a good relationship with participants led to retention in RCTs. Some TMs thought that having “personal” or “good” contact with participants contributed to this. Other PIs and RNs spoke about the importance of having a good rapport with the participant. This was maintained through continuity of RCT staff at follow-up visits. One RN mentioned that having warmth toward participants contributed to retention. Other RNs and PI’s felt that conveying enthusiasm for the RCT to participants was important for retention. Some interviewees talked about the need for RNs to be “flexible” and “sympathetic” toward RCT participants, and for TMs to be “competent”, “personable”, “persistent”, “enthusiastic”, and “good communicators”. This is described below by the different primary care research team members:

“[Being] friendly is very important. And I just think having the right approach to things in general. So you have a ‘can do’ attitude rather than a inflexible attitude. You have to have somebody who... Or people who... people who are prepared to go out of their way to do things. And have a very person focused way of doing things.”

Trial manager interview 26, RCT loss to follow-up <20%

“If you’re enthusiastic, and can give the information to the participants with, interest and,... also [are] sympathetic to their, queries, always being accommodating, always getting back to them if they have any queries if, there are messages left, being absolutely spot on with, so that they don’t feel they’ve been let down or you haven’t been bothered to get back to them.”

Research nurse interview 5, RCT loss to follow-up <20%

“I think there’s a paradox here because they [trial managers] need to be obsessional about detail but they also need to be relaxed and flexible in their response to different situations, different problems that come up. That’s asking quite a lot, I think. So you know it’s great if you find somebody who’s good at it.....Or be very kind hearted. And prepared to work out of hours!”

Principal investigator interview 25, RCT loss to follow-up >20%

6.5.3. PERCEIVED BENEFIT OF RCT PARTICIPATION

Some interviewees thought that if the RCT was of special interest to the participants that incentives may not be needed, because the participants were motivated by the perceived benefit of taking part. This was thought to be particularly so for participants with chronic

diseases where they may have more interest in the treatment of their condition and return for follow-up.

Some RNs thought that participants responded well to the “*extra attention*” they got from participating in an RCT and “*feeling their condition is better cared for than it is normally*”. The TMs and RNs thought that the participants may feel a benefit from having extra monitoring of their disease / condition. The examples given of such tests were: “*electrocardiograph (ECG)*”, “*blood pressure (BP)*”, “*cholesterol levels*”, “*special kidney tests*” and “*health checks*”. However, the perceived benefits were thought to vary. For example, one PI mentioned that if participants did not perceive a benefit from participating then they might not return for their follow-up visit. For example in RCTs for treatment of obesity, participants who were not losing weight may not return for follow-up to be weighed.

6.6. FACTORS THOUGHT TO CONTRIBUTE TO LOSS TO FOLLOW-UP

Some groups of RCT participants were thought by the interviewees to be challenging to retain in primary care RCTs. These included: teenagers enrolled in RCTs during their pre-teen years who - when they reach the age of consent - change their mind about participation. Working mothers juggling school runs with work time, and elderly participants who had either; lost their independence or are involved with extended family caring activities, or live abroad for a proportion of the year, were also thought to be challenging groups to retain in RCTs.

The disease under investigation by an RCT was also thought to have an impact on retention. Retention in RCTs involving behaviour change interventions was thought to be problematic if change targets were not achieved by participants. Other thought that healthy volunteers may drop out of RCTs because of lack of interest.

Some interviewees reported that the working environment at general practice RCT sites might impact upon RCT retention. Part-time RNs reported working in isolation, and sometimes struggled to find a vacant consulting room within which to conduct follow-up visits. This restricted the availability of flexible appointment times that they could offer to RCT participants. Some interviewees said that it was off-putting for participants who return for follow-up visits if practice staff or receptionists are not aware of the RCT they were participating in. Some RNs mentioned the importance of keeping all members of the practice informed about the RCTs running at the site to ensure this did not happen.

6.7. RETENTION STRATEGIES NOT YET EVALUATED

The interviewees spontaneously mentioned a range of retention strategies that they currently use or could use to retain participants and that were not identified by the Cochrane review. These retention strategies included types of communication, incentive and questionnaire format strategies that target participants directly or RCT management teams at either the coordinating centre or the study site. These strategies were:

6.7.1. COMMUNICATION STRATEGIES

a) Used at GP practice RCT sites:

- Flagging non-attenders on the practice computer program, (e.g. EMIS), for identification at their next GP practice visit.
- Collecting contact details of a friend / family member at recruitment as an alternative contact if a participant becomes lost to follow-up.
- Conducting home visits for participants who cannot attend the clinical site for follow-up.

b) Used at the RCT coordinating centre:

- Sending SMS text reminders to participants of follow-up appointments.
- Providing bright coloured credit card sized cards to record future follow-up appointments.
- Providing a letter to certify that the person is participating in an RCT.
- Posting study materials on Thursday for delivery on Saturday.
- Reminding sites about when to contact participants for future appointments.
- Adding a feedback / notes section on questionnaires for participants to feedback barriers to follow-up.
- Providing RCT information to participants via Facebook and Twitter.
- Arranging a social event for participants at study closure.
- Providing peer mentors as intermediaries for participants.
- Providing a blog for participants to keep up to date with RCT progress.
- Using television and radio to inform the public about RCTs and the responsibilities of RCT participation.
- Sending newsletters by text.
- Posting newsletters on the RCT website with answers to frequently asked questions.
- Giving change of circumstances postcards to participants at recruitment.

6.7.2. INCENTIVE STRATEGIES

- Giving colouring books, book vouchers, birthday cards, and stickers to children participating in paediatric RCTs.
- Increasing the value of the incentive with each questionnaire returned.

6.7.3. QUESTIONNAIRE STRATEGIES

- Shorter version of a questionnaire. Sent with a second reminder

6.8. STRENGTHS AND LIMITATIONS OF THE QUALITATIVE STUDY

6.8.1. STRENGTHS

The in-depth interviews conducted for this qualitative study facilitated exploration of an area that has not previously been explored in detail before. Interviews were conducted with experts who lead, manage, and implement RCTs in UK primary care who had used different participant retention strategies. The results help us to understand not only what is done in practice to retain participants in primary care RCTs but why retention strategies were used. The study also helps us to understand the relationship between theory as seen in the results of the systematic review and what actually happens in research practice. The results also provide a basis for further research. A rapport and openness was established between the interviewer and interviewee resulting in the collection of rich data for analysis. The early transcripts were critically reviewed for interview technique and improvements were made in the conduct of subsequent interviews. Refining both the interview schedule and interview technique was an iterative process and enhanced the quality of the data collected. Some PIs mentioned that prior to their interview, they had not thought deeply about loss to follow-up or attrition from RCTs, as the focus of their reporting to funders was of recruitment targets rather than retention. However, it was clear from some of the PI interviews that they did report retention but it was not thought to be as important as reaching and reporting recruitment targets. As a result of participating in this study, this cohort of primary care researchers is now more aware of the importance of the impact of loss to follow-up on RCT results and of the strategies used to improve follow-up.

6.8.2. LIMITATIONS

Although all of the interviewees had experience working on RCTs conducted through UK academic units, only some had experience of conducting pharmaceutical company RCTs.

Therefore opinions on the challenges of keeping participants in pharmaceutical company RCTs are limited. Interviewees were sampled from RCTs published between 2000-2010. This will have excluded the experience of researchers who were involved in unpublished RCTs that were stopped for poor retention, although some of the interviewees do represent RCTs with loss to follow-up rates above 20%. Furthermore, some of the RCTs included in the sampling frame were set up earlier than 2000 when electronic forms of follow-up were not established, therefore the views of interviewees on electronic forms of follow-up may be under represented. Most of the interviewees had used postal questionnaires for RCT follow-up but were nevertheless familiar with the current shift toward electronic methods of data collection and communication. This is reflected in the new retention strategies mentioned that have not yet been evaluated e.g. blogging, and sending newsletters by SMS text.

Sometimes, in the earlier interviews, because I was new to in-depth interviewing and conscious of completing the interview in the allocated time, (which was one hour) probing during the interview may have been limited.

6.9. CHALLENGES

Some interviewees discussed recruitment strategies when asked about strategies to increase retention. All the results presented here refer to discussions on retention of participants in RCTs. When interviewees mentioned strategies to increase recruitment, they were guided to focus on retention in RCTs.

6.10. SUMMARY OF RESULTS

In this phase of the project the use of strategies to improve retention in UK primary care RCTs was explored. The interviewees' views on the effectiveness of the strategies they use to increase retention are reported. Factors that lead to retention and loss to follow-up are also identified. The results show that follow-up is monitored systematically at coordinating centres by TMs and data managers for larger RCTs. The trigger to act on losses to follow-up is when participants either do not return for a follow-up interview at the RCT site, or they fail to return a questionnaire, or the level of loss to follow-up threatens the power of the RCT. Monitoring is conducted less formally at GP practice sites by RNs. If loss to follow-up persists, this is escalated upwards from sites to the RCT coordinating centre. This is then passed onto the data monitoring committee and the steering committee for discussion and resolution. Decisions made about the strategies

used to improve retention are agreed at the coordinating centre and implemented at site level by RNs and at the coordinating centre by TMs.

The retention strategies used most often by primary care researchers were: communication strategies in the context of encouraging RCT participants to return to sites for follow-up, and incentives in the context of increasing questionnaire response. New questionnaire formats are used but were not spontaneously mentioned by those interviewed. Case management is seldom used. Methodology and behavioural strategies are not used to improve retention in primary care RCTs.

Communication strategies were mentioned spontaneously and were the most frequently and creatively used strategies to retain RCT participants. Building up a rapport with participants from recruitment, providing the information needed to manage participant's expectations, and having flexible appointment schedules were all thought to contribute to RCT retention. Using the telephone to arrange, rearrange and remind participants to either return questionnaires or to keep their follow-up appointments was a strategy that was commonly used by RNs and TMs, and was thought to contribute to participant retention. TMs and RNs used and were aware of the benefits of using email to follow-up participants. SMS text messaging was used less often but there appears to be a demand for this strategy to be used more often to improve RCT retention. Different postal communication strategies were used by TMs and the interviewees were aware of the economic cost of these to RCTs.

Monetary incentives and offers of monetary incentives were used to increase questionnaire response by TMs and PIs. Interviewees were unsure of their effectiveness for increasing questionnaire response or RCT retention. The values of the incentives used were £5-£20. The interviewees felt that these incentives should be seen by participants as a thank you gesture rather than as payment for follow-up outcome data. This was in order to avoid any association with coercion or bribery and to be seen as good use of public money. Interviewees thought higher valued incentives might undermine the RCT if it caused suspicion among participants. There was a feeling that ethics committees are now more accepting of the use of small monetary incentives to either; thank the participants for their efforts, or when clearly justified, to improve questionnaire response. The interviewees generally thought that participants should be reimbursed for any expenses related to their participation in RCTs.

Non-monetary incentives were used as reminders to clinicians at sites and to increase RCT recruitment. Pens were sometimes used to increase the response to postal questionnaires. Interviewees thought that the standard gifts used in RCTs could be perceived as patronising and not useful and that these were perceived by some RCT participants as a waste of public money. Some interviewees thought that better use could be made if this money was put towards transport or to reduce the burden of follow-up for participants.

Shorter questionnaires were thought to be better than longer questionnaires, provided that measurement of the outcome was not compromised. However, if participants found the content of the questionnaire to be interesting, some PIs thought that questionnaire length may not affect response rates.

Behavioural strategies designed to give participants information about goal setting and time management, and a methodology strategy that compared a blind to an open RCT design were not spontaneously mentioned or used as ways to impact RCT retention in primary care RCTs. The feasibility of incorporating these retention strategies as part of the intervention being assessed was questioned by the interviewees. There was some concern that these strategies in particular could bias RCT results. Most of those interviewed felt that blinding participants to an intervention would lead to retention. Some PIs felt that using an open RCT as a strategy to improve retention could bias the RCT results.

Interviewees were overwhelmingly negative about the use of behavioural strategies to reduce loss to follow-up from RCTs. Of all of the retention strategies mentioned, this was the one considered the most unfamiliar and unusual. Some interviewees felt that this retention strategy could be counterproductive to RCT retention and should only be used as part of an intervention in an RCT.

Some interviewees were familiar with case management and thought that this was a favourable retention strategy to use but could be expensive to implement. However, they thought that some participants might become dependent upon the activities of the case manager. The success of this strategy was thought to be dependent on the personality of the case manager.

In the next chapter the results of the discussions of the qualitative study and the systematic review at two consensus workshops are presented, and the best practice guidance agreed for retention in RCTs is presented.

CHAPTER 7: DEVELOPMENT OF BEST PRACTICE GUIDANCE FOR RETENTION IN RCTs

7.1. INTRODUCTION

This systematic review and qualitative study are the first to examine the effectiveness and use of strategies to improve retention in RCTs. Researchers may therefore wish to use these results to inform the future use of retention strategies in the RCTs that they conduct. Because the results for some of the effective strategies are based on single RCTs, for example: recorded postal delivery, the open RCT design and the total design method of postal communication, there may therefore be uncertainty among researchers about which retention strategies are the best to use in different research settings. Furthermore, most of the retention strategies included in the systematic review were used to improve questionnaire response in RCTs and few were used to improve the number of participants returning to sites for follow-up.

The results of both studies are summarised in Table 20. It is clear from this table that the effective retention strategies i.e. monetary incentives and offers of monetary incentives are used in UK primary care RCTs to improve retention without knowledge of the evidence for the effectiveness of these strategies. It is also clear that ineffective strategies i.e. non-monetary incentives, additional reminders, enhanced letters and priority post, are also used. Furthermore, the findings of the qualitative study suggest that although some retention strategies appear effective e.g. recorded delivery and open RCT designs, they are not always considered by researchers to be suitable or appropriate to use to improve retention in RCTs because they may either inconvenience the participant or cause biased results. There is therefore a need for clear guidance to be developed for the use of retention strategies in RCTs. This would help researchers make informed decisions about the retention strategies that can be used generally in future RCTs based on the best available evidence and would also help to identify strategies for future evaluation.

7.2. AIMS

The aims of this chapter are therefore:

1. To explore any uncertainties around the use of the results of the systematic review and the qualitative study.
2. Where possible to develop best practice guidance for the use of retention strategies identified by the systematic review.
3. To identify areas for future research.

Table 20 Systematic review and qualitative study results

| Systematic Review Results | | | | | | | Qualitative Study Results |
|---|-------------------------|---------------------------------|---|---|------------|---|---|
| | Data collection method | Number of RCTs in meta-analysis | Total number of participants in meta-analysis | RR 95% CI | P value | Absolute benefit based on 50% baseline response | |
| Effective retention strategies | | | | | | | |
| Monetary incentives | | | | | | | |
| Addition of monetary incentive vs. none | Postal questionnaire | 3 | 3166 | RR 1.18; 1.09 - 1.28 | P< 0.0001 | 76 questionnaires per 1000 sent | Incentives are used e.g. £5 given at randomisation and £5 at RCT completion. Sent with questionnaire, or on return of questionnaire. Different voucher types used. General agreement that small monetary incentives were likely to be viewed favourably by ethics committees. Uncertainty about effect of giving monetary incentives up front or on return of questionnaire |
| Offer of a monetary incentive vs. none | Web based questionnaire | 2 | 3613 | RR 1.25; 1.14 - 1.38, heterogeneity P value = 0.14) | P< 0.00001 | 100 questionnaires per 1000 sent | Offers of monetary incentives used. |
| Higher value monetary incentive vs. lower value monetary incentive | Postal questionnaire | 2 | 902 | RR 1.12; 1.04 - 1.22 | P = 0.005 | 55 questionnaires per 1000 sent | Value of monetary incentives used £5- £20. Concern about coercion with incentives valued over £50. |
| Strategies with some evidence of effect based on single RCTs | | | | | | | |
| Communication | | | | | | | |
| Total Design Postal Method (TDM) vs. customary postal communication | Postal questionnaire | 1 | 226 | RR 1.43; 1.22 - 1.67 | P < 0.0001 | - | Some elements of TDM used. |
| Recorded delivery vs. telephone reminder | Postal questionnaire | 1 | 192 | RR 2.08; 1.11 - 3.87 | P = 0.02 | - | Recorded delivery used to send a second copy of questionnaire / study materials. Opinions mixed on usefulness. |
| Methodology strategies | | | | | | | |
| Open vs. blind RCT design | Postal questionnaire | 1 | 538 | RR 1.37; 1.16-1.63 | P=0.0003 | - | Not used to improve retention. Thought blinding should be used where possible to avoid bias associated with open RCTs. |
| Strategies with unclear evidence of effect | | | | | | | |

| Systematic Review Results | | | | | | | Qualitative Study Results |
|---|-------------------------|---------------------------------|---|---|----------|---|--|
| | Data collection method | Number of RCTs in meta-analysis | Total number of participants in meta-analysis | RR 95% CI | P value | Absolute benefit based on 50% baseline response | |
| New questionnaire strategies | | | | | | | |
| Short questionnaires vs. long | Postal questionnaire | 5 | 7277 | RR 1.04; 1.00 - 1.08 | P = 0.07 | 20 questionnaires per 1000 sent | Shorter follow-up questionnaire used when a second reminder is sent. Thought long questionnaires were off putting for participants. |
| More relevant questionnaires (i.e. those relating to alcohol use) vs. less relevant | Web based | 2 | 3893 | RR 1.07; 1.01 - 1.14 | P = 0.03 | - | No comments on the use of more or less relevant questionnaires. |
| Non-effective strategies | | | | | | | |
| Non-monetary incentives | | | | | | | |
| Addition of non-monetary incentive vs. none | Postal questionnaire | 6 | 6322 | RR 1.00; 0.98 - 1.02, some heterogeneity (P value = 0.02) | P = 0.91 | - | Gifts used as reminders about an RCT. Uncertainty about effectiveness for RCT retention. |
| Offer of a non-monetary incentive vs. no offer | Postal questionnaire | 2 | 1138 | RR 0.99; 0.95 - 1.03, | P = 0.60 | - | Offers of gifts not mentioned as a strategy to improve retention. |
| Addition of monetary incentive vs. offer of prize draw entry | Postal questionnaire | 2 | 297 | RR 1.04; 0.91 - 1.19 | P = 0.56 | - | Offers of entry into a prize draw seldom used but thought to be useful. |
| Offer of monetary donation to charity vs. none | Web based questionnaire | 1 | 815 | RR 1.02; 0.78 - 1.32 | P = 0.90 | - | Not mentioned as a way to improve retention. |
| Communication strategies | | | | | | | |
| Enhanced letter vs. standard letter | Postal questionnaire | 2 | 2479 | RR 1.01; 0.97 - 1.05 | P = 0.70 | - | Enhanced letter routinely used to improve questionnaire response. |
| Priority post vs. regular post | Postal questionnaire | 7 | 1888 | RR 1.02; 0.95 - 1.09 | P = 0.55 | - | First class post routinely used to send post to participants. |
| Additional reminder vs. usual follow-up practices | Postal questionnaire | 6 | 3401 | RR 1.03; 0.99 - 1.06 | P = 0.13 | - | SMS text reminders thought useful for young people. Thought a reminder system similar to the automated NHS clinic appointments system may improve retention. Telephone reminders routinely used. Concerns about harassment when too many reminders sent. Email reminders thought to be useful to improve response. |
| Early vs. late questionnaire administration | Postal questionnaire | 1 | 664 | RR 1.10; 0.96 - 1.26 | P = 0.19 | - | Questionnaires sometimes posted later in week to arrive at the weekend. |
| Additional monthly reminder to RCT site vs. usual reminder | Return to research site | 1 | 272 | RR 0.96; 0.83 - 1.11 | P = 0.57 | - | Additional reminders to sites not mentioned as a way to improve retention. |

| Systematic Review Results | | | | | | | Qualitative Study Results |
|--|-------------------------|---------------------------------|---|----------------------|----------|---|---|
| | Data collection method | Number of RCTs in meta-analysis | Total number of participants in meta-analysis | RR 95% CI | P value | Absolute benefit based on 50% baseline response | |
| Addition of telephone survey vs. monetary incentive plus questionnaire | Postal questionnaire | 1 | 700 | RR 1.08; 0.94 - 1.24 | P = 0.27 | - | Telephone survey seldom used to improve retention. |
| New questionnaire strategies | | | | | | | |
| Disease /condition questions before generic vs. generic questions before disease/condition questions | Postal questionnaire | 2 quasi-randomised | 9435 | RR 1.00; 0.97 - 1.02 | P = 0.75 | - | Many suggestions made to make questionnaire easy to follow. |
| Long and clear questionnaires vs. shorter condensed questionnaires | Postal questionnaire | 1 | 900 | RR 1.01; 0.95 - 1.07 | P = 0.86 | - | Shorter questionnaires used where possible. |
| Behavioural/motivational strategies | | | | | | | |
| Behavioural/motivational strategies vs. standard information | Return to research site | 2 | 273 | RR 1.08; 0.93 - 1.24 | P = 0.31 | - | Not used, very negative about the usefulness of using behavioural strategies for retention. |
| Case management | | | | | | | |
| Case management vs. usual follow-up | Return to research site | 1 | 703 | RR 1.00; 0.97 - 1.04 | P = 0.99 | - | Case management, seldom used, thought to be potentially useful for retention but expensive. |

7.3. CONSENSUS DEVELOPMENT METHODS

Different methods are used to develop consensus on uncertain areas in health or community care. The three most commonly used methods are: a) the Delphi method, b) the Nominal Group Technique, and c) Consensus development conferences (Fink et al. 1984, Murphy et al. 1998). The differences between these three methods relate to how the data is collected. This may be via mailed questionnaires or through face to face discussions. The methods also differ in how the participant's opinion is aggregated and whether decisions are fed back to the participants with an opportunity for further reconsideration and comment (Murphy et al. 1998). Each of these consensus methods are further described below.

The Delphi survey method uses rounds of postal questionnaires to record individual experts' views on a particular issue. The experts are polled individually by a self-administered questionnaire. The survey is conducted over 3-4 rounds and the consensus development process is therefore iterative. After each round the results are reported back to the experts in summary form indicating the expert's judgements and opinions (Fink et al. 1984, Murphy et al. 1998). The process is considered complete when the individual expert's opinions converge or when the point of diminishing returns is reached. There are disadvantages associated with the Delphi survey method. For instance, the experts can become fatigued after several survey rounds and therefore response rates can be low. Furthermore, Delphi surveys can be costly to administer in terms of time and money and complicated to coordinate and analyse (Fink et al. 1984, Murphy et al. 1998).

The Nominal Group Technique (NGT) method for consensus development involves structured interaction within a group by experts associated with a particular topic. The experts selected for the group discussions are initially invited to list their ideas about a specific topic. They are then asked to select the most important idea on their list. Each top choice from each individual is recorded on a master list which forms the basis for the discussion phase of the NGT. Each idea on the master list is then discussed by the group in turn and voted upon to reach consensus. This method allows each expert to express their opinion on a topic on the list.

The Consensus Development Conference method of reaching consensus is a face to face method where individuals are brought together to hear the best evidence available on a given topic area to help make decisions about best practice (Murphy et al. 1998). The National Institutes of Health use this method to advance the understanding of issues in

health and to help health care professionals and the public with informed decision making about the monitoring and treatment of different diseases e.g. cancers, arthritis (Ganz et al. 2012, NIH 2003). The conferences are usually held over two days and can take the following form:

1. Presentations of the evidence from systematic reviews focused on a disease treatment
2. Presentations by investigators working in the disease area
3. Questions and statements by conference attendees
4. Closed deliberations by experts in the field
5. Development of a consensus statement by experts in the field

With the Consensus Development Conference method individuals are encouraged to express alternative views if consensus is not reached during the conference. The judgments agreed tend to be qualitative or can involve a majority vote (Murphy et al. 1998). The methods of aggregation for the NGT and the Delphi consensus methods are usually quantitative statistical methods.

7.4. METHODS

To develop best practice guidance for the use of retention strategies in RCTs the Consensus Development Conference method was chosen because consensus is reached entirely through open discussion of the results of studies relevant to the topic of interest. As the area for best practice development was trial conduct methodology rather than treatment for a disease / condition, the consensus development conference method was modified in that consensus was reached through open discussion with RCT personnel. This required researchers working in the area of RCTs to convene to discuss the results and to reach consensus on best practice guidance for retention in RCTs among themselves rather than in a closed meetings. It was felt that the most appropriate way to achieve this was to conduct workshops at the researchers' place of work. Therefore, the following modified consensus development approach was used to develop best practice guidance for retention in RCTs:

1. Presentation of the evidence from the systematic review and the qualitative study to RCT personnel at workshops.
2. Consideration of questions and statements from RCT personnel attending each workshop.

3. Group discussions and deliberation on best practice for the use of different strategies to improve retention in RCTs based on the results presented.
4. Development of a consensus statement on best practice for RCT retention based on the group discussions.

Two consensus development workshops were convened with RCT personnel to discuss the results of the systematic review and the qualitative study in detail. The attendees were RCT personnel self-selected in response to an email invitation to attend a workshop on ways to improve retention in RCTs. The workshops were held at a UK department of Primary Care research, and a UK Clinical Trials Unit. These sites were chosen because they conduct a range of RCTs in different disease areas, and the personnel have a range of expertise in RCT related research methods e.g. RCT design, coordination, data management, and statistical analyses.

In order to widely publicise the consensus development workshops, an abstract (see Appendix 8.1) outlining the purpose of each workshop was circulated via email to all personnel on the seminar mailing list of each research unit identified for the workshop. An email accompanying the abstract invited those personnel within each unit with expertise in different aspects of RCTs to attend. The abstract specified that the consensus development workshop would be of particular interest to those interested in retention in RCTs. It was made clear that the results of a Cochrane systematic review on strategies to improve retention in RCTs, and the results of a qualitative study that examined the use of retention strategies in primary care RCTs would be presented. The abstract also explained that the purpose of the consensus development workshop was to develop best practice guidance for retention in RCTs based on the results.

7.4.1. CONSENSUS WORKSHOP QUESTIONS

Prior to the workshops a list of items for discussion was made informed by the results of the systematic review and the qualitative study. The overall question set for each workshop was:

“What are the best strategies to use to improve retention in RCTs?”

In order to answer this question, the following items were to be considered at each workshop:

1. How convincing is the evidence for the retention strategy discussed?
2. Identify clinical settings where effective retention strategies could be used.

3. Identify the types of follow-up the effective strategies could be used for.
4. Identify barriers, if any, to implementing the use of effective strategies.
5. For strategies with no evidence of impact on retention, to identify whether these are in use.
6. Identify the barriers to stopping the use of negative strategies.
7. Identify other retention strategies for evaluation.

7.4.2. CONDUCT OF WORKSHOPS

Each consensus development workshop included:

1. A Microsoft PowerPoint presentation of the results of the systematic review and the qualitative study (20-30 minutes).
2. Three discussion groups run simultaneously (35-45 minutes). Each focused on developing best practice guidance for either:
 - i. incentives
 - ii. communication strategies
 - iii. new questionnaire formats and other strategies
3. Group feedback to all workshop attendees on the best practice guidance agreed for the strategy discussed (5-15 minutes).

7.4.3. PRESENTATION OF RESULTS

Each consensus workshop was chaired by myself, the PhD student. A twenty minute Microsoft PowerPoint presentation on the results of the retention systematic review and qualitative study was presented at each workshop (See Appendix 8.2). The presentation included a brief introduction to the biases associated with loss to follow-up in RCTs, the methods used for the systematic review and the qualitative study, the findings of both studies i.e. the different types of retention strategies evaluated to date, the meta-analysis results, and the use of the retention strategies identified by the systematic review in primary care RCTs. The absolute effect of the strategies that showed a clear impact on questionnaire response in RCTs was also presented.

7.4.4. CONDUCT OF GROUP DISCUSSIONS

At each workshop, after the Microsoft PowerPoint presentation, the three discussion groups were formed. The workshop attendees were allocated to the different discussion groups by a number given to each from 1 to 3. The number indicated the discussion group the workshop attendee was allocated to. The workshop attendees in group 1 were

assigned to discuss incentive strategies. Workshop attendees in group 2 were assigned to discuss the results for communication strategies. Attendees assigned to group 3 were to discuss new questionnaire formats and other strategies.

The main tasks for each discussion group were:

1. To discuss the scientific evidence for the use of the strategy they were assigned to discuss, based on the items for consideration in section 7.4.1. of this chapter.
2. If possible to reach consensus about best practice to improve RCT retention for the use of the retention strategy discussed
3. To identify strategies for future evaluation

A secondary aim of the consensus workshops was to open up to debate the subject of strategies to improve RCT retention. Therefore, members of the discussion groups were encouraged to express alternative views about the retention strategy that they were assigned to discuss.

Each group discussion was facilitated by an experienced facilitator. Where possible, the facilitator facilitated the same group discussion at both consensus development workshops. Prior to each workshop the facilitators were asked to focus their group's attention on developing best practice guidance for retention in RCTs for the strategy assigned. At the beginning of each group discussion, the facilitator recapped on the results for the strategy assigned to the group for discussion. Each group was supplied with an information pack to further facilitate the discussion. This provided a list of the items for discussion, a copy of the Microsoft PowerPoint presentation slides, forest plots and tables of the meta-analysis results for the retention strategy assigned for discussion. Tables of the characteristics of the RCTs included in the systematic review relating to the retention strategy were also included. These tables reported the number of participants randomised in each retention RCT; the disease / condition e.g. cancer, mental health; the setting e.g. primary / secondary care; the intervention(s); the control group and the outcomes measured. The facilitator kept notes of the discussion as it progressed. A register of workshop attendees was kept for each workshop (see Appendix 8.3). The register recorded the occupation / role, contact details, research area, and discussion group allocation of each workshop attendee. At the end of each group discussion, feedback was given from each discussion group to all of the attendees at the workshop on the best

practice guidance agreed for the strategy discussed. Any alternative views expressed during the group discussions were also reported.

The same presentation and workshop format was used for each workshop. All group discussions were either recorded digitally or detailed hand written contemporaneous written notes were kept by the facilitator. Following each consensus workshop, the facilitators' notes were typed and sent back to the group facilitator for verification. Additions or corrections to the transcript were clarified via email between the workshop chairperson (PhD student) and the discussion group facilitator.

7.4.5. DATA MANAGEMENT AND ANALYSIS

Each discussion was digitally recorded with an: Olympus WS-300M voice recorder, or a Sony digital voice recorder model ICD-UX522. The discussion date, number, and strategy discussed were used as file identifiers. Digital voice recordings for each discussion group were uploaded to a secure password protected computer. These were checked for sound quality, and transcribed verbatim. Transcripts were checked for accuracy against the recording and corrected and anonymised by removing place and person names, RCT identifiers and acronyms. Misinterpretations in the transcripts were corrected by reference to discussion notes and recordings. These errors were minimal across the group discussion transcripts. The textual data were stored in Microsoft word folders labelled with the following identifiers: "incentives", "communication", "questionnaire formats" and "other strategies".

A qualitative content analysis was conducted. The data codes developed to label textual data were both deductive and inductive. Deductive codes were based on the retention strategy for discussion and were used as a framework for the content analyses. Inductive codes based on items in section 7.4.1. of this chapter, e.g. "convincing", "setting", "types of follow-up", "barriers", were used as sub codes. The approach to the analysis was similar to that conducted for the in-depth interviews described in Chapter 5, section 5.8. The analysis involved reading, rereading and coding group discussion transcripts and comparing coded content across both workshops for themes around:

1. How convinced the participants were about the evidence for each strategy.
2. The settings in which they thought effective strategies could be used.
3. The types of follow-up the effective strategies were considered useful for.
4. The barriers, if any, to implementing the results of effective strategies.

For retention strategies with no evidence of an effect, consensus and disagreement was recorded for whether the strategy was being used and the barriers to researchers changing this practice. Finally, data on other strategies that could be evaluated were also analysed. The key content from the discussions of incentives, communication, new questionnaire formats, and other strategies were tabulated side by side for each workshop in Microsoft word. Textual data and quotes were highlighted and labelled with comments and codes. The content of these tables were searched for agreement and disagreement across both workshops for each retention strategy discussed. The findings for each strategy were written-up and emailed to each group facilitator to check for accuracy of interpretation.

7.5. RESULTS

Two consensus workshops were held during November and December 2013. Each workshop was well attended by a range of RCT personnel (see Table 21). Attendees included those who design RCTs and who collect, manage, and analyse RCT data.

Table 21 Research roles of consensus development workshop attendees

| Research roles of workshop attendees | Number of attendees at the Primary care research unit workshop | Number of attendees at the Clinical Trials Unit workshop |
|---|--|--|
| RCT clinicians | 6 | 5 |
| RCT statisticians | 7 | 13 |
| RCT managers | 1 | 5 |
| RCT data managers / programmers | 1 | 11 |
| RCT assistants | 4 | 2 |
| Research scientist / fellow / associate | 6 | 3 |
| PhD students | 1 | 1 |
| Total | 26 | 40 |

During each consensus workshop three group discussions were held. The characteristics and number of participants attending each workshop is illustrated in Table 22. All of the workshop discussion groups were heterogeneous in terms of the attendees' occupation / research role and area of research (see Table 22). This mix resulted in lively discussion as the different discussion group members drew on their different knowledge and experiences around RCTs and the strategy that they were assigned to discuss. The results and consensus agreed for the use of retention strategies are presented below.

7.5.1. INCENTIVE STRATEGIES

Workshop attendees in the incentives group discussions were not entirely convinced by the result for the addition of monetary incentives to RCTs. The decision to add a monetary incentive to an RCT was thought to depend upon different factors associated with the study population. These were identified as: the age, socioeconomic group and educational level of the RCT participants. The absolute benefit gained from adding or offering a financial incentive to improve response to questionnaires in an RCT was considered small.

Table 22 Characteristics of consensus development workshops

| Consensus development workshop | Discussion groups | No of discussion group attendees | Research roles of attendees | Research area |
|-----------------------------------|--|----------------------------------|--|---|
| Primary care research unit | | | | |
| | Incentives | 10 | Statisticians (n=5) Trial managers (n=1) Research assistants (n=1) Data managers (n=1) Clinicians (n=2) | Sexual health, alcohol reduction, e-health, learning disabilities, cardiovascular disease |
| | Communication | 7 | Research scientist / fellow (n=2) Clinicians (n=2) PhD students (n=2) Qualitative researchers (n=1) | Aging, e-health, mental health, smoking cessation, cardiovascular disease, primary care |
| | New questionnaire formats, case management, behavioural, methodological strategies | 9 | Statisticians (n=2) Research assistants (n=4) Research fellows/associates (n=1) Clinicians (n=2) | Sexual health, smoking cessation, cardiovascular disease, primary care |
| Clinical trials unit | | | | |
| | Incentives | 19 | Statisticians (n=3) Trial managers (n=5) Trial assistants (n=2) Data managers (n=5) Research scientists / fellows (n=2) Clinicians (n=2) | Cancer, infectious diseases, statistical trial methodology |
| | Communication, case management, behavioural, methodological strategies | 12 | Statisticians (n=6) Data managers (n=5) Clinicians (n=1) | Cancers, infections |
| | New questionnaire formats | 9 | Statisticians (n=4) Data manager (n=1) Communication specialist (n=1) Research fellow/associates (n=1) Clinicians (n=2) | Cancers, infections |

It was also felt that any gain in the numbers of questionnaires returned as a result of adding a monetary incentive may not justify the additional cost of introducing the incentive to improve questionnaire response in an RCT. It was noted by one incentives discussion group that, in some countries, the addition of a monetary incentive to an RCT is a regulatory requirement e.g. in RCTs conducted in South Africa and Germany. It was

therefore agreed that more evidence for or against the use of incentives in these regions was not appropriate.

Even though the workshop attendees were not entirely convinced by the results for incentives, both incentive discussion groups did agree that financial incentives could be used as a means to increase response rates to questionnaires in RCTs. There was general agreement across the two groups that discussed incentives that researchers should be aware of the potential for coercion associated with adding monetary incentives to RCTs. This was thought to be the case particularly in RCTs with participants from areas of high social and economic deprivation. There was also agreement that the monetary value of incentives should be not so low that participants feel that their time is undervalued. There was also agreement that financial incentives of £5-10 in value could be considered. A £20 incentive was considered the upper limit to use without raising suspicions from RCT participants about the use of their data. It was also agreed that the value of the incentive should not be so high that it raises suspicions by RCT participants that public money is being miss used.

There was a lack of conviction across both incentive discussion groups that the non-monetary incentives, e.g. mugs and pens, currently used in RCTs do improve retention. However, there appears to be a barrier to stopping the use of non-monetary incentives. It was agreed that RCT personnel were keen to thank and to give something back to participants without necessarily doing so to increase retention. Examples of such non-monetary expressions of thanks were sending letters of appreciation and certificates of appreciation to the participants thanking them for their time and dedication to the RCT. There was also agreement in both incentive group discussions that the use of branded study materials (including branded letters, pens or mugs) could be detrimental to retention. This was particularly the case if these branded gifts identified or implied that the participant was associated with a medical condition that the RCT participant did not wish to be linked with even though they may have that condition. There was agreement across both groups that the addition of non-monetary incentives should not be recommended for retention in RCTs. However, it was thought that these could be considered for use as a token of appreciation for the participant's time.

7.5.2. COMMUNICATION STRATEGIES

Workshop attendees in the communication strategies discussion groups were not fully convinced by the results for communication strategies for several reasons. They felt that the results for some communication strategies were based on too few RCTs to be applied to other research contexts e.g. the results for recorded delivery of letters. They also thought that the results for the total design method (Sutherland et al. 1996) and recorded delivery of questionnaires (Tai et al. 1997) strategies were dated because these RCTs were conducted in the 1990's. They felt that communication methods had changed since then and that electronic methods of communicating with RCT participants were now used more than paper methods. There was agreement that some elements of the total design method could be useful for sending postal questionnaires e.g. sending personalised letters to RCT participants. The workshop attendees thought that this strategy could be useful if it were adapted to be used to improve responses to electronic questionnaires in RCTs.

It was thought that different types of communication strategies were needed to retain people from different age groups, social economic backgrounds and with different diseases and conditions. Therefore, a tailored approach to communicating with the RCT participants was thought to be more useful whereby during recruitment participants are asked how they would like to be contacted during follow-up e.g. via email, mobile phone, or SMS text message. It was agreed that their follow-up preferences could then be personalised and tailored accordingly. It was also agreed that this strategy would be worth evaluating in future.

There was no good evidence from the systematic review that sending letters to RCT participants by priority post was better than sending these by second class post. There was agreement across both communication group discussions that 1st class post was costly. Most workshop attendees said that they did not use 1st class post to send letters to RCT participants however, some attendees did use 1st class post and said that they would like to change and use 2nd class post instead. Some workshop attendees mentioned however that there were institutional bureaucratic barriers to changing the type of postage used and that if this practice was changed that they would have no guarantee that any savings made by using 2nd class post would be redirected toward the RCT.

The workshop attendees were not convinced by the results for sending additional reminders to RCT participants. In the systematic review additional reminders were in the form of prompts to remind an RCT participant to return a questionnaire through either a

telephone reminder (MacLennan unpublished), calendar with due dates to return questionnaires (Nakash unpublished), or fridge magnets with a reminder message (Severi et al. 2011). They said that additional reminders were routinely sent to participants in some disease prevention RCTs where response rates are known to be very low e.g. in smoking cessation RCTs, or in RCTs for the prevention or treatment of infectious diseases among young healthy volunteers. In these instances the discussion group attendees felt that an additional reminder would increase the number of questionnaires returned and that they were therefore reluctant to change the practice of adding an additional reminder to usual follow-up procedures because they had seen an increase in the numbers of questionnaires returned in their own research practice.

The workshop attendees thought that other factors also contributed to retention and response in RCTs. These factors were: how well the RCT participants were engaged with the RCT, the continuity of follow-up with RCT staff, and the flexibility of RCT staff and RCT participants around follow-up appointments.

7.5.3. NEW QUESTIONNAIRE FORMATS

The workshop attendees who discussed the results for new questionnaire format strategies were convinced by the evidence for these strategies except for the evidence for long versus short questionnaires, where there is only a suggestion of an effect. They were not entirely surprised by this result. They felt that human nature, the disease or condition, and the RCT context contributed to whether or not the participant returned a questionnaire. There was agreement across the discussion groups that questionnaires sent to participants in RCTs for treatments of e.g. cancers, have better response rates than other conditions e.g. prevention of infectious diseases or smoking cessation.

It was thought that some RCT participants may abandon completing an electronic questionnaire, particularly if this was thought to be too long or they could not save this part way through for completion at a more convenient time. It was agreed that if donations to a charity were to be used to improve responses to electronic questionnaires that the charity should be connected with the disease area being researched. It was thought that an electronic link from a questionnaire to a charity donation or a prize draw could be evaluated in future nested RCTs. There was agreement across both questionnaire discussion groups that giving the participants a choice to respond either by post, text, or email could improve questionnaire response and RCT retention.

The workshop attendees were interested in the retention RCT included in the systematic review that compared placing questions about the disease or condition first on the questionnaire versus placing more generic questions first (McColl et al. 2003). They thought that RCT participants may be more interested in answering questions about their own disease first and that this may encourage them to complete a questionnaire. The attendees were particularly sceptical about choosing a questionnaire that was less relevant to the condition as a means to improve RCT questionnaire response. They agreed that they would only ever use a questionnaire that best answered the question posed by the RCT. The questionnaire discussion groups agreed that the most relevant and validated questionnaire to measure outcomes for an RCT should be used where possible.

Even without evidence from the systematic review, it was thought that making questionnaires clearer by using plain simple English, specific to the disease condition, and including only necessary information and questions, would encourage the RCT participant to return a questionnaire.

7.5.4. OTHER STRATEGIES

There was no support among workshop attendees for the use of an open RCT design as a strategy to improve retention. It was felt that the decision about blinding would generally be dictated by other aspects of the RCT design for example the treatments being compared. Some workshop attendees said that they would use case management strategies. However, they would like more information about the time and resource implications for using case management in different research contexts before making the decision to use this. One PI was interested in using the behavioural strategy (see Chapter 3 section 3.4.5. for a description of the behavioural strategies used) to engage with participants in RCTs for the treatment or prevention of infectious diseases and thought that this strategy might be worth evaluating in future.

7.6. FURTHER RESEARCH

Agreement was reached in the consensus workshop group discussions about retention strategies that could be further evaluated. These strategies were:

1. Follow up by the same person versus usual follow-up procedures.
2. Having an additional follow-up visit soon after the recruitment visit to engage participants early in the RCT versus the usual follow-up schedule.

3. Tailored follow-up according to the participants' preference versus usual follow-up.
4. More frequent follow-up visits versus less frequent follow-up visits.
5. SMS text message follow-up versus telephone follow-up.
6. Electronic versus postal questionnaire follow-up.
7. Onsite face to face follow-up versus postal questionnaire follow-up.
8. Questionnaires with space for free text feedback from participants versus yes / no or tick boxes.
9. Shorter versus longer time given to return a questionnaire e.g. 10 days versus 3 weeks.
10. An electronic questionnaire linked to an entry into a prize draw versus an electronic follow-up questionnaire with no link.
11. An electronic questionnaire linked to a charity donation toward the condition being studied versus a web based follow-up questionnaire with no link.

It was also agreed that more evaluations of communication strategies to encourage participants to return to sites for follow-up were needed and that more electronic follow-up technologies needed to be used and evaluated.

It was noted in the discussions on communication strategies e.g. sending a letter with an extra sentence explaining how long it should take the participant to complete an accompanying questionnaire, that the intervention was too similar to usual procedures to make a real difference to response rates. It was agreed across all of the discussion groups that any retention strategies to be evaluated in future should be substantially different from usual follow-up procedures.

7.7. BEST PRACTICE GUIDANCE FOR THE USE OF RETENTION STRATEGIES

Because there were so few effective strategies in the systematic review clear consensus on good practice guidance was reached only for incentive strategies and the type of postage to use for sending post to participants. Consensus was also reached on good practice guidance for questionnaire formats and the use of the most relevant questionnaires to measure outcomes for a disease /condition under investigation.

The best practice guidance for retention in RCTs agreed at the consensus workshops was as follows:

- Financial incentives of £5-10 can be used to improve questionnaire response in RCTs.

- The upper limit of financial incentives given to RCT participants should be no more than £20.
- 2nd class post can be used for postal correspondence with participants.
- The content, design and flow of questionnaires should be clear for participants to follow.
- A relevant and validated questionnaire should always be used for outcome data collection.
- Future retention strategies for evaluation should clearly differ from usual follow-up procedures.

7.8. STRENGTHS AND LIMITATIONS OF THE CONSENSUS DEVELOPMENT WORKSHOPS

A considerable strength of this consensus development work is that the attendees were from many RCTs conducted across different disease areas. They had expertise in the design, management and analyses of RCTs. They also had an interest in RCT retention, and experience of loss to follow-up in RCTs. Therefore, rich data was gathered from these two well attended and lively consensus workshops and agreement reached on best practice guidance based on the results of the systematic review and the qualitative study.

Although the consensus development workshops were shorter (each was no longer than one and a half hours) than consensus workshops run by the National Institutes of Health (NIH) which are traditionally run over two days (Murphy et al. 1998), it is clear that the modified consensus conference workshop format used here was successful because the researchers found it convenient to attend workshops at their place of work and to contribute to discussions about an important aspect of their work.

The workshop attendees had some prior knowledge of the results of the systematic review and the qualitative study through earlier presentations of the results at both research units and at national and international conferences at e.g. the Society for Academic Primary Care (SAPC) (Appendix 7.2), Society for Clinical Trials (SCT) (Appendix 7.2) and the MRC Trials Methodology conference (Appendix 7.2). Therefore, most invitees were broadly familiar with the results of both studies and we found that there was enough time to explore all of the items for discussion. Furthermore, the consensus workshops were structured in such a way that the group discussions within each workshop were focused

on one strategy only giving the attendees enough time to focus their discussions on that strategy.

There is general agreement between the results of the consensus workshops and the results of the qualitative study. Common RCT retention themes were discussed spontaneously in each e.g. having easy to read questionnaire formats, the addition and value of monetary incentives, and the use of reminder strategies for RCT participants. The extent of agreement on good practice for the use of retention strategies was limited in the workshops. This was not due to limitations in the conduct of the consensus development workshops themselves, but in the heterogeneity of the data available.

7.9. SUMMARY OF RESULTS

In this chapter uncertainties around the use of the results of the systematic review and qualitative study were explored in two consensus development workshops with RCT personnel at two UK research units. Based on results of these discussions, consensus was reached on best practice guidance for the future use of monetary incentives and postage. Recommendations for areas for future research have been identified. The implications of these findings for the use of retention strategies in RCT are discussed in the next chapter.

CHAPTER 8: DISCUSSION

8.1. INTRODUCTION

This thesis reported on the effectiveness and use of strategies to improve retention in RCTs. It also provides guidance for the future use of retention strategies. The project comprised:

1. An exploratory study of the challenges of participant retention in RCTs.
2. A systematic review and meta-analysis of the retention strategies evaluated in RCTs.
3. A qualitative study exploring the use of retention strategies in primary care RCTs.
4. Consensus workshops to develop best practice for the future use of retention strategies in RCTs.

In this concluding chapter a lay summary of the project results is presented and the methodological problems and limitations of the project are addressed. The implications of the findings for optimising retention in RCTs are also discussed. Finally, conclusions and recommendations for future research and research practice are presented.

The objectives of this thesis were:

1. To identify the retention strategies that have been evaluated in RCTs.
2. To determine if the retention strategies that have been evaluated are used to improve retention in primary care RCTs.
3. To identify barriers to the use of retention strategies in primary care RCTs.
4. To identify retention strategies for further evaluation.
5. To make recommendations for the use of effective strategies to improve retention in RCTs.

Each objective has been addressed in the thesis and the results are summarised in the following lay summary.

8.2. LAY SUMMARY OF RESULTS

The results of this project show that six different ways to improve trial follow-up have been tested in 38 trials. Most of the trials tested ways to improve follow-up by questionnaires. Fewer trials tested ways to encourage people to return to clinics for follow-up.

Giving people a small amount of money e.g. £5 was found to improve the number of questionnaires returned by post. An offer of a small amount of money improved the number of questionnaires returned by email. Questionnaires sent by 1st class post, sending an extra reminder and giving people small gifts, e.g. a pen, showed no improvement in the number of questionnaires returned.

It is clear from the interviews with researchers that they often used small amounts of money to improve follow-up in trials. They also thought that having good communication with the people taking part in trials, and having flexible appointment times improved follow-up. Ways that do not improve follow-up are also used e.g. sending letters by first class post, giving people small gifts, and sending extra reminders to people to return questionnaires.

The researchers who were interviewed agreed that small amounts of money i.e. £5-£20 could be used to improve the number of questionnaire returned by post, and that 2nd class post could be used to send letters to people taking part in trials. The researchers felt that small gifts may be given to thank the people taking part in trials for their time. More research is needed to find out if other ways to keep people in trials do work.

8.3. LIMITATIONS OF THE RESEARCH

There were several limitations of the available data for the systematic review. The relatively few retention RCTs and the wide variety of populations and settings meant that only broad conclusions could be drawn. The consensus discussion groups were influenced

by this heterogeneity and it was felt that final decisions about using or not using particular interventions needed to take account of these differences. Furthermore, as so many of the included RCTs of retention strategies were identified through the grey literature / word of mouth / and the survey of clinical trials units, it is possible that there are more unreported retention RCTs that have not been identified by the systematic review. Also, poor reporting of retention RCT results could mean that our searches were less likely to identify retention RCTs via the database searches conducted.

This project explored loss to follow-up from the researcher's perspective. Therefore, the experiences and perspectives of RCT participants are not represented. Interviews with RCT participants who had dropped out of RCTs would have provided us with some of the reasons why participants fail to either return to sites for follow-up or to return their questionnaires. Such information would help researchers to address the barriers to follow-up in future RCTs and would help to identify ways to address these barriers.

There is an absence of involvement from patient and public representatives (PPI) in this project. Involving PPI groups in research helps researchers to ensure that relevant research questions and outcomes are understood by patients and the public. At a recent patient and public involvement (PPI) workshop at the MRC CTU at UCL, the problems associated with RCT drop out were discussed with RCT participants. Participants were well aware of their right to withdraw from an RCT without giving a reason but were concerned nevertheless that they did not know more about the problems withdrawal of consent caused for the analysis and interpretation of the outcome data in RCTs. The workshop participants encouraged researchers to be more forthright about this in participant information sheets (personal communication with Professor Sally Stenning, MRC CTU at UCL).

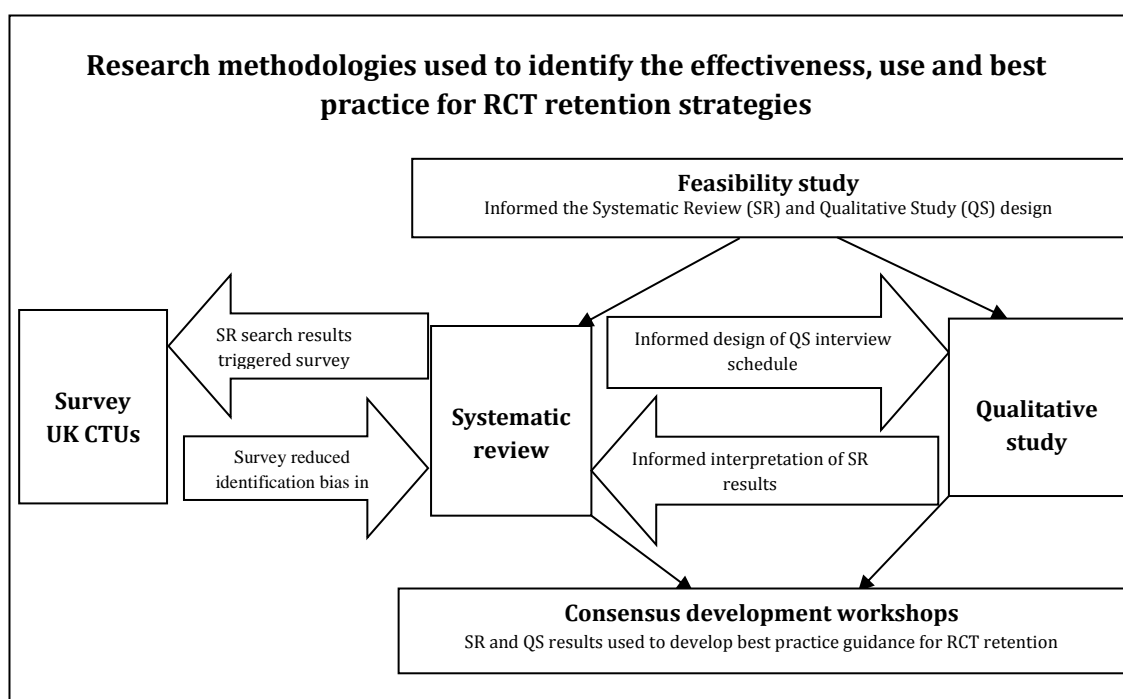
To date, few systematic reviews have involved PPI representatives. Those that have are in the fields of cancer and prion disease research (Vale et al. 2012). There has been no known PPI in methodology systematic reviews. Reasons for this may include the focus of research methodology reviews on the technical processes of research rather than investigations of disease treatments and patient care. In the context of our work we were looking specifically at RCT conduct methodology and in the early exploratory work we did approach researchers to inform the development of the project because they are involved in the design of RCTs. The researchers approached are known to have involved patients and the public in their RCTs, however more needs to be done to include patients and the public in methodology systematic reviews.

In order to improve the involvement of participants and the public in future methodological systematic reviews it would be important to involve people from those groups with an interest in trial conduct methodology. This could be achieved through the Cochrane Collaboration consumer group <http://consumers.cochrane.org/>. PPI involvement in methodological systematic reviews would facilitate mutual learning and understanding between PPI groups, RCT methodologists, and methodology systematic reviewers. This would contribute to the identification of key outcomes to assess in methodological systematic reviews, and would also help to improve the readability of the scientific language in such review summaries.

8.4. ADVANTAGES AND DISADVANTAGES OF CONDUCTING MIXED METHODS RESEARCH

An integrated mixed methods approach was used to understand the effectiveness and use of strategies to improve retention in RCTs, and to develop best practice guidance for the use of retention strategies (Bryman 2006, O’Cathain et al. 2010). The initial fact finding meetings with RCT researchers identified areas of uncertainty about retention and loss to follow-up in RCTs. This provided an insight into the challenges involved in retention for RCTs for the treatment of cancers and infectious diseases. The information gathered was used to inform the development of the research question for the systematic review and the qualitative study, both of which ran simultaneously (see Figure 26).

Figure 26 Mixed research methods used for this project



This integrated mixed methods approach helped to refine the research questions to be answered, and helped identify appropriate methods to answer those questions as the data collection continued. For example, when it became clear that one potentially eligible retention RCT was identified by word of mouth and not through the database searches (Smeeth et al. 2001), a survey of UK clinical trials units was conducted to identify other retention RCTs not picked up through other means (see Figure 26).

Incorporating in-depth interviews with the systematic review helped to explore the use, potential barriers to use, and appropriateness of the strategies to improve retention identified by the review in primary care RCTs (Creswell et al. 2004). The in-depth interviews also provided explanations and further understanding of the retention strategies used which complemented the review. The consensus workshops facilitated discussions of the results of both studies and the development of best practice guidance for retention in RCTs.

8.5. DISCUSSION OF THE RESULTS

8.5.1. INCENTIVES

Several qualitative study interviewees commented that they were unsure whether or not the incentives they use to improve questionnaire response actually worked in practice. The evidence from the systematic review is clear. Giving and offering small monetary incentives is effective. Researchers at the consensus workshop agreed that incentives can now be used to increase response to questionnaires. How much should be given and when will be context dependant.

A £5 voucher (Gates 2009, Kenyon 2005) was effective for the return of postal questionnaires in RCTs conducted between 2005 and 2009. More recently Bailey (unpublished) found that £20 vouchers were more effective. In the qualitative study, the researchers thought that the value of the monetary incentive should not be so high as to be perceived as payment for data. It was felt that it should be seen by participants more as a thank you for their effort and contribution to the RCT. The researchers in the qualitative study and the consensus workshops felt that the amount would need to strike a balance between an amount acceptable to an ethics committee, the tasks the participants were being asked to do, the participants' perceptions of how they feel their contribution to the RCT is being valued, and how best to spend the public money granted to fund the RCT. Therefore, based on these results, monetary incentives valued £10-£20 rather than £5 might be more appropriate to use in present day RCTs as the cost of living increases.

A cost effectiveness analysis for additional responses gained after incentive strategies were introduced in RCTs was reported for six of the incentive RCTs included in the systematic review (Couper et al. 2007, Gates et al. 2009, Kenyon et al. 2005, Khadjesari et al. 2011, Leigh-Brown et al. 1997). At the consensus workshops, some of the researchers felt that the absolute benefits of retention strategies were small and may not justify the cost, however they felt that this would depend on the level of retention in the RCT and the population group. As the costs of adding monetary incentives increase due to inflation, a cost benefit analysis would be needed if incentives were to be used to improve retention in future RCTs. The amount given to participants would need to be reviewed by RCT teams in conjunction with PPI groups, key research funders (such as NIHR) and ethics committees, to ensure that the amount offered is appropriate for improving response in RCTs. Furthermore, when planning RCTs that use incentives, researchers may wish to consider the potential impact of using strategies to improve retention on power versus the cost of the retention strategy.

An offer of a monetary donation to a cancer charity (Khadjesari 2011) showed no effect for improving electronic questionnaire response in the context of an RCT of a web based intervention to reduce alcohol consumption (Khadjesari 2011). Cancer Research UK was the charity chosen for donations because it is the UK's largest fund raising charity (Khadjesari 2011). Donations to charity were not spontaneously mentioned as a retention strategy in the qualitative study. However, it was agreed at the consensus workshops that it may be more appropriate for future donations to charity to be matched with the disease / condition for which a treatment is being evaluated. Matching the charity to the disease / condition may appeal to RCT participants' sense of altruism. However, the impact of this strategy may also be dependent upon other participant characteristics for example, the socioeconomic group, and age of the RCT participants.

Adding different non-monetary incentives e.g. pens and lapel pins showed no effect on retention in RCTs (Bowen 2000, Sharp 2006, Renfro 2002, Hughes 1989 Cockayne 2005). The qualitative study demonstrated that a possible explanation might be how these items are valued by participants, or their perceptions of how their participation in an RCT is valued by the research team. It was felt by the participants in the qualitative study and the consensus workshops that non-monetary incentives are not enough to keep participants involved in RCTs. They thought that these may even lead to scepticism about how well public money is being spent. However, they were considered by most researchers as a way of thanking RCT participants for their participation. Any saving from not using gifts in

RCTs could be used toward monetary incentives or to contribute toward reducing the financial costs incurred by participants attending RCT follow-up visits e.g. transport costs.

8.5.2. COMMUNICATION STRATEGIES

Additional reminders sent to non-responders, and variations in the letters sent to participants showed no good evidence for increasing response to questionnaires. However, the qualitative study and consensus workshops showed that such strategies are used by researchers in RCTs. Reminders play a role in engaging RCT participants especially where there is little face to face contact. This may occur when outcomes are self-reported, or where there are long intervals between data collection time points. The nature of some of the reminders used and evaluated is of a supplementary contact with the participant rather than a reminder sent in response to a lack of response. For example, Nakash (unpublished) gave calendars to RCT participants at recruitment that highlighted the months when questionnaires were due to be returned. Severi (2011) sent text messages after questionnaires were sent to the participants to remind them when a questionnaire was due back. Similarly, MacLennan (unpublished) made telephone calls to participants before they received their first reminder to return a questionnaire. However, too many of these types of reminders could be counterproductive to improving retention in RCTs if participants feel uncomfortable about the additional contact from the RCT coordinating team. A tailored approach to follow-up whereby the need for reminders is discussed with the participant at recruitment and their preferred method of contact, if any, is then agreed, may reduce the number of reminders from the RCT coordinating centre and enhance follow-up compliance through ensuring that the participant is more engaged at the beginning of the RCT.

Recorded delivery was found to be an effective strategy to improve responses to postal questionnaires in RCTs. However, the results are based on one RCT conducted in 1997 (Tai, 1997). This strategy was considered out dated in the consensus group discussions but it was considered a potentially useful strategy for ensuring RCT follow-up supplies reach their intended destination by the qualitative study interviewees, for example for the timely delivery of biomedical specimen kits. Although this strategy can ensure that follow-up supplies are delivered to RCT participants, they might have the additional burden of having an extra visit to collect a package with RCT supplies from a post office. This could be costly, inconvenient, and frustrating for the participants. Therefore, careful planning of delivery by recorded post with the participant to avoid inconvenience may be necessary if this strategy were to be used in future.

The evidence from the systematic review shows that priority post does not increase response to postal questionnaires in RCTs. However, it is clear from the qualitative study interviews that first class post is used to send letters to RCT participants in the hope that these letters will be opened by them. The consensus reached at the consensus workshops was that this is an expensive means of communicating with RTC participants and that savings could be made by using second class post.

8.5.3. QUESTIONNAIRE STRATEGIES

There was no clear evidence from the systematic review that modifying the format of a questionnaire improved questionnaire response in RCTs. The evidence from Edwards review (2009) of strategies to increase response to questionnaires is that shorter questionnaires improved response. However, Edwards (2009) review was not specifically focused on retention in RCTs. Some interviewees in the qualitative study mentioned that additional questions added to questionnaires but not analysed or reported caused an unnecessary and extra burden for participants. The addition of extra questions to questionnaires was thought to also impact on the RCT management team in terms of the human and financial resources associated with conducting extra analyses and reporting additional results. It was also thought that a balance between questionnaire length, readability, content and the acceptability of the topic to RCT participants were important aspects of questionnaire design that could improve questionnaire response. However, in some RCTs for treatments for terminal diseases e.g. cancer, participants might not be well enough to complete questionnaires. Therefore, shorter more convenient ways of collecting patient reported outcomes may need consideration for example collection of information by SMS text message or email.

8.5.4. METHODOLOGY STRATEGIES

In the systematic review, there is some evidence of better questionnaire response with an open rather than a blind RCT design in the context of secondary osteopathic fracture prevention. The interviewees in the qualitative study felt that blinding participants to their allocated intervention would improve retention. There was no support for the use of the open RCT design in the consensus group discussions. Blinding was seen as key to reducing bias and a fundamental part of RCT design. However, not all RCTs lend themselves to the double blind placebo design. There are instances where blinding cannot be applied as mentioned by the interviewees in the qualitative study. For example, in RCTs of

behavioural interventions, or in retention RCTs that evaluate monetary incentives. Avenell (2004) argues that double blind RCTs do not reflect usual health care activities and that a better measure of the differential effects in normal care settings might be given by using an open RCT design. As the evidence for the effect of open RCT designs on retention are based on only one RCT, and blinding is a key component of many RCTs, the use of an open trial design as an RCT retention strategy is therefore not advocated.

8.5.5. CASE MANAGEMENT

There was no evidence that case management improved RCT retention. The interviewees in the qualitative study recognised and use elements of case management to improve RCT retention. They were generally positive toward this strategy, even though they thought it may be costly to implement. Participants in the consensus groups were interested in the strategy and wanted more information about the time and resource implications for using case management. In the qualitative study, the personality of RCT personnel was mentioned as a factor contributing to RCT retention. As case management involves forging close partnerships with RCT participants, those responsible for RCT staff recruitment may consider placing emphasis on both the communication and the technical skills of candidates when appointing staff to such key roles particularly if case management is to be used.

8.6. COMPARISONS WITH OTHER REVIEW FINDINGS

This project includes the first methodology systematic review of strategies to improve retention specifically in RCTs. The differences between this systematic review of retention strategies and the other five literature reviews conducted to date on retention in research are illustrated in Appendix 9.1. Two of the prior systematic reviews of retention strategies conducted meta-analyses (Edwards et al. 2009, Nakash et al. 2006). The results of those meta-analyses are compared with the results of our review. Edwards (2009) large comprehensive Cochrane systematic review on methods to increase response to postal and electronic questionnaires included many RCTs and identified many strategies used to increase questionnaire response in surveys, cohort studies and RCTs. In agreement with the results of our systematic review, Edwards (2009) found that monetary incentives were effective for increasing response to postal questionnaires. However, Edwards (2009) also found that non-monetary incentives were effective for improving postal and electronic questionnaire response (OR 1.17; 1.08-1.25. $p=0.000029$). This result could be explained by the large number of included RCTs and participants in Edwards review. This contrasts with the results of our review where there was no evidence of an effect for the use of non-

monetary incentives (RR 1.00; 0.98-1.02, $p=0.91$). In agreement with our review, the other strategies found to be effective for postal questionnaire response by Edwards (2009) were recorded delivery and the use of a package of postal communication strategies known as the "Total Design Method". The package includes the use of hand-written addresses, stamped return envelopes as opposed to franked return envelopes and first class outward post. Our review also found that priority post was not effective (RR 1.02; 0.95- 1.09, $p=0.55$) whereas Edwards (2009) found this strategy to be effective (OR 1.11; 1.02 to 1.21) although the effect size is modest.

Edwards (2009) used a random effects model for the analyses which assumes that there is a variation in the underlying treatment effect amongst the included RCTs. For the analyses of our systematic review, we recognised up front that heterogeneity was a problem and therefore the retention RCTs were divided into more homogenous subgroups before the data were combined for analysis. For example the RCTs of incentives versus none were divided into five groups: the addition of monetary incentives versus none, the addition of offers of monetary incentives versus none, the addition of gifts versus none, the addition of offers of gifts versus none and the addition of offers of monetary donations to charity versus no offer. Subsequently, heterogeneity of results within the subgroups was generally not a problem and was explored by using a fixed effect model which assumes a common treatment effect (Deeks et al. 2008). Some heterogeneity was seen in the addition of the non-monetary incentives group ($p=0.02$). A random effects model was also fitted and the conclusions were unchanged. For the remaining subgroups in the incentives category heterogeneity was not significant.

There were some overlapping RCTs between the Edwards (2009) review and the retention RCTs included in our systematic review. However, there were seven unpublished RCTs and 18 other RCTs not included in the Edwards review that were included in our systematic review.

Nakash's (2006) systematic review examined ways to increase the response to postal questionnaires in health care research. Fifteen RCTs were included in the meta-analysis which found that reminder letters, telephone contact, and short questionnaires increased responses to postal questionnaires. Unlike the results of our review there was no evidence that monetary incentives were effective based on the results of four RCTs of incentives versus no incentive (OR 1.09; 0.94-1.27; $p=0.24$). Furthermore, the review by Nakash (2006) was not exclusive to evaluations conducted in RCTs. Six of the fifteen RCTs included were retention RCTs embedded in host RCTs all of which are included in our

review (Dorman et al. 1997, Leigh-Brown et al. 1997, McColl et al. 2003, Sutherland et al. 1996, Tai et al. 1997)³⁸. The fixed effect model was used for the analyses and no significant statistical heterogeneity was reported.

8.7. DIFFERENCES BETWEEN THE PROTOCOL AND THE SYSTEMATIC REVIEW

There were some differences between the published Cochrane systematic review protocol and the analyses conducted for the systematic review (Brueton et al. 2011, Brueton et al. 2013). With the diversity of retention RCTs found not all of the pre specified analyses set out in the protocol for the systematic review were appropriate (Brueton et al. 2011). Therefore new subgroups were defined prior to the analyses.

We planned to assess whether loss to follow-up was immediate or occurred in the longer term. For example, if response to a questionnaire was expected immediately or at time points further into follow-up. This was not used in the analyses for the systematic review as the time points for the primary analyses were generally poorly reported in the included retention RCT publications. Where data for different time points were reported, data for the primary outcome time point was used. It was also planned to group participant and management focused strategies up front in the review protocol. However, we found only one retention RCT (Land unpublished) that evaluated a management focused strategy to improve retention.

8.8. METHODOLOGICAL CHALLENGES IN THE SYSTEMATIC REVIEW

Several methodological challenges were encountered while conducting the systematic review. These are discussed individually in the sections that follow.

8.8.1. THE DEFINITION OF ATTRITION / LOSS TO FOLLOW-UP

The meetings with researchers at the MRC Clinical Trials Unit and a search of standard dictionaries of biostatistics and epidemiology highlighted that there is no clear definition of attrition or loss to follow-up to guide researchers (Armitage 2005, Last 1983). Hopewell (2011) found that loss to follow-up and discontinuation of an RCT intervention were sometimes combined in reports of loss to follow-up with no differentiation made between these participant groups. Toerien (2009) identified this as a problem in a review of the reporting of loss to follow-up in six major journals. The definition of attrition proposed by Akl (2009) “ascertainment of the primary outcome” was therefore used to guide the

³⁸ McColl (2003) trials 1 incomplete and 2

development of the research question and the data extraction for the systematic review. This definition was also used to explain attrition to the primary care researchers interviewed.

The CONSORT guidelines define loss to follow-up as “loss of contact with some participants, so that researchers cannot complete data collection as planned” (Altman et al. 2001). These guidelines recommend that for each randomised group the number of participants assigned to the treatment, the number that received treatment and the number analysed for the primary outcome is recorded. It is also recommended that any losses and exclusions after randomisation are also reported with reasons for their exclusion.

Although CONSORT has recommended guidelines on the reporting of loss to follow-up, clearer definitions and standardisation of the terms used for attrition, dropout, withdrawal and loss to follow-up are needed. Without clear definitions it remains unclear, as highlighted by the meetings and interviews with both cancer and primary care researchers, how attrition / loss to follow-up from RCTs is to be calculated. For this systematic review, the intention to treat approach was used where all participants randomised in the retention RCT were included in the denominator whether they received the intervention or not. Clearer guidance on how to measure attrition / loss to follow-up is needed for researchers and clearer definitions for these terms also need to be agreed and included in biomedical statistics text books and dictionaries.

8.8.2. SELECTION BIAS

A slightly modified search strategy was used to update the searches in May 2012. It was hoped to identify retention RCTs published since 2009 that were identified for inclusion in the review through the other sources searched. Therefore, the retention RCTs by Gates (2009), Khadjesari (2011), Severi (2011) and Ashby (2011) identified through other means in the initial searches were specifically searched for in the updated search results. All were identified. Therefore, the refined search strategy appears reliable and can be used for future updates of the systematic review (Appendix 1.4).

Unpublished data from nine retention RCTs was included in the systematic review (Bailey 1, Bailey 2, MacLennan, Letley, Edwards, Svobodva, Land, Marson, Nakash 2007). These RCTs were identified through word of mouth and through the survey of clinical trials units. The data from these RCTs contribute substantially to the meta-analysis on incentive strategies, additional reminders, and new questionnaire formats. To avoid selection bias

in future systematic reviews of methodology interventions, the importance of using methods beyond database searches to identify methodology RCTs - including direct contact with researchers and surveys of clinical trials units - is strongly emphasised in order to capture on-going or unpublished but completed eligible retention RCTs.

8.8.3. SELECTIVE OUTCOME REPORTING BIAS

The meta-analyses focused on the primary endpoint of retention (the proportion of participants retained) at the primary analysis point, as defined in each individual retention RCT. The concept of retention in RCTs was more intuitive to deal with than loss to follow-up i.e. the proportion retained versus the proportion lost. All included retention RCTs reported response or retention as expected. There was no evidence of selective outcome reporting bias in any of the retention RCTs included in the review. Where there was evidence of missing data that had the potential to bias the outcome of the systematic review, the authors of eligible retention RCTs were contacted for information. The letters sent were individualised and were followed up with up to three reminders. Where there was no response from authors, other co-authors on the RCT publication report were contacted. The outcomes of any retention RCTs with missing data after this process were described qualitatively. Therefore, selective outcome reporting bias is minimal in the retention systematic review.

8.8.4. DEALING WITH DIFFERENT TRIAL DESIGNS

The included retention RCTs were of different designs. These included cluster, factorial and multi armed RCT designs. The factorial RCTs included the conventional 2x2 design, and more complex 2x2x2 and 2x2x2x2 designs. The multi-armed RCTs were three and four armed. The variation in the RCT designs of included retention RCTs made the meta-analyses complex.

A problem with cluster RCTs is that participants randomised in clusters often respond in a similar pattern (Higgins et al. 2008b). Cluster RCTs are sometimes incorrectly analysed at the individual rather than cluster level, resulting in small p values and false positive results. For RCTs that ignore clustering in the analysis, the intra cluster correlation coefficients (ICC) are either excluded or poorly reported, this can be dealt with by approximate analysis if the data and external estimates of the ICC are available. For the one cluster RCT included in this review (Land unpublished), the mean of external estimates were sourced and used to avoid the biases associated with analysis at individual participant level.

Factorial designed RCTs have several advantages over head to head and multi armed RCTs in that they allow for the simultaneous evaluation of two or more interventions with fewer participants. Factorial RCTs are therefore cost effective, but are vulnerable to interaction effects which are only determined during analyses. If an interaction between the interventions is present, the effect of the individual comparisons rather than the main effects should be presented. However, this reduces power (Fox et al. 2006). To address potential interaction in the analyses of factorial designed retention RCTs included in the systematic review, data for each factorial cell was used where available for the meta-analysis. This gave many RCT comparisons but meant that the subgroup heterogeneity statistics had the potential to capture any interactions. For one of the eligible retention RCTs by Renfroe (2002), data for all of the individual factorial cell comparisons were not available; therefore the available data was collapsed into the main effects, ignoring the potential interaction effect.

For multi-armed RCTs where more than one intervention arm was relevant to an intervention category, the intervention arms were combined and compared with the control arm (Higgins et al. 2008b). This avoided double counting of control arm participants using the most appropriate current approaches for analysis to prevent misleading results. However, it is acknowledged that further methodological research is needed to allow appropriate inclusion of pairwise comparisons in meta-analyses as the approach recommended in the Cochrane handbook is pragmatic but imperfect (Higgins et al. 2008b)

8.8.5. OTHER SOURCES OF BIAS

Three of the retention RCTs included in the systematic review were conducted after the corresponding host trial was completed. Hughes (1989) offered reprints of the study results to improve follow up of participants six months after a smoking cessation RCT completed follow-up. Bauer (2004) used incentives to try to improve follow up of participants in the COMMIT smoking cessation RCT eight years after the original/host RCT was completed. Kenyon (2005) used monetary incentives to improve follow-up seven year old children of mothers enrolled in the ORACLE RCT. These three retention RCTs were included in the systematic review because the participants were randomised in the original host RCT and the same participant pool was used for the follow-on retention RCT. The results of a sensitivity analysis excluding the RCTs by Bauer (2004) and Kenyon (2005) from the main analysis of incentives shows that incentives remain effective, (RR 1.14; 1.05-1.24 $p=0.003$) compared to (RR 1.18; 1.09-1.28 $p<0.0001$) in the main analysis.

A similar lack of impact is seen when the retention RCT by Hughes (1989) is excluded from the addition of an offer of non-monetary incentive subgroup analysis, (RR 0.98; 0.94-1.02 p=0.36) compared to (RR 0.99; 0.95-1.03 p=0.60) in the main analysis.

8.9. METHODOLOGICAL CHALLENGES IN THE QUALITATIVE STUDY

8.9.1. SAMPLING AND SELECTION BIAS

The sampling for the qualitative study relied on the chief investigators willingness to allow their RCT to be included in the sampling frame. Those approached were generally enthusiastic. The sampling frame included interviewees experienced in RCTs conducted through primary care in a range of disease areas and different follow-up methods. More interviewees were sampled from RCTs with lower levels of loss to follow-up, which may reflect their interest in controlling loss to follow-up in RCTs. The PIs / CIs interviewed were academic GPs apart from one. As these interviewees were GPs with clinical posts their views may be broadly representative of the views of non-academic GPs who act as PIs at site level. The RNs interviewed were also a select group because they were employed by a primary care research unit and held RN positions at GP practice sites. They may also be representative of the RNs who collect data at site level. Two of the RNs were recently recruited to the unit and their data was not divergent from that of the other nurses interviewed. While most of the interviewees were from RCTs conducted through the MRC GPRF, one third of those interviewed were from RCTs conducted outside of the GPRF. Therefore, the results of the qualitative study are generalisable to the wider UK primary care trials community.

8.9.2. CONTROLLING FOR INTERVIEWER BIAS

There could have been assumed knowledge about the conduct of RCTs in primary care contexts between the interviewees and the interviewer because of familiarity through previous research collaborations. This could have resulted in superficial discussions about the retention strategies used in RCTs. However, to control this, interviewees known to the interviewer were asked at the beginning of each interview to treat the interview as if they were being interviewed by someone they were not acquainted with. They were also probed to expand on key points of interest during the interviews. This resulted in rich discussions probably because the interviewees understood the bias that this familiarity could have potentially caused.

The early interview transcripts were critically reviewed for interview technique by the qualitative study group. This process enhanced the quality of the data as the interviews progressed. The card system developed for data collection relating to the use of the different strategies identified by the review (see Chapter 5 section 5.6.1) gave the interviewer more control over the interview. This meant that the subsequent transcripts were easier to read, code and analyse.

8.9.3. RECALL BIAS

In the sampling frame, more RCTs were included in the 2005-2010 group than the 2000-2004 group. This reflected the increase in RCTs conducted through the MRC GPRF and conducted in primary care generally in more recent years. The inclusion of RCTs from this later period may have reduced interviewee recall bias. For some of the interviews the RNs and TMs came prepared with notes on the strategies they used to prevent loss to follow-up in RCTs. This would have also contributed to reducing recall bias.

8.10. IMPLICATIONS FOR THE CONDUCT OF FUTURE METHODOLOGICAL SYSTEMATIC REVIEWS

8.10.1. BIBLIOGRAPHIC DATABASE SEARCHES

Systematic reviews set out to gather all the evidence available to answer a specific question which is usually a clinical research question. Bias is reduced by having clear pre specified methods (Green et al. 2008b). Selection, language and publication bias are associated with limiting systematic review searches to too few bibliographic databases. The broad search strategy used for the systematic review of retention strategies avoided the selection biases associated with restricted searches. As there is no clear guidance for searching for methodology studies the searches conducted for this systematic review were time consuming because; a) of the range of search terms used to describe retention and attrition, b) the variation in syntax for the electronic databases searched and, c) the large number of records generated from the searches conducted.

In contrast to systematic reviews of clinical treatments, in this methodology systematic review, the eligible retention RCTs were identified through several sources and most were identified through means other than bibliographic databases. The Cochrane handbook recommends searches of MEDLINE and CENTRAL as a minimum when searching for eligible studies. A search of EMBASE is also recommended, although there is some overlap between the content of these databases (Lefebvre et al. 2008). EMBASE was included in

the searches for our systematic review. The database includes reports on drug development, toxicology, safety, medical devices, regulatory affairs, pharmacoeconomics and pre-clinical reports (Elsevier 2011). However, no eligible retention RCTs were identified through EMBASE. Searches of EMBASE have been used for similar Cochrane methodology systematic reviews for example for the reviews of strategies to increase recruitment (Treweek et al. 2010) and response to questionnaires (Edwards et al. 2009). However, it is unclear if any of the retention RCTs included in those reviews were identified through EMBASE. Given that the focus of EMBASE is on pharmacology topics, this may not be an appropriate source to search for methodology RCTs evaluating recruitment and retention strategies. It may have been beneficial therefore to consult a Cochrane information specialist to ascertain if this was an appropriate database to search for eligible retention RCTs for this methodology review.

The CINAHL database searches returned two retention RCTs (Chaffin et al. 2009, Cox et al. 2008). CINAHL is a subject specific database and contains nursing and allied health subjects (Ebscohost 2013). The two retention RCTs identified through CINAHL were community based social / psychology (Chaffin et al. 2009) and exercise / physiotherapy (Cox et al. 2008) RCTs using behavioural strategies to improve RCT retention. The retention RCT by Chaffin (2009) included in the systematic review was identified only through this source. The retention RCT by Cox (2008) however, was also identified through MEDLINE and CENTRAL. This was probably because it is an exercise RCT related to general physical health. Therefore, to avoid selection bias, it is important to include a search of CINAHL to identify methodology RCTs conducted in medical and health care settings for future methodology reviews.

PsycINFO, another subject specific database, contains reports on behavioural sciences and mental health research (American Psychological Association 2013). No eligible retention RCTs were identified through searches of this database. Although the behavioural strategy RCTs by Chaffin (2009) and Cox (2008) were not picked up through searches of the PsycINFO bibliographic database, this may be explained by a miss-match between the controlled vocabulary used to index studies in the PsycINFO database and our search terms (Lefebvre et al. 2008). It may therefore be appropriate to include a search of this database for future methodology systematic reviews by adapting our search strategy to include the controlled vocabulary used to index studies in the PsycINFO database. Although consultation with a Cochrane information specialist is advisable.

The ERIC and C2 SPECTRE databases contain education and social science publications. ERIC is focused on education literature to support the use of educational research and information to improve teaching. C2 SPECTRE holds citations in the fields of sociology, psychology, education, and criminology research. Although both of these databases were searched in the reviews by Treweek (2010) and Edwards (2009), it is unclear from those systematic reviews if any of the included RCTs in those reviews were identified from either of these sources. No retention RCTs were identified through these sources for our systematic review. Therefore, systematic reviewers might reconsider the appropriateness of using these bibliographic databases when searching for methodological research in health care settings for future methodology systematic reviews.

The Database of abstracts of reviews of effects (DARE) publishes systematic reviews on the effects of health care interventions and also on the delivery and organisation of health services (Centre for Reviews and Dissemination 2013b, Lefebvre et al. 2008). This database is useful for identifying related reviews on any subject. It could therefore be a useful database to search for methodological systematic reviews for future reviews in RCT conduct methodology.

Many other bibliographic databases which focus on the area of social science, nursing, allied and international health are used to search for eligible studies to include in systematic reviews (Lefebvre et al. 2008). Given that there are no RCTs from low income countries, searches of the Global health, POPLINE, LILACS and African Index Medicus databases could have been included in our review. However, searches of these databases would have required extra time, human and financial resources (Lefebvre et al. 2008).

8.10.2. SEARCH FILTERS

Search filters are designed to control the number of abstracts and titles generated by bibliographic database searches. They allow for selective retrieval of reports of RCTs specifically. Bibliographic databases such as MEDLINE hold reports of different study designs e.g. cohort studies, surveys and RCTs, and such filters can be applied to select only RCTs from the database. These filters are not standardised across bibliographic databases because of the variability in indexing across the different databases available (Wong et al. 2006a).

Filters that offered the best sensitivity and specificity with good precision were added to our search strategy to identify abstracts for retention RCTs (Eady et al. 2008, Wong et al. 2006a, Wong et al. 2006b). The sensitivity and precision maximising version of the

MEDLINE search filter was used to search MEDLINE. This filter has been tested and recommended by the Cochrane collaboration. Search filters to identify RCTs in PsycINFO, CINAHL, EMBASE and ERIC were identified through the InterTASC Information Specialists' Sub-Group Search Filter Resource (Centre for Reviews and Dissemination 2013a). These filters are updated regularly and are assessed for reliability, accuracy and relevance to accommodate changes to the different database interfaces and indexing. They should therefore be considered when building future searches for methodology related reports of RCT results (Lefebvre et al. 2008).

PreMEDLINE is a non-indexed dataset of MEDLINE. The database was searched initially using the MEDLINE sensitivity and precision maximising search filter. However, a Cochrane information specialist peer reviewer commented that this filter had not been validated for PreMEDLINE and that the database should be searched using free text terms. A range of truncated free text terms were suggested e.g. random\$, placebo\$, and trial\$, to identify any non-indexed potentially eligible records. The searches returned 8663 records. As the time and resources to screen these were limited, this search was excluded from the search updates conducted in 2012. Any eligible RCTs in PreMEDLINE should appear in later MEDLINE searches. A search of the PreMEDLINE database may therefore be excluded from a search strategy where time and resources are limited as research reports are available eventually in MEDLINE.

8.10.3. SEARCH TERMS

The search term “response” was not included in the initial search strategy because response to questionnaires was addressed in Edwards (2009) Cochrane review on methods to increase response to postal and electronic questionnaires. It was felt that a hand search of Edwards (2009) table of characteristics of included RCTs would identify retention RCTs within RCTs for inclusion in our retention systematic review. However, “response” was subsequently added to the updated search strategy. This decision was informed by the results of the survey of clinical trials units (see section 3.2.6 Chapter 3). The survey highlighted four further published eligible retention RCTs not identified through the initial search of Edwards’ systematic review (2009). These additional RCTs were by Cockayne (2005), Leigh-Brown (1997), and McColl (2003 trials 1 and 2). They were however found in a subsequent recheck of Edwards (2009) review, and were not recorded as nested retention RCTs in host RCTs. Therefore, the search term “response” should be included in future updates of the searches used for this systematic review. Careful consideration of qualifying or combining terms is needed with the search term

“response” because the term returned many irrelevant records on response to different medical treatments. Similarly, searches with the term “retention” returned references for retention of e.g. information, staff, catheters, fluid etc. To avoid the many ineligible abstracts generated for response to treatment, the search terms for the review were refined for the search updates in 2012 by adding the search term "questionnaire" to "response" in all remaining search terms with "response" or "response*" to make the search more specific to questionnaire response.

8.10.4. SEARCH DATES

A requirement of Cochrane systematic reviews is that the searches cover all of the years spanned by the different bibliographic searched. It is recognised in the clinical trials community that RCTs conducted post 1950 recognise the importance of: randomising participants, defining the participant eligibility criteria, defining the intervention and schedules, and describing appropriate statistical analyses (Pocock 1983). RCTs conducted to test methodology interventions are even more recent. The earliest retention RCT included in this systematic review was published in 1989 (Hughes 1989). Therefore, searches as far back as 1806, for PsycINFO or 1950 for MEDLINE may not be necessary for methodological systematic reviews. Further exploration and consensus is needed to ascertain an appropriate cut-off date to search from for methodology research for similar methodological systematic reviews. This could be achieved by checking other methodological reviews for methodology RCT publication dates to evaluate and agree a range of years to search across databases for eligible methodology related RCTs. The outcome of such research would reduce the numbers of irrelevant abstracts and titles generated by extensive searches.

8.10.5. MANAGEMENT OF BIBLIOGRAPHIC SEARCH RESULTS

The results of the bibliographic searches were saved separately in designated Microsoft Office 2003 Word files. Each potentially eligible RCT screened was logged in a Microsoft Excel 2003 database. Therefore the number of RCTs eligible for the review identified from each database was readily identifiable for the different sources searched. In systematic review reports it is unusual to find the number of RCTs identified from the individual bibliographic and other sources searched. For example, such detail has not been reported in the published Cochrane methodology systematic reviews by Treweek (2010) and Edwards (2009). Furthermore, in Cochrane reviews published by the different Cochrane disease groups, the results for the number of RCTs identified from the different databases is also unreported. Therefore, this is the first time that a breakdown of the numbers of

RCTs identified from each of the different databases searched has been reported in any Cochrane systematic review. One systematic review of treatment for non-small cell lung cancer (personal communication with S Burdett MRC CTU at UCL) reported that of the 12 eligible RCTs included, six were identified from MEDLINE, two from CENTRAL, one from hand searches and three from abstracts of the American Society of Clinical Oncology (ASCO). However, this detail is not reported in the final paper (Burdett et al. 2006).

Recording the source of each study included in a systematic review is not mentioned in the PRISMA guidelines on reporting for systematic reviews (Preferred Reporting Items for Systematic Reviews and Meta-analysis) (Liberati et al. 2009). Better recording of the sources of RCTs included in systematic reviews is needed. This would inform future decision making about the most effective and efficient databases to search in order to answer specific RCT related methodology questions. Which in turn would impact upon the time and costs associated with managing and screening large numbers of irrelevant records generated from irrelevant database searches.

8.10.6. DE-DUPLICATION OF RECORDS ACROSS DATABASES

The CENTRAL database of RCTs contains records from both MEDLINE and EMBASE. Duplicate records were excluded from the search updates for CENTRAL, MEDLINE and EMBASE, using the commands outlined in the Cochrane handbook (Lefebvre et al. 2008). To facilitate more efficient handling of large numbers of abstracts, the updated searches were de-duplicated in the OVID search platform. This reduced the number of abstracts and titles generated for screening in the search results. An alternative approach to record de-duplication is to de-duplicate references in a reference management system by downloading the search results for each database into a separate database folder and subsequently de-duplicating across folders. However, no standardised published guidance was found on how to conduct this in the different reference management systems available. There is clearly a need for such guidance to assist the management of future systematic reviews where large volumes of records are generated for screening.

8.10.7. IDENTIFICATION OF RCTs AND DATA EXTRACTION

The screening of abstracts and titles for eligibility for our systematic review was conducted by one systematic reviewer (VB). The process used was deliberately over inclusive, 0.007% (n= 168/24,304) of records identified were sent for screening to the second reviewer (GR), i.e. 22.8% (n= 168/735) of all of the potentially eligible records identified. Edwards (2002) found that screening by a single reviewer missed ~8% (range

0-24) of eligible reports, whereas no eligible reports were missed when screening was conducted by two reviewers and the number of RCTs identified increased by ~9% (Edwards et al. 2002). We checked the results of our updated searches and found all of the eligible retention RCTs in that were previously unpublished and identified through other sources e.g. the survey of UK clinical trials units. Because the process we used was deliberately over inclusive we are confident that all potentially relevant retention RCTs were identified. Nevertheless, the length of time taken to conduct the review would have been reduced if two reviewers had been involved in the screening and data extraction process.

The data extraction for each eligible RCT was conducted by one systematic reviewer (VB) and thoroughly checked by a second (JT). There are known risks associated with single data extraction, for example this can result in more errors and is more time consuming for the reviewer than sharing the load with fellow systematic reviewers (Buscemi et al. 2006). When the data were extracted for this review no identifiers indicating the page or paragraph numbers the data were extracted from were used on the associated printed retention RCT publication. The second systematic reviewer (JT) was not involved in the screening process and had no prior knowledge of any of the eligible retention RCT publications. Each eligible retention RCT publication paper was read and verified by the second systematic reviewer and the data extracted by the first systematic reviewer interrogated. Where there were discrepancies or disagreements over the data extracted, consensus was reached through discussion about data uncertainties. These were escalated to the wider project and management group for discussion if uncertainty about the data extracted remained. Authors were contacted to confirm the data extracted if there was any ambiguity around this from the retention RCT report. Thus the data included in the meta-analysis is of the highest quality. The review may have taken less time to complete if simultaneous data extraction was conducted, but this would have required additional resources.

8.10.7. SURVEYING CLINICAL TRIALS UNITS

The survey of UK clinical trials units was an important source of eligible unpublished retention RCTs for the systematic review. Conducting a UK survey to identify potentially eligible retention RCTs is not standard practice for a systematic review. The advertisement at the Society for Clinical Trials conference 2010 (SCT) and particularly the poster presented at SCT in 2010 were important for raising the awareness of the work. These methods drew attention to the inclusion / exclusion criteria for conference delegates who

might have had an on-going eligible retention RCT in their place of work. Although delegates were interested in the systematic review, no new retention RCTs were identified through this method. The SCT conference delegates could have been emailed and surveyed to ascertain if there were any potentially eligible unpublished RCTs. This would have captured eligible retention RCTs from outside of the UK. However, the time and costs required to survey approximately 500 SCT delegates was prohibitive.

8.11. OTHER METHODS OF SYSTEMATIC REVIEW

A rapid review could have been conducted to identify eligible retention RCTs, however there are limitations associated with such methods. Rapid reviews use various methodologies to speed up the review process by restricting search variables e.g, the language, publication date, research setting, database, references lists, and grey literature to be searched. There is no clear guidance on ways to conduct rigorous rapid reviews that avoid bias (Ganann, 2012). If we had used a targeted hand search of journals that published methodology research for our systematic review by searching e.g. BMC Trials, BMC Methodology, Clinical Trials, Journal of Clinical Epidemiology and British Medical Journal then several eligible retention RCTs included in the systematic review would have been missed. These retention RCTs were identified from: the Journal of Health Psychology, Nicotine and Tobacco Research, Journal of Medical and Internet Research, Child Maltreatment, Journal of Public Health. This would have impacted considerably on the systematic review results for communication, incentive and behavioural strategies, as six out of the 38 included retention RCTs (by Bowen et al 2000, Bauer et al 2004, Tai et al 1997, Khadjesari et al 2011 and Chaffin et al 2000) would have been excluded.

These six eligible retention RCTs were identified through searches of MEDLINE, CENTRAL and CINAHL. Future methodology reviews considering the use of systematic or rapid methods to identify eligible RCTs should include these databases as a minimum to avoid selection bias. Searches of other databases e.g. C2 SPECTRE, EMBASE, PsycINFO, PreMEDLINE and ERIC should be considered depending on the research question. For example the C2 SPECTRE and ERIC databases could be used to search for research methodology in the fields of education, social sciences and criminology research but are inappropriate for searches for health care research. Furthermore, 27/38 (71%) of included retention RCTs were identified by means other than database searches e.g. through the survey of UK CTUs, networking and through word of mouth. Therefore, these methods should also be used for future reviews of methodological research.

8.12. IMPLICATIONS FOR THE FUTURE CONDUCT OF RCTS WITHIN RCTS

It is surprising that there were so few retention RCTs nested in host RCTs since this could be an efficient way to resolve uncertainty and produce improvements in RCT design.

To overcome the potential barriers to conducting nested RCTs outlined in Chapter 1 (section 1.6), researchers could consider applying for funding for nested RCTs during the funding application stage for the host RCT. Funding bodies could be made more aware of the need for, and efficiency of, nested retention methodology RCTs, particularly when – as here – the interventions being evaluated could lead to cost-savings in future RCTs they may fund. Creating such awareness may result in funding bodies being more open to such funding requests, if not actively requesting grant applicants to consider using nested RCTs in order to evaluate interventions to improve RCT conduct and retention where appropriate.

Researchers could identify any potential retention problems when planning their RCTs by engaging with patient and public involvement (PPI) groups during RCT set up. This would help identify the potential barriers and facilitators to follow-up for participants. The opinions of PIs at study sites about the potential risks associated with loss to follow-up for a population group or a site team would also be valuable. The RCT risk register could also be set up and used at the RCT coordinating centre to monitor the risks to loss to follow-up identified for the host RCT. The information gathered could support an application for funding for a nested retention RCT.

A factorial RCT design as an alternative to a nested RCT design could be considered to evaluate RCT conduct methodologies. This might eliminate loss to follow-up associated with a preference for one RCT over another and reduce the burden for participants of having to return to the clinic or send additional questionnaires associated with a nested RCT. Participants would thereby be given information about all of the interventions to be evaluated and subsequently be recruited and consented at the same time for each factor evaluated. However, the factorial design RCT can be prone to interactions between the groups being evaluated as discussed earlier in this chapter in section 8.8.4.

The growing interest in the area of embedding RCTs in RCTs in order to evaluate methods to improve RCT conduct has given rise to such initiatives as SWAT (The Studies Within A Trial 2012). This initiative plans to use an on line library / data repository of methodology studies that deal with issues of uncertainty in RCTs. The aim is to help researchers with decisions about the strategies to use in different research situations. By means of this

initiative, researchers will be able to log their nested RCT and findings to feed into to a meta-analysis of the individual studies. Other forums for discussing RCT conduct methodology issues are also becoming popular. These include RCT specific methodology conferences such as those hosted in the USA e.g. the annual meeting of the Society for Clinical Trials, and in the UK e.g. the Clinical Trials Methodology bi-annual conference. These platforms are useful for raising awareness of issues of concern in RCT conduct and could be useful platforms to seek and voice opinion about the challenges, barriers and solutions to conducting nested RCTs in RCTs.

It is clear from the results of the systematic review that the results of some nested RCTs remain unpublished as priority is given to publishing the results of the host RCT (See Chapter 3 section 3.2.). Embedding RCTs within RCTs provides other opportunities for publications and can give different first authors opportunities to publish research. This could be seen as another way to “reward” contributing to an RCT which may take many years to publish if the outcome is measured over a long time period.

In order to overcome the barriers to writing up the results of nested RCTs for publication, principle investigators could form a repository of nested RCT datasets perhaps through the SWAT (The Studies Within A Trial) (2012) initiative. The aim would be to engage post graduate students to analyse and write up the results for publication. This has obvious advantages for the RCT team, the student, and the RCT conduct research community. Furthermore, to encourage publication of the results of nested methodological RCTs, editors of journals that publish such research could call for more nested RCTs that evaluate RCT conduct methodologies to be published. Dissemination of these evaluations may improve the conduct of future RCTs. The publication of these results would contribute to future meta-analyses updates for our retention review and Treweek’s (2010) systematic review on the effects of strategies to improve recruitment to RCTs (Brueton et al. 2013,Treweek et al. 2010).

8.13. IMPLICATIONS FOR REPORTING METHODOLOGY RESEARCH

Although the nested retention RCTs in the systematic review appeared to be well conducted, as evidenced by the risk of bias assessments, they were often not well reported as evidenced by the efforts to communicate with authors for clarification on aspects of the retention RCT reports. There was great variability in the quality of the reporting for included retention RCTs and this made data extraction complicated and lengthy. Some of the retention RCTs included did not meet the standard of reporting for parallel group

RCTs outlined by CONSORT (Schulz et al. 2010). Approximately half of the included published retention RCTs reported a CONSORT diagram or a power calculation (see section 3.8.2. Chapter 3). Furthermore, the primary and secondary outcomes reported were not well defined, and often the time points for analysis were unclear (see section 3.3.4. Chapter 3). For some retention RCTs that compared two different types of strategies, it was unclear from the publication report which group was the control group and which was the intervention group. Examples of this are illustrated in the retention RCT publications by Tai (1997), McColl (2003) and Couper (2007).

When the risk of bias assessment was conducted for each included retention RCT, it was not possible to make a clear judgement about the risk of bias for some of the Cochrane risk of bias criteria because reporting was poor. Considerable time was spent contacting authors to clarify statements made for the methods of randomisation, blinding, and concealment of the allocation to make a more informed assessment of the risk of bias. The data supplied from the authors made subsequent judgements about the risk of bias easier to make, while for others the judgements remain unclear.

There is clearly a need for guidance on the standardised reporting for RCTs that evaluate RCT conduct methodologies. There is also a need for the CONSORT principles to be applied to the reporting of such RCTs. It is clear from our systematic review that the CONSORT guidelines do not guarantee clear reporting. Editors of journals who publish methodology research should consider promoting the use of such guidelines for reporting of nested RCTs. A specific item in the Consort guidelines for reporting the results of nested RCTs would be useful to authors and would highlight the importance of clear reporting of nested RCTs.

The retention RCTs included in our systematic review were often unplanned and were initiated in response to loss to follow-up during follow-up for the host RCT. None of the included retention RCTs had an associated published protocol and were therefore not listed in RCT registers. Advance planning about appropriate strategies or combinations of strategies suitable to address RCT loss to follow-up should be considered at the host RCT protocol stage and any proposed evaluations registered with the SWAT initiative.

Publication of peer reviewed protocols for nested methodological RCTs may help to ensure that the design of such RCTs is robust and reliable with appropriate power calculations and outcome measures (Chan et al. 2013). This would benefit the RCT conduct methodology knowledge base. The publication of such protocols could provide

researchers wishing to nest methodological RCTs in host RCTs with examples of how to implement such RCTs.

8.14. FUTURE RESEARCH

The consensus workshops and qualitative study identified different communication, questionnaire and incentive strategies for further evaluation in future RCTs. These evaluations would provide clearer evidence to researchers about the effectiveness of more up to date RCT retention strategies. Such nested RCTs would therefore build on the knowledge generated by this project. Well planned and adequately powered evaluations of these retention strategies are needed. Furthermore, only interventions that clearly differ from current practice should be evaluated. Researchers could incorporate the evaluations of these new retention strategies at the design stage of a host RCT so that the sample size and funding are considered for the rigorous evaluation of such strategies.

With the increased use of internet based RCT data collection methods, the use of different types of incentives linked to web based RCT questionnaires, e.g. a link to a prize draw or disease associated charity donation, were identified for further evaluation at the consensus workshops. An assessment of the role and best use of new electronic technologies e.g. media / internet to improve retention would be appropriate as the use of electronic data collection methods become more widespread.

Based on one single retention RCT included in the systematic review, there was also no evidence that entry into a prize draw was better than giving a small monetary incentive (Kenton 2007). This strategy may also need further evaluation with a cost benefit analysis. If this strategy is found to be cost effective the savings associated with offering participants entry into a prize draw rather than giving or offering a monetary incentive could benefit the RCT budget.

An offer of a monetary incentive was also effective at least in the context of increasing the response to electronic questionnaires (Khadjesari et al. 2011). This could also be a more cost effective strategy to improve questionnaire response than the addition of a monetary incentive, as only those who return the data are reimbursed. This strategy could be further evaluated with postal questionnaires in different RCT contexts as the results are based on two web based RCTs. Furthermore, no RCTs with a direct comparison between an offer of a monetary incentive or an upfront monetary incentive were found. It would also be beneficial for researchers to know which of these strategies is more effective in terms of retention and cost. A comprehensive health economic assessment of offering versus

giving monetary incentives of different values may be useful to investigators planning grant applications to see how much power they would gain in an RCT if they spent different amounts on monetary incentives with different base line response / retention rates. Such economic assessments should form part of all retention strategy evaluations.

The communication strategies identified to potentially help retain participants were: variations in the frequency and timing of follow-up, follow-up by the same person at the clinical trial site, and tailored follow-up. Evaluations of these strategies would go some way to identify further effective ways to encourage participants to return questionnaires and to return to sites for follow-up. Evaluations of electronic reminders to participants to keep RCT follow-up appointments at sites were also identified for further evaluation. Evaluations of these strategies will be important for future RCTs as the use of electronic methods of communication are utilised more.

There was no good evidence in the systematic review that telephone follow-up compared with a monetary incentive sent with a questionnaire is an effective RCT retention strategy. However, this strategy may merit further evaluation possibly with an economic evaluation. Telephone reminders were identified by interviewees in the qualitative study as the preferred method to remind participants to return to sites for follow-up or to return a questionnaire. A clear well planned evaluation of telephone reminders would help to determine if there could be gains that outweigh the cost of this strategy, as this can be expensive to use in terms of staff time and financial resources.

The questionnaire administration strategies identified for further evaluation through the consensus workshops focused on: a) the effect of different lengths of time given to participants to return questionnaires, and b) the different methods for questionnaire completion e.g. electronic versus paper completion, and face to face versus self-completion. The results of these evaluations would help to inform PIs, TMs, and RNs about the most effective methods to administer questionnaires with different populations groups in different RCT settings. Thus providing a stronger evidence base in which to support and enhance RCT management.

Further research is needed to explore the barriers to retention in RCTs from the participant's perspective. This could be challenging research to undertake because the participants that drop out of RCTs are often not contactable. There has been no published work identified that determines from participants why they do not return to sites for RCT follow-up or return related questionnaires. Increasingly clinical RCT sites are asked to

provide reasons for participant withdrawal where available. However, those participants who do provide reasons may not be typical of all those who withdraw from follow-up.

There may be barriers from ethics committees for such research. For example, participants who drop out of RCTs could be difficult to locate. They are also often informed at recruitment that they can withdraw from an RCT without giving a reason. Participants may feel harassed and uncomfortable about any further contact with the RCT team once they have decided to discontinue from being followed up. They may feel that they do not wish to re-engage and give reasons for dropping out particularly if they have feelings of guilt for having dropped out for personal reasons, or because of how they feel about the way they were communicated with during follow-up. Researchers would need to consider whether these participants were likely to be representative of all those who drop out from RCT follow-up before embarking on such research.

An alternative approach to determine why participants drop out of RCTs would be to identify the potential barriers to follow-up for potential participants during recruitment. An explanation of the consequences of withdrawing from RCT follow-up in patient information sheets and at recruitment visits may increase awareness of the negative impact loss to follow-up has on the RCT results. This may influence future participant engagement in follow-up, and help to identify specific retention strategies to use to minimise drop out during follow-up. Obtaining consent to contact the participant should they subsequently drop out of follow-up after randomisation may overcome any perceived feelings of harassment. Ethics committees may be more inclined to consider such a proposal. The results of such a project would be useful for researchers and may help target and tailor strategies to meet the needs of different population groups to keep them specifically engaged in RCT follow-up (Kimmel et al. 2012).

It is clear from the systematic review and the qualitative study that there is less research on the effectiveness of strategies targeting RCT sites (rather than trial participants) to improve retention. Although sites seldom withdraw from RCTs, if this were to occur the impact of losing several participants as a result of a site withdrawing from an RCT could compromise the validity of the RCT by impacting on follow-up of participants recruited at the site. Evaluations of RCT management methods to help retain RCT sites and to improve retention are needed. Evaluations of such strategies e.g. sending electronic newsletters with information about site retention statistics and trial information could be considered.

8.15. CONCLUSION

This project identified effective strategies to retain participants in RCTs as well as strategies that do not work and those that need further evaluation. Small monetary incentives and offers of small monetary incentives do increase response to postal and electronic questionnaires by a modest amount and can be used where loss to follow-up is problematic in RCTs. There was evidence for the effectiveness of some strategies based on single RCTs. These would need further evaluation in different settings to determine their effectiveness with different participant groups. There was no clear evidence that short questionnaires are more effective than long questionnaires or that priority post was better than 2nd class post. Application of these results would depend on the RCT context, budget, and follow-up procedures. The qualitative study has shown that the results of the systematic review are broadly applicable in the context of primary care RCTs. The consensus workshops highlighted that RCT context is important to researchers and that the results of the systematic review may not be generalizable to all settings because of the heterogeneity of the data.

Future research proposals for retention RCTs and reporting of retention RCT results should include clear methods and outcomes to make the synthesis of nested retention RCT results in future methodology systematic reviews of retention strategies less complicated. This would rely on adherence to the CONSORT guidelines to improve the reporting and quality of the results of retention RCTs. This thesis forms an evidence base from which to build future evaluations of strategies to improve retention in RCTs.

8.16. RECOMMENDATIONS

8.16.1. RECOMMENDATIONS TO RESEARCHERS

- Consider using small monetary incentives and offers of monetary incentives to improve response to postal and electronic questionnaires in RCTs.
- Reconsider the use of non-monetary incentives to improve retention in RCTs.
- Consider the use of 2nd class post for outgoing mail relating to RCT follow-up.
- Consider dissemination of these results to ethics committees, steering groups and research funders to increase awareness of the effect of monetary incentives as strategies to improve retention in RCTs.

8.16.2. RECOMMENDATIONS TO RESEARCHERS WHO CONDUCT TRIAL CONDUCT METHODOLOGY RCTs

- Consider including well thought out evaluations of strategies to improve retention in RCTs at the planning / grant application phase of host RCTs.
- Consider publishing protocols for proposed evaluations of strategies to improve retention and registering such studies with appropriate databases e.g. SWAT initiative.
- Consider reporting to CONSORT the need for standards for reporting of methodology RCTs as for clinical RCTs.
- Clearly report the findings of retention RCTs to facilitate clear interpretation and data extraction for future systematic reviews.

8.16.3. RECOMMENDATIONS TO RESEARCHERS CONDUCTING METHODOLOGY SYSTEMATIC REVIEWS

- Be aware of the limitations of database searches for identifying methodology RCTs and include other appropriate means to identify eligible studies e.g. surveying clinical trials units.
- Consider refining search strategies to reduce the number of records to be screened.
- Consider using qualitative research methods to help to explain the results of systematic reviews and to determine any barriers to the implementation of the results.

8.16.3. RECOMMENDATIONS FOR FUTURE METHODOLOGICAL RESEARCH ON RETENTION IN RCTs

- More research is needed on how to encourage participants to return to RCT sites for follow-up.
- More evaluations are needed of electronic methods to improve retention in RCTs.
- Qualitative research to identify the barriers to retention for participants participating in RCTs may help to develop tailored follow-up strategies which could be compared with standard follow-up practice.

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Appendix 1: Systematic review tools

- 1.1. Study screening form.
- 1.2. Data extraction form.
- 1.3. Email letter to authors for study information.
- 1.4. Search terms.
- 1.5. Society for clinical trials advertisement.

Appendix 1.1. Systematic review: Study screening form

| | |
|--|----------------------|
| Study Eligibility Screening Form | |
| Systematic Review: Strategies to reduce attrition from randomised controlled trials | |
| Study ID Number (e.g. MEDLINE 1-1000 no 16 plus the unique study identifier) | |
| Date form completed: | |
| Study title: | |
| Lead author: | |
| Corresponding author contact details: | |
| Journal citation: | |
| 1. Does the study describe strategies to reduce attrition in RCTs? | Yes No Unclear |
| 2. Is the study an RCT? | Yes No Unclear |
| 3. Is this study an RCT embedded within an RCT? | Yes No Unclear |
| 4. Does the study compare one or more strategies to reduce attrition in RCTs. | Yes No Unclear |
| 5. Does the study compare one or more strategies versus no strategy to reduce attrition in RCTs? | Yes No Unclear |
| 6. Is the study complete? <i>(If the study is not complete or this is not clear then contact the study author)</i> | Yes No Unclear |
| Is the study eligible for inclusion (i.e. the answer to questions 1,2,3, 6 and either 4 or 5 is yes)? | Yes No Unclear |
| If the answer to any of the above is unclear, the study may need further discussion with the wider group and contact with the authors. | |
| Notes: | |
| Form completed by: | |

Appendix 1.2. Systematic review: Data extraction form

Cochrane Review: strategies to reduce attrition/improve retention in randomised trials

Study ID: _____
Study source: _____
Publication title: _____
Reference: _____
Lead author: _____
Corresponding author contact details: _____
Reviewer 1: _____ Date: _____
Reviewer 2: _____ Date: _____
Date finalised: _____
Host trial reference _____

Host trial methods

Is the host trial a prevention trial or treatment trial?

Prevention trial Treatment trial Other

Disease/Condition (**host trial**) _____

Participants (**host trial**)
(*e.g. drug users, pregnant women etc.*) _____

Host trial setting

Tick appropriate box

Primary health care *eg. GP practice*

Secondary health care *e.g. Hospital*

Primary education

Secondary education

Tertiary education

Social/community *e.g. youth group, elderly group*

Internet

Other (*List here*)

| |
|--|
| |
| |
| |
| |
| |
| |
| |
| |

Aim (**host trial**) _____

Intervention/s (**host trial**) _____

Arm 1 _____

Arm 2 _____

Arm 3 _____

Control arm (**host trial**) _____

Primary outcome (**host trial**) _____

Other outcomes (**host trial**) _____

Definition of attrition used (**host trial**) _____

Is the host study multi or single centred?

Tick appropriate box

Multicentre Single centre Unclear Other (provide details)

List the country/ countries where the **host trial** was conducted

Randomisation (host trial)

Was the allocation sequence adequately generated?

No=0 Yes=1 Unclear=2

Description of sequence allocation (host trial)

Was allocation adequately concealed?

No=0 Yes=1 Unclear=2

Description of allocation concealment

Date host trial opened / /
Date host trial closed / /

**Participants
randomised (host trial)**
record no for each arm

| Overall | Intervention arm 1 | Intervention arm 2 | Intervention arm 3 | Control arm |
|----------------------|-----------------------|-----------------------|-----------------------|----------------------|
| <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |

Retention trial methods

What is the source of the retention trial sample

Tick one

- All host trial participants
- All host trial participants lost to follow-up
- All host trial participants in the control arm
- All host trial participants lost to follow-up in the control arm
- All host trial participants in the intervention arm
- All host trial participants lost to follow-up in the intervention arm
- Other (*List here*)
- Not clear

Aim (**retention trial**) _____

Definition of attrition used (**retention trial**)

(NB Include time points e.g. participants not returning questionnaires at x time point) _____

Primary outcome (**retention trial**)

(NB Include time points) _____

Other outcomes (**retention trial**)

(NB Include time points) _____

Was a power calculation done? Yes No Unclear
Was its target accrual met? Yes No Unclear

Type of retention measured (retention trial)

Tick appropriate box

| | |
|---|--------------------------|
| Treatment non-compliance | <input type="checkbox"/> |
| Questionnaire non-compliance | <input type="checkbox"/> |
| Visit noncompliance | <input type="checkbox"/> |
| Combination of any of the above <i>(list combination)</i> | <input type="checkbox"/> |
| Other <i>(List here)</i> | <input type="checkbox"/> |

Randomisation (retention trial)

Was the allocation sequence adequately generated?

No=0 Yes=1 Unclear=2

Description of sequence allocation

Was allocation adequately concealed?

No=0 Yes=1 Unclear=2

Description of allocation concealment

Was knowledge of the allocated intervention adequately prevented during the study?

No=0 Yes=1 Unclear=2

Describe measures used

Were incomplete outcome data adequately addressed?

No=0 Yes=1 Unclear=2

Describe completeness of outcome data for each main outcome

Are reports of the study free of selective outcome reporting?

No=0 Yes=1 Unclear=2

Describe how this was examined (e.g. if the authors say they are going to report results for 12 month f/u and they report 6month f/u)

Was the study apparently free of other problems that could put it at a high risk of bias?

No=0 Yes=1 Unclear=2

Describe any other concerns about bias

When did the retention trial start?

Tick one

| | |
|--|--------------------------|
| At the beginning of host trial follow-up | <input type="checkbox"/> |
| At the end of host trial follow-up | <input type="checkbox"/> |
| During host trial follow up <i>(Specify when)</i> | <input type="checkbox"/> |
| When loss to follow-up occurs <i>(Specify when)</i> | <input type="checkbox"/> |
| Other <i>(List here; Specify when)</i> | <input type="checkbox"/> |

Date retention trial opened / / Date retention trial closed / /

Is the retention trial multi or single centred? *Tick appropriate box*

Multicentre Single centre Unclear Other (provide details)

Section B

Intervention (retention trial): Communication

Intervention arm

What type of communication was evaluated? *Tick one*

- Email
- Telephone call
- Letter by post
- Letter by recorded delivery
- Letter by hand
- Postcard by post
- Postcard by hand
- Other (*List here*)

Control Arm

What type of communication was used? *Tick one*

- Email
- Telephone call
- Letter by post
- Letter by recorded delivery
- Letter by hand
- Postcard by post
- Postcard by hand
- Other (*List here*)

Intervention arm

Timing of communication Single/Repeated. If repeated describe schedule

Describe control

Timing of control Single/Repeated. If repeated describe schedule

Record for each group

Intervention group **Control group**

- No of participants contacted
- No of participants not contacted

Section C

Intervention (retention trial): Questionnaire Type

Intervention Arm

What type of questionnaire was evaluated?

- Food frequency questionnaire (*e.g. FFQ*) *Type (List here)*
- Quality of life (*e.g. EuroQol; SF 36*) *Type (List here)*
- Other questionnaire *Type (List here)*

Control Arm

What type of questionnaire was used?

- Food frequency questionnaire (*e.g. FFQ*) *Type (List here)*
- Quality of life (*e.g. EuroQol; SF 36*) *Type (List here)*
- Other questionnaire *Type (List here)*

Intervention arm

Timing of administration Single/Repeated. If repeated describe schedule

Control arm

Timing of administration Single/Repeated. If repeated describe schedule

Record for each group

Intervention group **Control group**

- No of participants given the questionnaire
- No of participants not given the questionnaire

Section D

Intervention (retention trial): Case Management

Intervention Arm

What definition of case management was used? _____

Who delivered the case management intervention?

Type of assistance given

Control Arm

Describe the control _____

Intervention arm

Timing of assistance Single/Repeated. If repeated describe schedule

Control arm

Timing of control Single/Repeated. If repeated describe schedule

Record for each group

Intervention group Control group

No of participants assigned to case management / control

No of participants that did not start case management / control

Section E

Intervention (retention trial): Behavioural

Intervention Arm

Describe the behavioural intervention

Mode of delivery of behavioural intervention _____

Intervention delivered by _____

Control arm

Describe the control

Mode of delivery of control _____

Control delivered by _____

Intervention arm

Timing of behavioural intervention Single/Repeated. If repeated describe schedule

Control arm

Timing of control Single/Repeated. If repeated describe schedule

Record for each group

Intervention group Control group

No of participants assigned to the behavioural intervention / control

No of participants who did not start the behavioural intervention / control

Section F

Intervention (retention trial): Methodological

What type of Methodology was tested?

Intervention Arm

Open trial

Blind trial

Other (*List here*)

Control Arm

Open trial

Blind trial

Other (*List here*)

Record for each group

Intervention group Control group

No of participants assigned to the

Methodological intervention / control

No of participants who did not start the

Methodological intervention / control

Other information**Participants (retention trial)**

If figures are not available for the retention trial then supply host trial figures

Overall % of Male participants

Overall % of Female participants

Age groups:

Range:

Mean:

Median:

Difficulties for participants as a result of strategies to improve retention in randomised trials

Benefits to participants as a result of strategies to improve retention in randomised trials:

e.g. participants might like the contact they had with case managers or may like coming back to meet other members of the group (*esprit de Coeur*)

Main conclusion of the trial publication

Notes

Attach consort diagram

Appendix 1.3. Example of email / letter requesting trial information

Dear.....,

I am a research fellow based at the UK Medical Research Council (MRC) General Practice Research Framework leading a systematic review of strategies to reduce attrition in randomised trials. This review is registered with the Cochrane Methodology Group.

Studies that are eligible for the systematic review are RCTs that include a second randomised evaluation of strategies to reduce attrition. The additional randomisation may compare different strategies to reduce attrition or one strategy with no strategy. We plan to include studies from all disease areas and settings. To date we have identified 23 trials meeting these criteria.

The paper you wrote entitled ***Compliance with Patient-Reported Outcomes in Multicentre Clinical Trials: Methodologic and Practical Approaches***, published in *Journal of Clinical Oncology*, Vol 25. No 32 (2007) 5113-5120 may be eligible for inclusion in our review. It describes interventions undertaken by the National Surgical Adjuvant Breast and Bowel Project (NSABP) to improve compliance with patient reported outcome assessments in multicentre cancer clinical trials. I am in the process of doing data extraction and would be very grateful if you would clarify the following about the trials mentioned in the paper:

Can you confirm if institutions participating in the Raloxifene and Tamoxifen (STAR) and B-32 trials were also randomly assigned to receive automated reminders of upcoming assessments or no upcoming assessments similar to that mentioned for trial B-35.

Are these sub-studies completed?

Can you send a protocol for the sub-studies in each trial?

Can you supply details of a more up to date reference for each sub-study?

I may need to contact you again for further information about this study. Any help that you are able to give now, or in the future, will of course be fully acknowledged in the final review. Also, if you know of any other randomised trials that include a second randomised evaluation of strategies to reduce attrition that you think we could include in our review please let me know.

If any of the above is unclear or you have any queries, please do not hesitate to contact me.

Yours sincerely,

Appendix 1.4. Search terms used

(minimi\$ adj2 attrition).ab,ti.
(prevent\$ adj2 attrition).ab,ti.
(lessen\$ adj2 attrition).ab,ti.
(decreas\$ adj2 attrition).ab,ti.
(reduc\$ adj2 attrition).ab,ti.
(minimi\$ adj2 drop-out).ab,ti.
(prevent\$ adj2 drop-out).ab,ti.
(lessen\$ adj2 drop-out).ab,ti.
(decreas\$ adj2 drop-out).ab,ti.
(reduc\$ adj2 drop-out).ab,ti.
(minimi\$ adj2 drop-out\$).ab,ti.
(prevent\$ adj2 drop-out\$).ab,ti.
(lessen\$ adj2 drop-out\$).ab,ti.
(decreas\$ adj2 drop-out\$).ab,ti.
(reduc\$ adj2 drop-out\$).ab,ti.
(minimi\$ adj2 drop\$-out).ab,ti.
(prevent\$ adj2 drop\$-out).ab,ti.
(lessen\$ adj2 drop\$-out).ab,ti.
(decreas\$ adj2 drop\$-out).ab,ti.
(reduc\$ adj2 drop\$-out).ab,ti.
minimi\$ adj2 dropout\$).ab,ti.
(prevent\$ adj2 dropout\$).ab,ti.
(lessen\$ adj2 dropout\$).ab,ti.
(decreas\$ adj2 dropout\$).ab,ti.
(reduc\$ adj2 dropout\$).ab,ti
(strateg\$ adj2 drop\$-out) .ab,ti.
(strateg\$ adj2 dropout\$).ab,ti.
(loss adj2 follow-up).ab,ti.
(lost adj2 follow-up).ab,ti.
(loss adj2 followup).ab,ti.
(lost adj2 followup).ab,ti.
(minimi\$ adj2 withdrawal).ab,ti.
(prevent\$ adj2 withdrawal).ab,ti.
(lessen\$ adj2 withdrawal).ab,ti.
(decreas\$ adj2 withdrawal).ab,ti.
(reduc\$ adj2 withdrawal).ab,ti.
(minimi\$ adj2 withdrawal\$).ab,ti.
(prevent\$ adj2 withdrawal\$).ab,ti.
(lessen\$ adj2 withdrawal\$).ab,ti.
(decreas\$ adj2 withdrawal\$).ab,ti.
(reduc\$ adj2 withdrawal\$).ab,ti.
(strateg\$ adj2 attrition).ab,ti.
(strateg\$ adj2 drop-out).ab,ti.
(strateg\$ adj2 dropout).ab,ti.
(strateg\$ adj2 follow-up).ab,ti.
(strateg\$ adj2 followup).ab,ti.
(increas\$ adj2 retention).ab,ti.
(encourag\$ adj2 retention).ab,ti.
(maximi\$ adj2 retention).ab,ti.
(promot\$ adj2 retention).ab,ti.
(improv\$ adj2 retention).ab,ti.
(strateg\$ adj2 response\$).ab,ti.

(strateg\$ adj2 (questionnaire\$ adj3 response\$)).ab,ti.
 (increas\$ adj2 (questionnaire\$ adj3 response\$)).ab,ti.
 (encourag\$ adj2 (questionnaire\$ adj3 response\$)).ab,ti.
 (maximi\$ adj2 (questionnaire\$ adj3 response\$)).ab,ti.
 (promot\$ adj2 (questionnaire\$ adj3 response\$)).ab,ti.
 (improv\$ adj2 (questionnaire\$ adj3 response\$)).ab,ti.
 (increas\$ adj2 response\$).ab,ti.
 (encourag\$ adj2 response\$).ab,ti.
 (maximi\$ adj2 response\$).ab,ti.
 (promot\$ adj2 response\$).ab,ti.
 (improv\$ adj2 response\$).ab,ti.
 (retention adj2 strateg\$).ab,ti.
 retention rate\$.ab,ti.
 (retention adj2 method\$).ab,ti.
 (retention adj2 technique\$).ab,ti.
 attrition rate\$.ab,ti.
 (questionnaire\$ adj3 (response\$ adj2 method\$)).ab,ti.
 (questionnaire\$ adj3 (response adj2 technique\$)).ab,ti.
 (questionnaire adj response rate\$).ab,ti. (1145)
 (difficult\$ adj2 (retain\$ or retention)).ab,ti.
 Patient Dropouts/

Syntax adapted as follows for MEDLINE, EMBASE and PsycINFO via OVID:

pt- Publication type.
adj2- words within 2 words of each other.
ab- word in abstract.
sh- sub heading.
ti word in title.
 / - Subject heading MEDLINE.
 \$ - Truncation symbol.
Codes used to de duplicate in OVID were:
 use mesz
 use emez
 use psych

Syntax adapted as follows for Cochrane Central Register of Controlled Trials (CENTRAL) and Database of Abstracts of Reviews of Effects (DARE) via the Cochrane Library:

* Truncation symbol
 NEAR/2 - words within 2 words of each other.
 :kw- keyword
 Codes used to de duplicate in CENTRAL were:
 "accession number " near pubmed
 "accession number " near2 embase

Syntax adapted as follows for CINAHL (Cumulative Index to Nursing and Allied Health) searched via EBSCOHost

MH Major heading (CINAHL via EBSCOHost -)

+ - (e.g. Treatment Outcomes **+**) (CINAHL via EBSCOHost -)

N2 - words within 2 words of each other.

* Truncation symbol.

Syntax adapted as follows for Campbell Collaboration's Social, Psychological, Educational and Criminological Trials Register (C2-SPECTR
<http://geb9101.gse.upenn.edu/>

* - Truncation symbol.

Syntax adapted as follows for Education Resource Information Centre (ERIC) via Dialog datastar.

\$ - Truncation symbol

ab- word in abstract.

ti word in title.

MeSH headings used:

exp Patient Dropouts/: This was used in MEDLINE, only as a subject heading.

In PsycINFO **Experimental attrition** was used

In CINAHL plus **Research subject retention** was used ("research dropouts" - term scope = mechanisms used to keep study participants willing and able to contribute to participate in the study for its duration).

For MEDLINE the Cochrane Sensitivity and precision maximising filter 2008 revision Lefebvre 2008; Ovid format was used.

#1 randomized controlled trial.pt.

#2 controlled clinical trial.pt.

#3 randomized.ab.

#4 placebo.ab.

#5 clinical trials as topic.sh.

#6 randomly.ab.

#7 trial.ti.

#8 1 or 2 or 3 or 4 or 5 or 6 or 7

#9 exp animals/ not humans. sh.

#10 8 not 9

#11 10 AND Attrition terms (Appendix 1)

For EMBASE the sensitivity and specificity maximising search filter for identifying clinically sound treatment studies was used Wong 2006.

- #1 random\$.tw.
- #2 placebo\$.ti,ab,sh.
- #3 double-blind\$.tw.
- #4 1 or 2 or 3
- #5 4 AND Attrition terms (Appendix 1)

For CINAHL sensitivity and specificity maximising filter was used Wong 2006

- #1 PT Clinical trial
- #2 (MH "Treatment Outcomes+")
- #3 randomi?ed
- #4 1 or 2 or 3
- #5 4 AND Attrition terms (Appendix 1)

For PsycINFO the search strategy for identifying high quality studies on treatment Sensitivity and specificity maximising filter version was used. Eady 2008

- #1 double-blind.ab,ti.
- #2 "random\$ assigned.".ab,ti.
- #3 control.ab,ti.
- #4 1 or 2 or 3
- #5 4 AND Attrition terms (Appendix 1)

C2-SPECTR: Campbell Collaboration's Social, Psychological, Educational and Criminological Trials Register C2-SPECTR advanced search Non indexed fields and indexed fields. Terms used: [retention] OR [attrition] OR [dropout] OR [drop-out] OR [withdrawal] OR [response].

ERIC search strategy Petrosino 2000

- #1 RANDOM\$.TI,AB.
- #2 RANDOM\$.TI,AB.
- #3 (ALLOCAT\$ OR ALLOT\$ OR ASSIGN\$ OR BASIS OR DIVID\$ OR ORDER\$).TI,AB.
- #4 (2 NEAR 3).TI,AB.
- #5 RANDOM\$.TI,AB. NOT (4 ADJ or 1).TI,AB.
- #6 ((SINGL\$ OR DOUBL\$ OR TREBL\$ OR TRIPL\$) NEAR (BLIND\$ OR MASK\$)).TI,AB.
- #7 ((COMPAR\$ OR CONTROL\$ OR EXPERIMENT\$ OR INTERVENT\$ OR THERAP\$ OR TREATMENT\$) NEAR (GROUP\$ OR CLASS\$)).TI,AB.
- #8 (ALLOCAT\$ OR ALLOT\$ OR ASSIGN\$ OR DIVID\$ OR ORDER\$).TI,AB.
- #9 (7 NEAR 8).TI,AB.
- #10 crossover.TI,AB.
- #11 (LATIN NEAR SQUARE).TI,AB.
- #12 ((CLINIC\$ OR CONTROL\$) NEAR (TRIAL\$ OR STUDY\$ OR STUDIES\$)).TI,AB.
- #13 PLACEBO\$
- #14 (1 OR 4 OR 5 OR 6 OR 9 OR 10 OR 11 OR 12 OR 13).TI,AB.
- #15 Attrition
- #16 (attrition ADJ research ADJ studies). TI,AB.
- #17 14 AND 16
- #18 17 AND Attrition terms (Appendix 1)

Appendix 1.5 Society for clinical trials advertisement

Poster number P87: Strategies to reduce attrition from randomised trials

Do you know of any RCTs eligible for this systematic review?

We are looking for more RCTs within which are embedded RCTs evaluating strategies to reduce attrition.

- Completed, published or unpublished (but let us know if you have an ongoing trial)
- Randomised or quasi randomised
- Comparing one or more strategies to reduce attrition or comparing one or more strategies with no strategy

Appendix 2: Survey of UK CTUs tools

- 2.1. Letter to clinical trials units.
- 2.2. Reminder letter to non-responding CTUs.
- 2.3. One page questionnaire sent to CTUs.

Appendix 2.1. Letter to clinical trials units requesting unpublished evaluations of strategies to improve retention/reduce attrition

Dear,

Re: Systematic review: Strategies to reduce attrition in randomised trials.

I am a research fellow based at the Medical Research Council (MRC) General Practice Research Framework leading a systematic review of strategies to reduce attrition in randomised trials. The project is funded by the MRC Population Health Sciences Research Network. Attached is a short version of the review protocol for information. This review protocol has been submitted to the Cochrane Methodology Group.

I am writing to ask if you have conducted trials at Leicester Clinical Trials Unit that might be eligible for inclusion in our review. In summary, I am interested in trials either published or unpublished and those that have been run in the past or are currently in progress. Studies that are eligible for the systematic review are randomised trials that include a second randomised evaluation of strategies to reduce attrition (defined as incomplete ascertainment of the primary outcome). The additional randomisation may compare different strategies to reduce attrition or one strategy with no strategy. Also, we plan to include studies from all disease areas and settings. To date, we have identified over 20 trials meeting these criteria.

I would be grateful if you would complete the attached reply sheet to indicate whether you have any potentially eligible trials for the review and return it to me by email or fax to Valerie Brueton at **vcb@gprf.mrc.ac.uk** Fax no: 0207 670 4897 **by Friday the 14th of May 2010**. If you do not have any eligible trials please return the form anyway. Any help that you are able to give now, or in the future, will of course be fully acknowledged in the final review. We can also supply you with a copy of the completed review, if you think you will find it useful.

If any of the above is unclear or you have any queries, please do not hesitate to contact me.

Yours sincerely,

Valerie Brueton,

Appendix 2.2. Reminder letter to non-responding CTUs

Dear ,

Re: Systematic review: Strategies to reduce attrition in randomised trials.

I am following up on my recent email to you inquiring if you have conducted trials at the South East Wales Trials Unit that might be eligible for inclusion in our Cochrane systematic review of strategies to reduce attrition from randomised trials. To date we have surveyed all clinical trials units in the UK and 14 further potentially eligible trials have been returned to us, which will increase the power of the review considerably.

I would be grateful if you would complete the attached reply sheet to indicate whether you have any potentially eligible trials for the review and return it to me by email or fax to Valerie Brueton at vcb@gprf.mrc.ac.uk Fax no: 0207 670 4897 **by Tuesday the 15th of June 2010**. If you do not have any eligible trials please return the form anyway. Any help that you are able to give now, or in the future, will of course be fully acknowledged in the final review. We can also supply you with a copy of the completed review, if you think you will find it useful.

If any of the above is unclear or you have any queries, please do not hesitate to contact me.

Best wishes,
Valerie

Appendix 2.3. One page questionnaire sent to Clinical Trials Units

Contact person:

Name of CTU: _____

Have you ever conducted a randomised trial of strategies to reduce attrition?

(For example this could be a trial comparing incentives with usual follow-up procedures or a trial comparing two different types of follow-up strategy)

Yes If Yes go to question 2

No If No please return this form by fax or email (see details below)

Is this trial a randomised trial embedded within another randomised trial?

(For example this could be a trial comparing incentives with usual follow-up procedures embedded within a randomised trial comparing two treatments for hypertension)

Yes If Yes go to question 3

No If No please return this form by fax or email (see details below)

3. Is this trial completed?

Yes If Yes go to question 4

No If No go to question 5

4. Is there an up to date reference for this trial?

Yes If Yes please supply an up to date reference for the trial.

Enter the up to date reference for your trial here:

No If No go to the question 5

5. Can you supply a trial protocol?

Yes If Yes please supply a copy of the trial protocol.

Enter the name of the trial protocol here:

No If No please return this form by fax or email (see details below)

Thank you for your help completing this form

**Please return the form to Valerie Brueton at vcb@gprf.mrc.ac.uk or by fax to 0207 670 4897
FAO Valerie Brueton.**

**If you would like more information about the project please contact Valerie Brueton on
telephone no 0207670 4923.**

Appendix 3: Qualitative study tools A

- 3.1. Ethics approval letters.
- 3.2. Participant information sheet.
- 3.3. Participant consent form.
- 3.4. Topic guide.

Appendix 3.1. Ethics approval letters



Dr Greta Rait
UCL Department of Primary Care
& Population Health
Upper Third Floor
Royal Free Hospital
Rowland Hill Street
London
NW3 2PF

19 April 2010

Dear Dr Rait

Notification of Ethical Approval:

Ethics Application: 2342/002: Strategies to reduce attrition from randomised trials: An in-depth exploration of trialists experiences using strategies to reduce attrition in randomised clinical trials

I am pleased to confirm that in my capacity as Chair of the UCL Research Ethics Committee I have approved your project for the duration of the study (i.e. until May 2012).

Approval is subject to the following conditions:

1. You must seek Chair's approval for proposed amendments to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the 'Amendment Approval Request Form'.

The form identified above can be accessed by logging on to the ethics website homepage: <http://www.grad.ucl.ac.uk/ethics/> and clicking on the button marked 'Key Responsibilities of the Researcher Following Approval'.

2. It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. Both non-serious and serious adverse events must be reported.

Reporting Non-Serious Adverse Events

For non-serious adverse events you will need to inform Dr Angela Poulter, Ethics Committee Administrator (ethics@ucl.ac.uk), within ten days of an adverse incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair of the Ethics Committee will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

Reporting Serious Adverse Events

The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an

independent expert. The adverse event will be considered at the next Committee meeting and a decision will be made on the need to change the information leaflet and/or study protocol.

On completion of the research you must submit a brief report (a maximum of two sides of A4) of your findings/concluding comments to the Committee, which includes in particular issues relating to the ethical implications of the research.

Yours sincerely

Sir John Birch
Chair of the UCL Research Ethics Committee

Cc. Valerie Brueton, MRC General Practice Research Framework

to card format.

The reasons for this amendment are:

1. With the current list of strategies participants read through the list and point or say "with this one" or "with that one" referring to each strategy on the list.
2. The strategy referred to is not identifiable in the interview transcripts and data analysis becomes difficult because the researcher cannot identify which strategy the participant is referring to.

To resolve this, each strategy will be presented on one of 7 cards. The interviewee is given the cards individually in sequential order and then asked questions as outlined in the original interview schedule. This will greatly assist the data analysis.

3. We wish change the process of recruitment of principal investigators to a one stage process rather than in two stages.

The reasons for this amendment are:

1. Currently, principal investigators are contacted and asked if their study can be included in the sampling frame. They are then contacted again if we want to invite them for interview.
2. We would like to simplify this process by asking principal investigators for an interview at the time of asking permission to include a trial in the sampling frame. This will save time and be less confusing for principal investigators.

5 Please give any other information you feel may be necessary:

The following study documentation will be affected by these changes:

1. Letter of invitation to principal investigators
2. Summary proposal to principal investigators
3. Information sheet for potential participants
4. Reply slip for principal investigators
5. Interview schedule

Updated documents are attached to this amendment.

Signature of Principal Investigator:



Date of Submission:

3.2.11

FOR OFFICE USE ONLY:

Amendments to the proposed protocol have been ... *approved* ... by the Research Ethics Committee.

Chair's Signature:




Date:

7/2/2011

Please return completed form to:

Secretary of the UCL Research Ethics Committee
Graduate School, North Cloisters, Wilkins Building
Gower Street, London WC1E 6BT

Appendix 3.2. Participant information sheet

| | | |
|---|---|---|
| Information Sheet for Trialists in Research Studies <i>(i.e. Principal investigators, Research Managers, Research Nurses)</i> | |  |
| You will be given a copy of this information sheet. | | |
| Title of Project : | Methods to improve follow-up in randomised trials | |
| This study has been approved by the UCL Research Ethics Committee [Project ID Number]: 2342/002 | | |
| Name, Work Address and Contact Details of the Principal Researcher and Applicant | | Principal Researcher and Applicant Professor Irwin Nazareth MRC General Practice Research Framework (GPRF), Stephenson House, 158-160 North Gower Street, London, NW1 2ND. Email: IN@gprf.mrc.ac.uk Telephone: 0207 670 4850 Fax: 0207 670 4890 |
| <p>We would like to invite you to participate in this research project.</p> <p>You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.</p> <p>What is the aim of the study?</p> <p>Many randomised trials report loss to follow-up. The level of loss to follow-up can affect trial results and the application of those results to wider populations. There are many methods for improving loss to follow-up in randomised trials conducted in different disease areas and with different population groups. This study is designed to explore the methods used by trialists to retain participants in randomised trials. We also want to explore barriers to using these methods. By exploring trialists experiences and opinions about methods to improve trial follow-up, this study will help improve our knowledge of methods to reduce loss to follow-up from trials. The results will help us decide the future use of methods to reduce loss to follow-up in trials.</p> <p>Why have you been chosen?</p> <p>You have been chosen because you have either lead or worked on a randomised trial run through the General Practice Research Framework (GPRF) or the Clinical Trials Unit (CTU) during the past 10 years. We are interested to hear your views on ways to reduce loss to follow-up in randomised trials.</p> <p>What will happen to me if I agree to take part? What do I have to do?</p> <p>You will be invited for an in-depth interview at a time and place suitable to you. The interview will take no longer than one hour. Before the interview you will be asked to sign a consent form. The interview will be recorded. We will ask about your experience working on trials with different levels of loss to follow-up. We want to know which methods work best for keeping participants in trials and any preferred methods you may have. We also want to know about barriers to using methods to keep participants in trials. It is not necessary to have used any methods to improve follow-up in order to take part in this study.</p> <p>Are there any risks involved?</p> <p>Taking part in the interview will not involve any risks.</p> <p>Are there any benefits in my taking part?</p> <p>By taking part in this study you will be making a valuable contribution to the knowledge base and future use of methods to reduce loss to follow-up in randomised trials. You will be given a copy of any publication that arises from the data collected.</p> <p>Will my participation be confidential?</p> | | |

Yes. Everything you tell us in the interview will be kept confidential. All papers and notes collected during the interview will be kept in a locked filing cabinet at the MRC GPRF, only the interviewer will have access to this. Audio recordings will be assigned an ID code and then transcribed. Audio recordings will be deleted after the study is finished in May 2012. Interview transcripts will be stored in a password protected computer. Transcripts will not be shown to anyone outside the research management team. You may withdraw your data from the project at any time up until it is transcribed for analysis. A decision to withdraw at any time, or a decision not to take part, will not affect your position in the organisation.

What happens if there is a problem?

If you have any complaints about the way you have been dealt with during the study please contact the study coordinator Valerie Brueton vcb@gprf.mrc.ac.uk, telephone: 0207670 4923 in the first instance. If you are not happy with the response or you do not wish to raise the issue with the study coordinator you can contact the GPRF Unit director on 0207670 4850.

Who is organising and funding the research

This research is part of a cross unit project between the MRC General Practice Research Framework (GPRF) and the Clinical Trials Unit (CTU). The study is funded by the Medical Research Council Population Health Sciences Research Network.

It is up to you to decide whether to take part or not. If you decide to take part you are still free to withdraw at any time and without giving a reason. If you decide to take part you will be given this information sheet to keep and you will be asked to sign a consent form.

All data will be collected and stored in accordance with the Data Protection Act 1998.

Appendix 3.3. Participant consent form

Informed Consent Form for Trialists in Research Studies

(Trialists- Principal investigators, Research Managers, Research Nurses)

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Project: Methods to improve follow-up in randomised trials

**This study has been approved by the UCL Research Ethics Committee
Project ID Number: 2342/002**

Thank you for your interest in taking part in this research. Before you agree to take part the person organising the research must explain the project to you.

If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you to decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

Participant's Statement

I

have read the notes written above and the Information Sheet, and understand what the study involves.

understand that my interview will be audio recorded and I am aware that the recordings will be destroyed at the end of the project.

understand that the information I give may be published as a report and I will be sent a copy of any publication. Confidentiality and anonymity will be maintained and it will not be possible to identify me from any publications.

I am assured that the confidentiality of my personal data will be upheld through the removal of identifiers.

understand that if I decide at any time that I no longer wish to take part in this project, I can notify the researchers involved and withdraw immediately.

understand that all information given by me will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.

I agree to take part in the above study

Signed

Date:

Appendix 3.4. Topic guide: strategies to improve retention in trials

Background / introduction

I am **interested** in attrition from **randomised trials**

We **define attrition** as incomplete ascertainment of the primary outcome, but will subsequently use the term “**loss to follow-up**”

I want to explore trialist’s **opinions** on if and when **loss to follow-up has been a problem** in their experience.

and

the **strategies** they may have used to deal with or prevent loss to follow-up.

I also want to find out more about trialists **preferred** strategies.

Topic guide questions

Can you tell me about recent trials you have worked on?

Were there any with **high follow-up**?

Were there any with **low follow-up**?

What do you think are the **factors that lead to loss to follow-up** in trials?

Why do you think it can be difficult to keep participants in randomised trials?

What are the **factors that lead to retention in randomised trials**?

What **strategies to increase follow-up have been successful** for you in trials you have worked on? Why do you think these have worked?

What strategies have **been unsuccessful**?

Why have these not worked?

Decision making around strategies to reduce attrition

When do you perceive loss to follow-up to be a problem?

How do you decide which strategies to improve follow-up work best?

How did/ do you implement the strategies to improve follow-up that worked best?

How is loss to follow-up monitored in trials you have worked on?

Who deals with loss to follow-up when it presents?

Impact of research governance

What do you feel about using incentives to keep participants in trials?

Have you had any experience with ethics committees?

What do you feel about ethics committees asking about payments or giving other incentives to participants?

Has ethics committees approach to payments affected any trials you have worked on in anyway?

Ask this next question at the end of the interview

These are the strategies to reduce attrition identified by the Cochrane review.

Show participant each card separately. Then ask the following questions for each strategy:

Have you used these?

What do you think about using this strategy?

Might you have considered using this strategy in your trial?

What could be the advantages of using the strategy?

What could be the disadvantages of using this strategy?

Each flash card then shown individually

Card no 1

Communication strategies. e.g. email, telephone, text messages, letters signed by different study personnel, type of delivery- e.g. post 1st 2nd class, or recorded delivery, type of envelope used for response.

Card no 2

Incentives to either participants or trialists e.g. gifts pens, pins, monetary incentives, offers of incentives, vouchers.

Card no 3

Methodological strategies blind versus un blind trials.

Card no 4

Different length of questionnaire: Short versus long.

Card no 5

Using case management. Having trial assistants manage participant follow-up, for example arranging transport and services to enable participants to keep trial follow-up appointments.

Card no 6

Motivational/educational strategies. Such as arranging workshops to give participants information about goal setting and time management.

Appendix 4: Qualitative study tools B:

- 4.1. Letter to PIs seeking permission to include a trial in the sampling frame.
- 4.2. Letter of invitation, reply slip and reminder letter to recruit participants.
- 4.3. Email and reminder email to trial managers network members about the qualitative study.

Qualitative study data analysis:

- 4.4. Qualitative study inductive and deductive codes.

Appendix 4.1. Letter sent to principal investigators seeking permission to include a trial in the qualitative study sampling frame

MRC General Practice Research Framework



Address

Date

Dear ,

Re: Methods to improve follow-up in randomised trials

The Medical Research Council Population Health Sciences Research Network has funded the above study which is a two year cross unit project between the General Practice Research Framework (GPRF) and the Clinical Trials Unit (CTU) looking at strategies to reduce attrition from randomised trials.

As part of the project a qualitative study has been designed to explore problems around loss to follow-up and preferred strategies for dealing with different loss to follow-up situations. An outline protocol is attached. The study has been reviewed by UCL ethics committee.

To facilitate the study members of the management team have identified a number of primary care trials published since 2000. The insert name of trial here trial has been identified as one such trial. As the Principal Investigator we would like to ask permission to include this trial in the sampling frame to be used to identify Principal Investigators, Research Managers and Research Nurses for the qualitative study.

If you were agreeable we may then invite you, the Research Manager and/or the Research Nurse working on the trial to take part in the qualitative study. You do not have to have used strategies to prevent loss to follow-up to participate in this study and we are including trials that have experienced minimal loss to follow-up.

If you require further information please contact me on 0207 670 4923 or vcb@gprf.mrc.ac.uk. I have attached a reply slip for your response.

I look forward to hearing from you.

Yours sincerely,

Valerie Brueton

(On behalf of the Strategies to reduce attrition group)

Members of the group:

Prof Irwin Nazareth, Dr Greta Rait, Dr Jayne Tierney, Dr Sarah Meredith, Sally Stenning, Seeromanie Harding.

Direct line: 0207 670 4923

Email: vcb@gprf.mrc.ac.uk

Stephenson House, 158-160 North Gower St, London NW1 2ND

Tel: +44 (0)20 7670 4850 Fax: +44 (0)20 7670 4890

Website: www.gprf.mrc.ac.uk

Appendix 4.2. Letter of invitation, reply slip, and reminder letter associated with recruiting trialists for the qualitative study

MRC General Practice Research Framework



Address

Date

Dear ,

Re: Methods to improve follow-up in randomised trials.

I am writing to you in relation to a qualitative study we are carrying out to explore methods to improve participant follow-up in randomised trials. We are looking to recruit Principal Investigators, Trial Managers and Research Nurses (trialists) who have worked on or lead randomised trials. This study is part of a cross unit project between the General Practice Research Framework (GPRF) and the Clinical Trials Unit (CTU) looking at strategies to reduce attrition from randomised trials. It is funded by the Medical Research Council Population Health Sciences Research Network and has been reviewed by UCL Ethics committee. The study is also part of a PhD project at UCL department of Primary Care and Population Health.

If you do decide to take part we would like to carry out an in-depth interview at a time and place convenient to you. This will take no more than one hour. The interview will explore if and when loss to follow-up has been a problem in trials you have worked on and any strategies used to deal with or prevent loss to follow-up. We also want to find out about preferred strategies for different loss to follow-up situations and any barriers to using strategies to improve follow-up. You do not have to have used strategies to prevent loss to follow-up to participate in this study. You can also participate if the trials you have worked on have had minimal loss to follow-up.

I have enclosed an information sheet and a reply slip for your response. If you are interested in taking part and would like further information you can contact me on the email address and telephone number provided below.

I look forward to hearing from you.

Yours sincerely,

Valerie Brueton

(On behalf of the Strategies to reduce attrition group)

Members of the group:

Prof Irwin Nazareth, Dr Greta Rait, Dr Jayne Tierney, Dr Sarah Meredith, Sally Stenning, Seeromanie Harding.

Direct line: 0207 670 4923

Email: vcb@gprf.mrc.ac.uk

Stephenson House, 158-160 North Gower St, London NW1 2ND

Tel: +44 (0)20 7670 4850 Fax: +44 (0)20 7670 4890

Website: www.gprf.mrc.ac.uk

Appendix 4.2. Reply slip
MRC General Practice Research Framework



Address

Date

Name of potential Participant:

I would like to participate in the study Methods to improve follow-up in randomised trials.

Please tick the appropriate box

Yes No

If yes, please also complete the following

1st preferred date for interview _____

2nd preferred date for interview _____

Preferred location for interview _____

Please send the completed reply slip to Valerie Brueton at the email address below

vcb@gprf.mrc.ac.uk

Stephenson House, 158-160 North Gower St, London NW1 2ND

Tel: +44 (0)20 7670 4850 Fax: +44 (0)20 7670 4890

Website: www.gprf.mrc.ac.uk

Appendix 4.2. Reminder letter
MRC General Practice Research Framework



Address

Date

Dear,

Re: Methods to improve follow-up in randomised trials

I wrote recently inviting you to participate in the above study. I have re attached the letter of invitation and the information sheet for your information. I would be grateful if you could send your reply before the enter date here

If you need more information please contact me on 0207 6704923 or email vcb@gprf.mrc.ac.uk

I look forward to hearing from you.

Yours sincerely,

Valerie Brueton

Research Fellow

MRC GPRF

Direct line: 0207 670 4923

Email: vcb@gprf.mrc.ac.uk

Inc information sheet and letter of invitation

Stephenson House, 158-160 North Gower St, London NW1 2ND

Tel: +44 (0)20 7670 4850 Fax: +44 (0)20 7670 4890

Website: www.gprf.mrc.ac.uk

Appendix 4.3. Email and reminder email to trial managers network members

Strategies to reduce attrition from randomised trials: Qualitative study

Many randomised trials report loss to follow-up. The level of loss to follow-up can affect trial results and the application of those results to wider populations. Many methods for improving loss to follow-up are used in randomised trials.

We are conducting a qualitative study funded by the MRC PHSRN to explore methods used by trialists to retain participants in randomised trials conducted in primary care settings. The results will help us decide the future use of methods to reduce loss to follow-up in trials.

We are looking to recruit experienced trial managers who have worked on randomised trials conducted in primary care settings. This study has ethics approval.

Participation will involve an interview that will take no longer than 1 hour. All info will be kept confidential.

For further information about participation please contact Valerie Brueton before **Friday the 11th of March 2011** by either email: vcb@gprf.mrc.ac.uk or telephone on 0207670 4923.

Appendix 4.3. Reminder email to trial managers network members

Strategies to reduce attrition from randomised trials: Qualitative study

A big thank you to everyone who requested information about the attrition qualitative study. It's not too late to get involved! If you are interested in participating contact Valerie Brueton (contact details below) before Wednesday the 23rd of March 2011.

Strategies to reduce attrition from randomised trials in primary care: A qualitative study

Many randomised trials report loss to follow-up. The level of loss to follow-up can affect trial results and the application of those results to wider populations. Many methods for improving loss to follow-up are used in randomised trials.

We are conducting a qualitative study funded by the MRC PHSRN to explore methods used by trialists to retain participants in randomised trials conducted in primary care settings. The results will help us decide the future use of methods to reduce loss to follow-up in trials.

We are looking to recruit experienced trial managers who have worked on randomised trials conducted in primary care. This study has ethics approval. Participation will involve an interview that will take no longer than 1 hour. All info will be kept confidential.

For further information about participation please contact Valerie Brueton before Friday the 23th of March 2011 by either email: vcb@gprf.mrc.ac.uk or telephone on 0207670 4923.

Appendix 4.4. Qualitative study inductive and deductive codes

| | |
|-----------------------------------|--|
| <hr/> Incentives | New strategies |
| Expenses | New strategy |
| Gifts | <hr/> Ethics approval |
| Incentive value of | Ethics |
| Incentives | <hr/> Factors retention / loss to follow-up |
| Incentives effectiveness of | Age |
| Prize draw | Altruism |
| Reimbursement of costs | Appointment schedules |
| Transport/travel costs | Benefit to participant |
| Vouchers | Burden |
| <hr/> Communication | By in (by participants) |
| Calendar | Case management |
| Cards | Child care |
| Communication | Participant commitment |
| Contactable | Communication |
| Emails | Disease/condition |
| Face to face | Expenses paid |
| Feedback trial | Staff flexibility |
| Home visit | Gender |
| ID Cards | GP involvement |
| Information to participants | Information to participant |
| Letter | Knowledge nurse |
| Media | Knowledge participant |
| Newsletters | Lay involvement |
| Post | Length appointment |
| Telephone | Length of follow-up |
| Text messaging | Trial management |
| Web based data | Motivation participant |
| <hr/> Questionnaires | Newsletters |
| Diary | Personality of trial staff |
| Questionnaire | Trial population |
| Questionnaire length | Public awareness |
| <hr/> Methodology | Relationship with participant |
| Blinding | Social class |
| Methodology | Staff training |
| <hr/> Case study | Dropout |
| Case study | Site environment |
| <hr/> Behavioural strategy | GP Practice staff |
| Behavioural strategy | Invasive procedure |
| <hr/> Other | Length appointment |
| Spontaneous | Organise work |
| Prompted | Other GP practice commitments |

Appendix 5: Additional forest plots and analysis of cluster RCTs

Appendix 5.1. Fig 1a Exploratory analysis: separating trial arms incentive analysis

Appendix 5.2. Fig 1b Sensitivity analysis: removing quasi randomised trials, incentive analysis

Appendix 5.3. Analysis of cluster randomised trials

Appendix 5.4. Analysis of cluster randomised trials: application to Land (unpublished)

Appendix 5.5. Figure 13a Sensitivity analysis: removing quasi randomised trials, questionnaire strategies

Appendix 5.1. Exploratory analysis: separating RCT arms incentive analysis

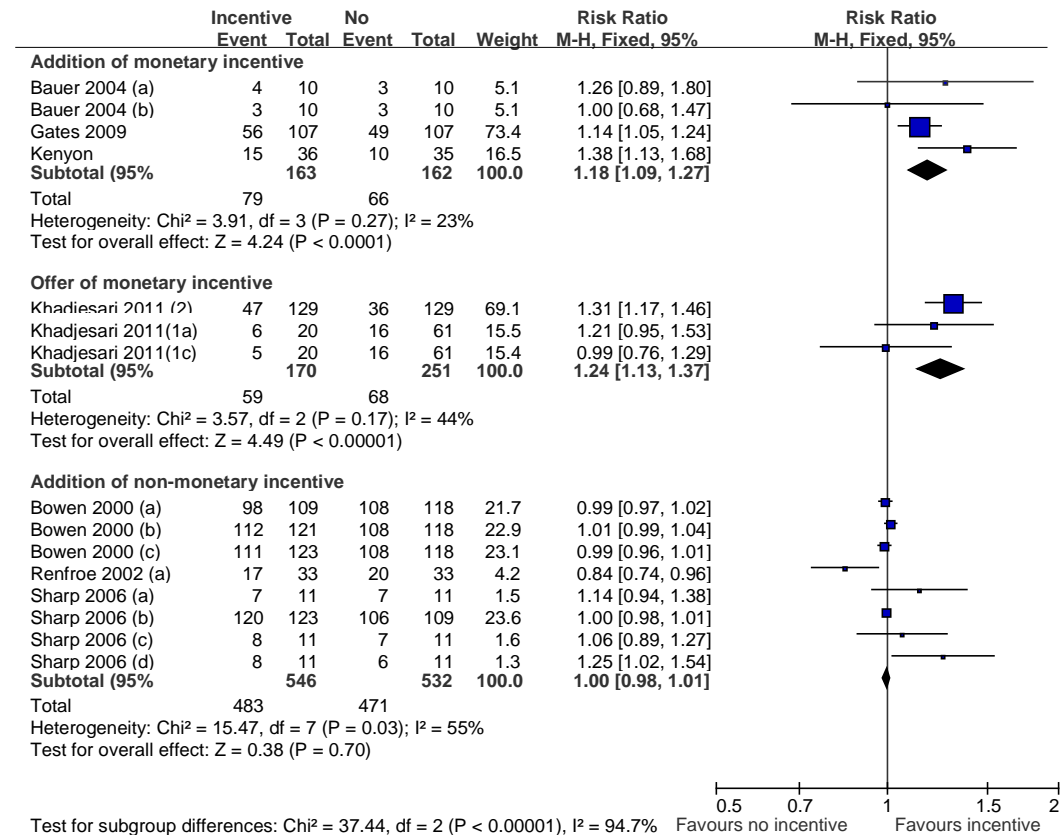
For addition of incentive vs none: Bauer (ab), Khadjesari 1(ac), Bowen (abc).

Figure 1a Addition of incentive versus none: separating trial arms

Review: Strategies to improve retention in randomised trials

Comparison: incentive versus none

Outcomes: trial retention



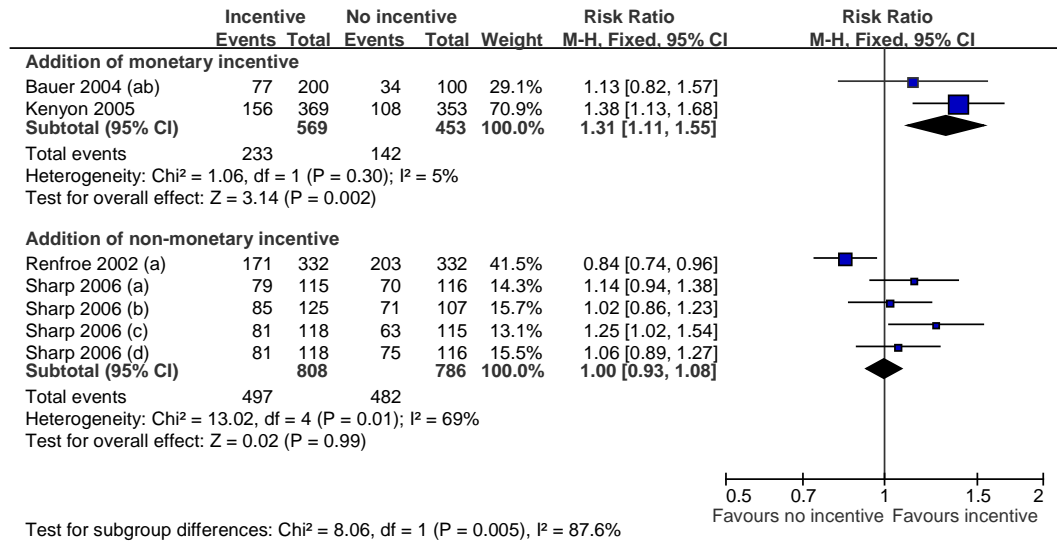
Appendix 5.2. Sensitivity analysis removing quasi randomised trials, incentive analysis

Figure 1b Addition of incentive versus none: removing quasi randomised trials by Gates and Bowen

Review: Strategies to improve retention in randomised trials

Comparison: incentive versus none

Outcomes: trial retention



Appendix 5.3. Analysis of cluster randomised trials

Approximate analysis of cluster randomised trials for a meta-analysis: inflating standard errors Cochrane Handbook page 497 (Higgins et al. 2008).

Application to Land (unpublished)

Methods for inflating the standard error of cluster randomised trials

Calculate the effect estimate based on all participants and inflate the standard errors to account for clustering.

The RR and 95% CI based on participants is calculated in the usual way in RevMan5 (i.e. ignoring clustering).

The 95% CI is used to derive the standard error: $SE = (Inlower\ limit - Inupper) / 3.92$

The SE of the effect estimate ignoring clustering is inflated using the design effect to get an adjusted estimate: $adjusted\ SE = SE \times \sqrt{\text{design effect}}$.

The ICC is uncommon in reports but estimates can be obtained from similar studies.

Design effect = $1 + (M - 1) ICC$

Where:

M = average cluster size

ICC = intraclass correlation coefficient

The technique is unsuitable for small trials as the results have to be rounded.

The effect estimate and the new SE are used in RevMan5.

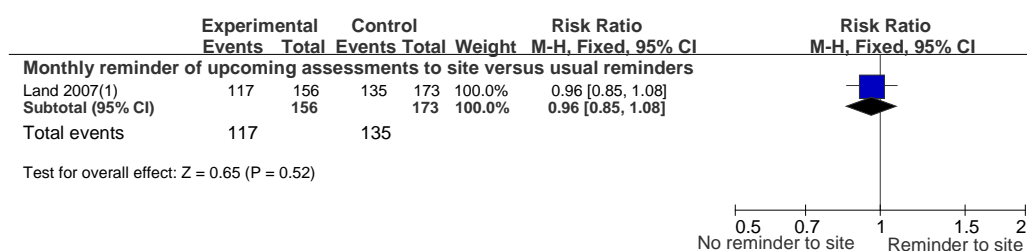
Appendix 5.4. Analysis of cluster randomised trials application to Land (unpublished)

Note:

Land (unpublished): B35 host trial breast cancer treatment. Still running. No ICC s.

Retention trial reminders to units/sites about QOL assessments for participants in the B35 trial. Sites got reminder versus no reminder.

The effect ignoring clustering based on the events and numbers at risk at 36 months (as supplied by the author) is: RR 0.96 (95% CI 0.85- 1.08).



The **InRR for Land is -0.040821994** and is entered into RevMan under the Generic inverse variance.

The Standard error is derived from the 95% CI [0.85, 1.08]

In lower CI limit for the Risk Ratio = -0.162518929

In upper limit for the Risk Ratio = 0.076961041

SE = (Upper limit - lower limit)/3.92

(0.076961041 - (-0.162518929))/3.92 = 0.061091829

SE= 0.061091829

Calculation of adjusted SE:

Prospective reminder sent to sites: 75 institutions with 713 participants

No reminder sent to sites: 77 institutions with 562 participants

The average cluster size is (713 +562) / (75+77) = 8.3 **M=8.3**

In the absence of an ICC Cochrane advise that the ICC is obtained from an external reliable source (Higgins et al. 2008).

The following are recommended:

Ukoumunne 1999 HTA Methods for evaluating area-wide and organisation-based interventions in health care: a systematic review. Chapter 9 provides tables of ICCS.

The next table gives cancer mortality and incidence data.

TABLE 28 Cancer mortality and incidence data

| Variable | Source of data | Setting | Unit type | Cluster type | Cluster size | Number of clusters | Average number of events per cluster | Incidence rate | Variance component – between cluster | Variance component – within cluster | Intraclass correlation coefficient | Design effect |
|---------------------------|----------------|---------------|------------------------|--------------|--------------|--------------------|--------------------------------------|----------------|--------------------------------------|-------------------------------------|------------------------------------|---------------|
| Lung cancer mortality | PHCDS | England, 1995 | Men aged < 75 years | DHA | 216,947 | 105 | 113.1 | 0.000521 | 1.5×10^{-8} | 0.000520 | 0.0000284 | 7.16 |
| Lung cancer mortality | PHCDS | England, 1995 | Women aged < 75 years | DHA | 215,232 | 105 | 59.1 | 0.000274 | 7.0×10^{-9} | 0.000274 | 0.0000271 | 6.83 |
| Lung cancer mortality | PHCDS | England, 1995 | All aged < 75 years | DHA | 432,180 | 105 | 172.2 | 0.000398 | 1.0×10^{-8} | 0.000398 | 0.0000261 | 12.3 |
| Prostate cancer incidence | TCR | England, 1992 | Men aged 65–74 years | DHA | 18,484 | 27 | 48 | 0.00256 | 1.8×10^{-7} | 0.00256 | 0.000072 | 2.33 |
| Colon cancer incidence | TCR | England, 1992 | Men aged 45–64 years | DHA | 52,031 | 27 | 31 | 0.000593 | 1.3×10^{-9} | 0.000592 | 0.0000223 | 2.16 |
| Colon cancer incidence | TCR | England, 1992 | Women aged 45–64 years | DHA | 53,420 | 27 | 26 | 0.00482 | 7.0×10^{-9} | 0.000481 | 0.0000141 | 1.76 |
| Breast cancer incidence | TCR | England, 1992 | Women aged 50–64 years | DHA | 36,983 | 27 | 94 | 0.00252 | 4×10^{-8} | 0.00251 | 0.000016 | 1.59 |

PHCDS, Public Health and Common Data Set; TCR, Thames Cancer Registry

The host trial for Land (unpublished) B35 is set in the USA (Land S 2007). ICCs listed in Table 28 (screen shot above) are based on UK cancer registries. We considered the ICC listed 0.000016 and the design effect 1.59 inappropriate for this analysis because: a) it is for registry data, and b) it is for the outcome of host trial, rather than a quality of life trial, we were looking for an ICC for the outcome for the retention trial i.e. for return of QOL life questionnaires in breast cancer patients.

An alternative list of external ICCs recommended is hosted by Aberdeen University available at URL <http://www.abdn.ac.uk/huru/uploads/files/iccs-web.xls>. See the table below for examples of QOL ICCs.

As the unpublished trial by Land is embedded in a cancer trial the ICCs for EuroQol is the most appropriate to use. The mean of the two ICCs cited is 0.054.

| | | | | | |
|--------|----------|---------|-------------|--------------|------------|
| COGENT | Practice | EuroQol | Outcome | 0.060 | Continuous |
| COGENT | Practice | EuroQol | Outcome | 0.048 | Continuous |
| | | | Total | 0.108 | |
| | | | Mean | 0.054 | |

ICC = .054

Design effect = $1 + (M - 1) ICC$ = $1 + (8.3 - 1) \times .054$ Design effect = 1.3942

Using the design effect calculated above for Land = **1.3942**

An **inflated SE** is given by $0.061091829 \times \sqrt{1.3942}$ = 0.072134938

This inflated standard error can be entered into RevMan5

LAND Inflated SE = 0.072134938 InRR for Land = -0.040821994

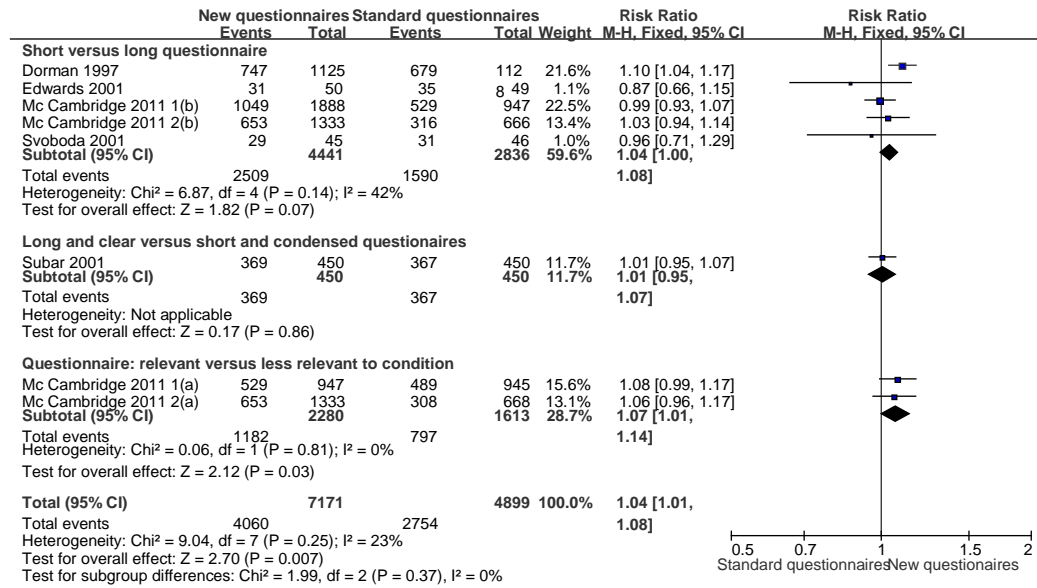
Appendix 5.5. Sensitivity analysis: removing quasi randomised trials, questionnaire strategies

Figure 13a Questionnaire strategies: new versus standard questionnaire sensitivity analysis removing quasi randomised trials

Review: Strategies to improve retention in randomised trials

Comparison: new versus standard questionnaires

Outcomes: trial retention



Appendix 6: Results of searches

- 6.1. The characteristics of each host trial and associated retention trial
- 6.2. PRISMA diagram

Appendix: 6.1. Characteristics of the host RCT and associated retention RCT

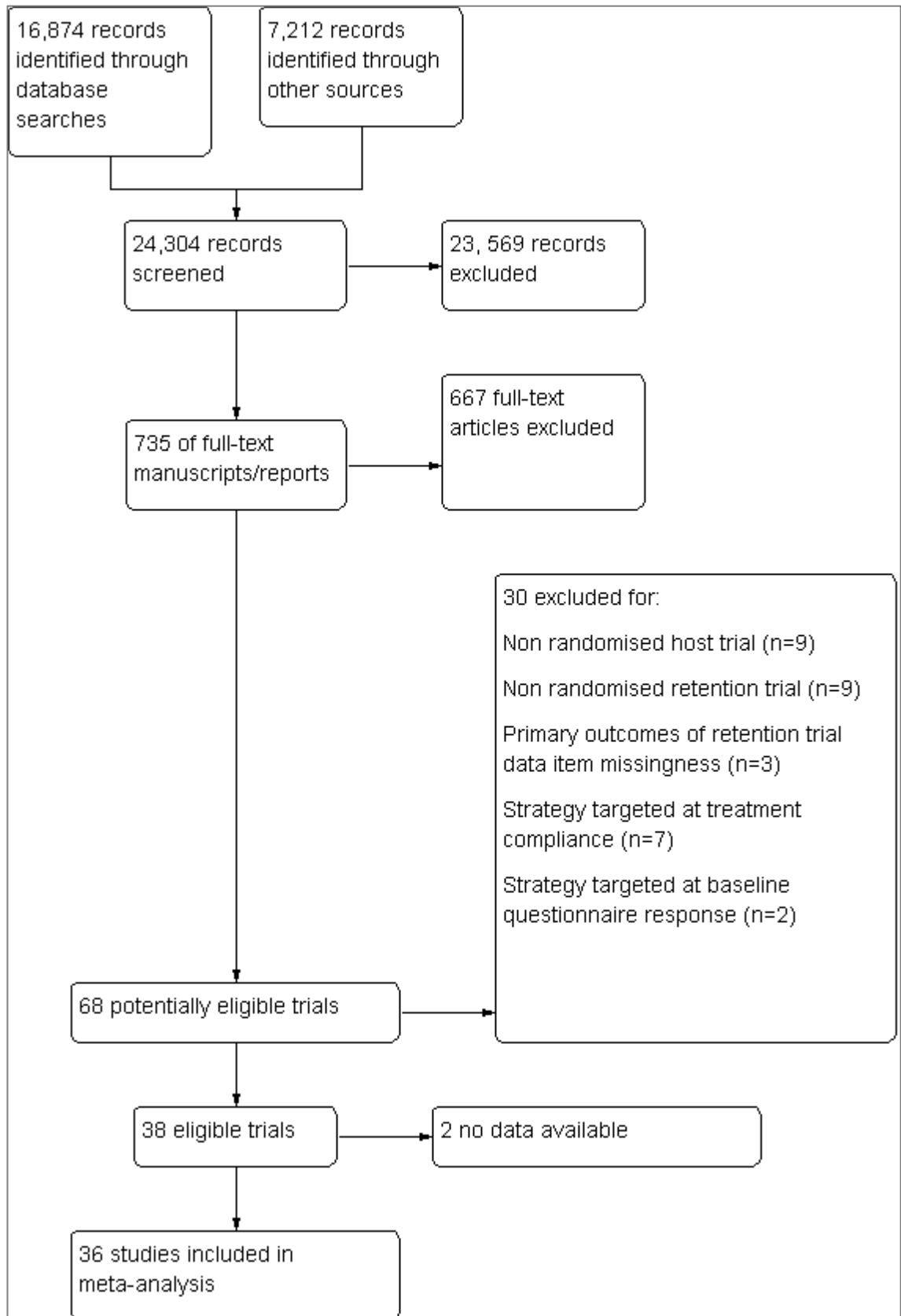
| Clinical area host RCT | Condition | Participants | Setting | Retention RCT |
|------------------------|-----------|---|---------------------------------------|---------------------|
| Dependence | | | | |
| | Alcohol | Adults scoring +5 on Audit C, mean age 37yrs in an online trial comparing interactive computer intervention plus web information vs web information for modifying alcohol intake (Murray 2007) | Community: on line | Khadjesari 2011 (1) |
| | Alcohol | Adults scoring +5 on Audit C mean age 37yrs in an online trial comparing interactive computer intervention plus web information vs web information for modifying alcohol intake (Murray 2007) | Community: on line | Khadjesari 2011 (2) |
| | Smoking | Adult smokers 38-77yrs in a smoking cessation trial of public education through media and community wide events, health care providers work sites and other organisations vs no intervention (Mitchell 1992) | USA community | Bauer 2004 |
| | Smoking | Adult smokers mean age 36.7yrs in a trial of Nicotine gum vs placebo gum. Smokers for > one year (Hughes 1984) | USA community | Hughes 1989 |
| | Smoking | Adult smokers willing to quit >16yrs in a trial comparing Txt2stop motivational messages and behaviour change support vs text messages unrelated to quitting (Free 2011) | UK community | Severi 2011(1) |
| | Smoking | Adult smokers willing to quit >16yrs in a trial comparing Txt2stop motivational messages and behaviour change support vs text messages unrelated to quitting (Free 2011) | UK community | Severi 2011(2) |
| Injury | | | | |
| | Neck | MINT trial: Adults with whiplash injury 18-87yrs in a 2x2 cluster randomised trial comparing whiplash book vs usual advice. Individuals randomised to physiotherapy vs single advice session reinforcing advice given (Lamb 2007) | UK hospital trusts | Gates 2009 |
| | Ankle | Cast trial: Adults 16-57yrs with acute severe ankle sprain in a trial comparing tubular bandage vs below knee cast vs Aircast® ankle brace vs Bledsoe® boot (Cooke 2009) | UK Accident and emergency departments | Nakash 2007* |

| Clinical area host RCT | Condition | Participants | Setting | Retention RCT |
|--------------------------|---|--|--|---|
| | Head | Adults with head injury >16yrs in trial of 48 hour infusion of methylprednisolone vs placebo (CRASH Trial Collaborators 2004) | UK hospital intensive care units | Edwards 2001 |
| | Head | Adults with head injury >16yrs CRASH Trial: 48 hour infusion of methylprednisolone vs placebo (CRASH Trial Collaborators 2004) | Czech republic hospital intensive care units | Svoboda 2001 |
| Disease treatment | | | | |
| | Cancers: Breast | Women with ductal carcinoma in situ >49yrs in a trial comparing Anastrozole vs tamoxifen (unpublished) | Hospital sites USA, Canada, Puerto Rico | Land 2007 |
| | Cardiovascular disease: Stroke | Acute stroke patients 50-80yrs in an international stroke trial of heparin 125,000 IU bd + aspirin 300mg daily vs heparin 125,000 IU bd vs heparin 5000 IU bd + aspirin 300 mg daily, heparin 5000 IU bd vs aspirin 300mg daily vs no heparin or aspirin (International Stroke Trial Collaborative Group 1997) | UK hospital | Dorman 1997 |
| | Ventricular fibrillation Ventricular tachycardia | Adults cardioverted from VT or resuscitated from VF 54-76yrs participating in the AVID Trial comparing an implanted cardioverter defibrillator vs antiarrhythmic drugs (The Antiarrhythmics Versus Implantable Defibrillators (AVID) Investigators 1997) | USA hospital | Renfro 2002 |
| | Other diseases: Epilepsy | Adults with epilepsy mean 38.3yrs in the SANAD trial. ARM A: Carbamazepine vs gabapentin vs lamotrigine vs oxcarbazepine vs topiramate. ARM B: valproate vs LTG vs TPM (Marson 2007) | UK hospital outpatient departments | Marson 2007 |
| | Back pain | Adults with low back pain 18-65 yrs in a trial comparing exercise manipulation vs exercise plus manipulation (UK BEAM trial team 2004) | UK primary care | Letley 2000 |
| Screening | | | | |
| | Cancer: Prostate, Lung, Ovarian, Colorectal | Adults 55- 74 yrs in PLCO trial comparing PSA and CA125 at baseline, and annually for 5 years. Digital rectal examination, transvaginal ultrasound and c x-ray at baseline and 5 years vs usual follow-up (Prorok 2000) | USA sites | Subar 2001, Ford 2006 (African American Men >55+yrs only from PLCO) |
| | Cervical | Women with low grade abnormal cervical smear 20-59yrs in the TOMBOLA Trial: Colposcopy vs six | UK | Sharp 2006 |

| Clinical area host RCT | Condition | Participants | Setting | Retention RCT |
|----------------------------|--|---|--------------------|-----------------|
| | | monthly smears (TOMBOLA Group 2009) | | |
| | Other: Post natal depression | Women childbearing age >18 < 2 weeks post-partum at high risk of postnatal depression in a trial comparing proactive individualised telephone based peer support vs standard postpartum care (Dennis 2009) | Canada community | Kenton 2007 |
| Prevention | | | | |
| | Fracture | Adults with history of osteoporotic fracture >70yrs in the RECORD trial:oral calcium + vitamin D vs oral calcium vs vitamin D vs placebo (RECORD Trial Group 2005) | UK hospital | MacLennan |
| | Fracture | Adults with history of osteoporotic fracture >70yrs in the RECORD trial:oral calcium + vitamin D vs oral calcium vs vitamin D vs placebo (RECORD Trial Group 2005) | UK hospital | Avenell 2004 |
| | Fracture | Women with hip fracture risk factors >70yrs in a fracture prevention trial of 1000mg calcium plus 800 IU vit D3 plus information sheet on dietary calcium intake and falls prevention vs information sheet (Porthouse 2005) | UK primary care | Cockayne 2005 |
| | Migraine | Adults history of 2 migraine attacks 18-65yrs pts with migraine randomised to true diet vs sham diet (unpublished) | UK community | Ashby 2011 |
| | Cancer: Lung | Adults exposed to smoking and asbestos >45yrs in the CARET Trial 2x2: beta-carotene + retinol daily vs beta-carotene vs retinol vs placebo (Omenn 1996) | USA sites | Bowen 2000 |
| | Breast | Women with 50% of breast volume dysplasia >30yrs in Canadian diet and cancer prevention trial. Counselling and individualised dietary prescription vs taught principals of a healthy diet not counselled to change fat content (Boyd 1992) | Canada Hosp clinic | Sutherland 1996 |
| Clinical management | | | | |
| | Asthma | Adult with asthma >70yrs in COGENT Trial: computerised decision support guidelines for asthma vs angina care (Eccles 2002) | UK primary care | McColl 2003 |
| | Asthma and diabetes | Adults with asthma mean age 47yrs. Study template for diabetes vs study template for asthma (Tai 1999) | UK primary care | Tai 1997 |
| | Angina | Adult with asthma >70yrs in the COGENT Trial: | UK primary care | McColl 2003 |

| Clinical area host RCT | Condition | Participants | Setting | Retention RCT |
|------------------------|--|--|-----------------------------|------------------------|
| | | computerised decision support guidelines for asthma vs angina care (Eccles 2002) | | |
| | Orthopaedics | Adults with non-surgical musculoskeletal condition 18yrs+ in OMENS Trial: orthopaedic patients management from single musculo-skeletal medicine physician vs orthopaedic surgeon-led management (Leigh-Brown 2001) | UK Hosp OPD | Leigh-Brown 1997 |
| Other areas | | | | |
| | Exercise | Women sedentary 50-70yrs SWEAT 2 Trial: Moderate walking program vs swimming program (Cox 2008) | Australia Community | Cox 2008 |
| | Parenting | Adults referred for parenting mean age 29yrs Parent child interactive therapy vs standard didactic parenting condition (Chaffin 2009) | USA community | Chaffin 2009 |
| | Weight management | Adults with BMI ? 25 >18yrs Web based tailored weight management materials vs web based non tailored user navigated weight management materials (Rothert 2006) | USA community | Couper 2007 |
| | Effect of antibiotics on neonatal outcomes | Women < 37 weeks gestation in ORACLE 1 + 2 Trial: 2x2 factorial: co-amoxiclav + erythromycin vs co-amoxiclav vs erythromycin vs placebo qds x 10 days or until birth (Kenyon 2001) | UK secondary care/community | Kenyon 2005 |
| | Health promotion | Young people 16-20 years in the sex unzipped pilot feasibility trial: interactive intervention web site vs information only web site (Host trial unpublished) | UK on line | Bailey (1) unpublished |
| | Health promotion | Young people 16-20 years in the sex unzipped pilot feasibility trial: interactive intervention web site vs information only web site (Host trial unpublished) | UK on line | Bailey (2) unpublished |

Appendix 6.2. PRISMA diagram



Appendix 7: Publications, presentations, and posters from this thesis

7.1. Publications.

7.2. Presentations and podcast.

BMJ Open Use of strategies to improve retention in primary care randomised trials: a qualitative study with in-depth interviews

V C Brueton,¹ F Stevenson,² C L Vale,¹ S P Stenning,¹ J F Tierney,¹ S Harding,³ I Nazareth,² S Meredith,¹ G Rait²

To cite: Brueton VC, Stevenson F, Vale CL, *et al.* Use of strategies to improve retention in primary care randomised trials: a qualitative study with in-depth interviews. *BMJ Open* 2014;4:e003835. doi:10.1136/bmjopen-2013-003835

► Prepublication history and additional material for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2013-003835>).

Received 16 August 2013
Revised 29 November 2013
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CrossMark

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³MRC Social & Public Health Sciences Unit, University of Glasgow, Glasgow, UK

Correspondence to
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v.brueton@ucl.ac.uk

ABSTRACT

Objective: To explore the strategies used to improve retention in primary care randomised trials.

Design: Qualitative in-depth interviews and thematic analysis.

Participants: 29 UK primary care chief and principal investigators, trial managers and research nurses.

Methods: In-depth face-to-face interviews.

Results: Primary care researchers use incentive and communication strategies to improve retention in trials, but were unsure of their effect. Small monetary incentives were used to increase response to postal questionnaires. Non-monetary incentives were used although there was scepticism about the impact of these on retention. Nurses routinely used telephone communication to encourage participants to return for trial follow-up. Trial managers used first class post, shorter questionnaires and improved questionnaire designs with the aim of improving questionnaire response. Interviewees thought an open trial design could lead to biased results and were negative about using behavioural strategies to improve retention. There was consensus among the interviewees that effective communication and rapport with participants, participant altruism, respect for participant's time, flexibility of trial personnel and appointment schedules and trial information improve retention. Interviewees noted particular challenges with retention in mental health trials and those involving teenagers.

Conclusions: The findings of this qualitative study have allowed us to reflect on research practice around retention and highlight a gap between such practice and current evidence. Interviewees describe acting from experience without evidence from the literature, which supports the use of small monetary incentives to improve the questionnaire response. No such evidence exists for non-monetary incentives or first class post, use of which may need reconsideration. An exploration of barriers and facilitators to retention in other research contexts may be justified.

INTRODUCTION

Retention in primary care randomised controlled trials conducted across different disease

Strengths and limitations of this study

- This study is the first to explore the use of retention strategies in UK primary care trials and the factors associated with retention and loss to follow-up.
- Interviews were conducted with researchers experienced in UK primary care trials, many of whom had used strategies to improve retention.
- The thoughts and experiences of trial participants have not been gathered to further explore the barriers and facilitators to retention in primary care trials.

areas and communities can be challenging. Inadequate retention can reduce the power of a trial and introduce bias, particularly if drop-out differs across trial arms. Reasons for loss to follow-up can include a change in the participants' location, withdrawal from treatment and/or loss of commitment to the trial, for example, due to complicated treatment regimens.¹ A Cochrane review of strategies to improve retention in trials demonstrated that adding a monetary incentive and offering higher valued monetary incentives increased postal and electronic questionnaire response.² Questionnaire response was also increased by recorded delivery of questionnaires, a 'package' of postal communication strategies known as the total design method (TDM)³ and an open trial design,⁴ although these were based on the results of single trials. The evidence of an effect for shorter questionnaires and questionnaires relevant to the disease/condition was less clear. Also, there was no good evidence that the following strategies improved retention: adding or offering a non-monetary incentive, communication strategies (including use of first class mail), behavioural motivational strategies, new questionnaire formats and case management.

Only 6 of the 38 retention trials included in the Cochrane review were embedded in

BMJ Open Strategies to improve retention in randomised trials: a Cochrane systematic review and meta-analysis

V C Brueton,¹ J F Tierney,¹ S Stenning,¹ S Meredith,¹ S Harding,² I Nazareth,³ G Rait³

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ABSTRACT

Objective: To quantify the effect of strategies to improve retention in randomised trials.

Design: Systematic review and meta-analysis.

Data sources: Sources searched: MEDLINE, EMBASE, PsycINFO, DARE, CENTRAL, CINAHL, C2-SPECTR, ERIC, PreMEDLINE, Cochrane Methodology Register, Current Controlled Trials metaRegister, WHO trials platform, Society for Clinical Trials (SCT) conference proceedings and a survey of all UK clinical trial research units.

Review methods: Included trials were randomised evaluations of strategies to improve retention embedded within host randomised trials. The primary outcome was retention of trial participants. Data from trials were pooled using the fixed-effect model. Subgroup analyses were used to explore the heterogeneity and to determine whether there were any differences in effect by the type of strategy.

Results: 38 retention trials were identified. Six broad types of strategies were evaluated. Strategies that increased postal questionnaire responses were: adding, that is, giving a monetary incentive (RR 1.18; 95% CI 1.09 to 1.28) and higher valued incentives (RR 1.12; 95% CI 1.04 to 1.22). Offering a monetary incentive, that is, an incentive given on receipt of a completed questionnaire, also increased electronic questionnaire response (RR 1.25; 95% CI 1.14 to 1.38). The evidence for shorter questionnaires (RR 1.04; 95% CI 1.00 to 1.08) and questionnaires relevant to the disease/condition (RR 1.07; 95% CI 1.01 to 1.14) is less clear. On the basis of the results of single trials, the following strategies appeared effective at increasing questionnaire response: recorded delivery of questionnaires (RR 2.08; 95% CI 1.11 to 3.87); a 'package' of postal communication strategies (RR 1.43; 95% CI 1.22 to 1.67) and an open trial design (RR 1.37; 95% CI 1.16 to 1.63). There is no good evidence that the following strategies impact on trial response/retention: adding a non-monetary incentive (RR=1.00; 95% CI 0.98 to 1.02); offering a non-monetary incentive (RR=0.99; 95% CI 0.95 to 1.03); 'enhanced' letters (RR=1.01; 95% CI 0.97 to 1.05); monetary incentives compared with offering prize draw entry (RR=1.04; 95% CI 0.91 to 1.19); priority postal delivery (RR=1.02; 95% CI 0.95 to 1.09); behavioural motivational strategies (RR=1.08; 95% CI 0.93 to 1.24); additional reminders to participants (RR=1.03;

Strengths and limitations of this study

- This is the most comprehensive review of strategies specifically designed to improve retention in randomised trials, including many unpublished trials and data.
- Although our searches were extensive, some less well reported, ongoing, or unpublished trials, or trials conducted outside the UK might have been missed.
- Most of the evidence relates to increasing questionnaire response rather than ways to increase return of participants to sites.

95% CI 0.99 to 1.06) and questionnaire question order (RR=1.00, 0.97 to 1.02). Also based on single trials, these strategies do not appear effective: a telephone survey compared with a monetary incentive plus questionnaire (RR=1.08; 95% CI 0.94 to 1.24); offering a charity donation (RR=1.02, 95% CI 0.78 to 1.32); sending sites reminders (RR=0.96; 95% CI 0.83 to 1.11); sending questionnaires early (RR=1.10; 95% CI 0.96 to 1.26); longer and clearer questionnaires (RR=1.01, 0.95 to 1.07) and participant case management by trial assistants (RR=1.00; 95% CI 0.97 to 1.04).

Conclusions: Most of the trials evaluated questionnaire response rather than ways to improve participants return to site for follow-up. Monetary incentives and offers of monetary incentives increase postal and electronic questionnaire response. Some strategies need further evaluation. Application of these results would depend on trial context and follow-up procedures.

INTRODUCTION

Loss of participants during trial follow-up can introduce bias and reduce power affecting the generalisability, validity and reliability of results.^{1 2} If losses are fewer than 5% they may lead to minimum bias, while 20% loss can threaten trial validity.² Missing data from losses to follow-up can be dealt with statistically; however, the risk of bias can remain.³

POSTER PRESENTATION

Open Access

Complexities of retention in primary care randomised trials: A thematic analysis of in-depth interviews

Valerie Brueton^{1*}, Fiona Stevenson², Claire Vale³, Greta Rait^{1,2}

From Clinical Trials Methodology Conference 2011
 Bristol, UK. 4-5 October 2011

Introduction

Loss to follow-up in randomised trials can cause bias, compromise study power, and affect the generalisability and reliability of results [1]. Many strategies are used to try to retain participants, however little is known about trialists' experiences of implementing such strategies, or their perspectives of effectiveness. The complexity of these experiences and perceptions may influence the type of strategies used in different disease areas and with different population groups. We explored factors that trialists think contribute to loss to follow-up in primary care randomised trials, and whether some strategies to improve retention are perceived to be more successful than others.

Methods

29 purposively sampled UK trialists including principal investigators n=10, research nurses n=9, and trial managers n=10 were invited for an in depth interview. Trialists were sampled from randomised trials conducted in UK primary care settings and published between 2000-2010. Randomised trials with high (>20%), moderate (5-20%) and low (<5%) rates of attrition were included in the sampling frame [2]. In-depth interviews were digitally recorded, transcribed verbatim, and anonymised. Concurrent thematic analysis was conducted. ATLAS ti 6.1 was used to organise and explore coded transcripts. Themes around each category were verified and confirmed by constant comparison and searching across all interviews for similar themes and categories for analysis.

Results

29 in-depth interviews were conducted with 10 principal investigators, 10 trial managers, and 9 research nurses from primary care randomised trials in mental health, nutrition, elderly care, and chronic diseases. A major theme emerging across all interviews is the importance of communication between participant and trialist. Factors thought to contribute to retention include: rapport between participant and trialist, participant altruism, and flexibility around appointment schedules. Giving information about what the trial involves at the initial recruitment visit was considered to influence retention. Reducing burdens, both financial and physical, by provision of transport and reimbursement of costs were also considered useful.

Conclusions

The findings provide a deeper understanding of the complexity of retention in randomised trials and may inform trialists' choice of potentially effective strategies in future trials. In combination with an ongoing systematic review of randomised trials of retention strategies, we will highlight strategies or combinations of strategies that should be evaluated prospectively.

Author details

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Published: 13 December 2011

References

1. Fevitrell MS, Kennedy K, Singhal A, Martin RM, Ness A, Hadders-Algra M, *et al*: How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? *Arch Dis Child* 2008, **93**:458-461.

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ORAL PRESENTATION

Open Access

Strategies to reduce attrition in randomised trials

Valerie Brueton^{1*}, Jayne Tierney³, Sally Stenning³, Irwin Nazareth^{1,2}, Sarah Meredith³, Seeromanie Harding⁴, Greta Rait^{1,2}

From Clinical Trials Methodology Conference 2011
 Bristol, UK. 4-5 October 2011

Background

Attrition from randomised trials can introduce bias and reduce study power affecting the generalisability, validity, and reliability of results [1]. Many strategies are used by trialists to reduce attrition, including motivating and engaging participants and sites to optimise data return or compliance to follow-up procedures [2].

Objective

To quantify the effect of strategies to reduce attrition from randomised trials in any healthcare setting.

Methods

Included studies were randomised evaluations of strategies to reduce attrition embedded within randomised trials from all disease areas and settings. The following sources were searched for eligible studies [3]: MEDLINE (1950 to present), EMBASE (1980 to present), PsycINFO (1806 to present), DARE (most recent issue), CENTRAL (most recent issue), CINAHL (1981 to present), C2-SPECTR (most recent date), and ERIC (1966- present), Cochrane Methodology Register, Current Controlled Trials *metaR*-register, WHO trials platform, Society for Clinical Trials (SCT) conference proceedings (1980-2010), and publication reference lists. A survey of all UK clinical trials units (CTU) was also conducted to identify studies.

Two authors reviewed potentially eligible titles and abstracts. Data extracted were checked by two authors. Study investigators were contacted for missing data. Risk of bias was assessed using the Cochrane risk of bias tool. Data were entered into RevMan5 and pooled using the fixed effect model. Heterogeneity was explored to determine whether some types of strategies to reduce attrition were more effective than others. The analyses focused on the primary endpoint of attrition.

Results

From 19,281 abstracts 31 unique RCTs were identified from the following sources: MEDLINE, CENTRAL, CINAHL n=9; SCT abstracts 1980-2010 n=4; reference lists of relevant reviews n=7; and of included trials n=8 (7 duplicates); word of mouth n=4; and CTUs survey n=6. Six types of strategies to reduce attrition were identified: a) communication i.e. email, letters signed by different study personnel, type of post, and delivery method; b) questionnaire length i.e. short versus long; c) incentives i.e. monetary incentives, offers of monetary incentives or vouchers, and gifts; d) case management i.e. trial assistants assigned to manage participant follow-up; e) behavioural e.g. workshops giving participants information about goal setting; and f) methodological interventions e.g. blinded versus open trials. Final results of the review will be presented.

Author details

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Published: 13 December 2011

References

1. Fewtrell MS, Kennedy K, Singhal A, Martin RM, Ness A, Hadders-Algra M, et al: How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? *Arch Dis Child* 2008, **93**:458-461.
2. Valerie Brueton C, Greta Rait, Jayne Tierney, Sally Stenning, Sarah Meredith, Janet Darbyshire, et al: Strategies to reduce attrition in randomised trials: A systematic review. *Clinical Trials* 2010, **7**:418-504.
3. Brueton VC, Rait G, Tierney J, Meredith S, Darbyshire J, Harding S, et al: Strategies to reduce attrition in randomised trials. *Cochrane Database of Systematic Reviews Art* 2011, No :MR000032 DOI: 10.1002/14651858.MR000032.

doi:10.1186/1745-6215-12-S1-A128

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Appendix 7.4. Presentations and podcasts

Oral Presentations

V Brueton, Strategies to reduce attrition from RCTs. PRIMENT Clinical Trials Unit. 3.11.2010.

V Brueton, Strategies to reduce attrition from RCTs. Primary Care Research Network meeting. 23.11. 2010. Regency Hyatt, Birmingham.

V Brueton, Retention in Primary Care RCTs: A qualitative study. Primary Care Research Network National team meeting 15.11.2011. Renaissance Hotel, Manchester.

V Brueton, Strategies to reduce attrition in RCTs MRC. HTMR Clinical Trials Methodology Conference, 4.10.2011. Bristol.

V Brueton, Complexities of retention in primary care RCTs: A thematic analysis of in-depth interviews. Research methods parallel session 40th Annual Scientific Meeting of SAPC. 7.7.2011. University of Bristol.

V Brueton, Complexities of retention in RCTs: A Cochrane systematic review and associated qualitative study. Methodology Seminar. 13.10.2011. MRC CTU, Aviation House, London.

V Brueton, Systematic review of retention interventions MRC HTMR RCT recruitment and retention workshop, 16.01.2013. University of Manchester.

V Brueton, Systematic review of retention interventions update. Trial Managers Network Annual Meeting. 7.10.2013. London.

V Brueton, Systematic review of strategies to increase retention in RCTs 34th annual SCT conference. 20.05.2013. Boston, Massachusetts, USA.

V Brueton, Systematic review of strategies to improve retention in RCTs. 6.05. 2014. Comprehensive Clinical Trials Unit. UCL, London.

Poster Presentations

V Brueton, G Rait, J Tierney, S Stenning, S Meredith, J Darbyshire, S Harding, I Nazareth. Strategies to reduce attrition from RCTs: A systematic review. Society for Clinical Trials 31st International conference. Baltimore. USA. May – 16th -19th 2010.

V Brueton, J Tierney, S Stenning, I Nazareth, S Meredith, S Harding, G Rait. Strategies to reduce attrition in RCTs: a methodology review. 19th Cochrane Colloquium. 19-22 October 2011. Madrid, Spain.

V Brueton, Fiona Stevenson, Claire Vale, Greta Rait. Complexities of retention in primary care randomised trials: A thematic analysis of in-depth interviews. MRC HTMR Clinical Trials Methodology Conference, 4th and 5th October 2011 Bristol, England.

Podcasts

<http://www.cochrane.org/podcasts/issue-10-12-october-december-2013/strategies-improve-retention-randomised-trials>

Appendix 8: Best practice guidance consensus development

- 8.1. Abstract to publicise consensus workshops.
- 8.2. PowerPoint presentation of results of both studies.
- 8.3. Consensus workshop register.

Appendix 8.1. Abstract to publicise consensus workshops


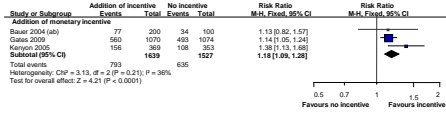
Abstract

Development of best practice guidance for retention in randomised trials

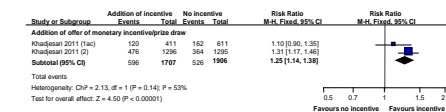
Loss to follow-up from randomised trials can cause bias affecting the reliability of trial results. A Cochrane review of the effectiveness of strategies to improve trial retention found that monetary incentives were effective for questionnaire response. Other strategies evaluated were found to be less effective e.g. priority post. A qualitative study conducted among primary care trial personnel found that some strategies identified by the Cochrane review are being used without knowing the full impact on trial retention. Other factors thought to impact upon trial retention were also identified.

The purpose of this seminar is to discuss best practice guidance for retention in randomised trials based on the results of these two studies. The seminar will be of particular interest to chief / principal investigators, trial managers, trial nurses and researchers involved in trial planning and trial management. The key findings of the Cochrane review and the qualitative study will be presented. This will be followed by small group discussions focused on best practice for retention in randomised trials based on the evidence presented. Feedback from the group discussions will be summarised and used to develop a consensus statement on best practice guidance for retention in randomised trials.

Appendix 8.2. Consensus workshop: PowerPoint presentation of results

| <div style="text-align: right;">  </div> <h3 style="text-align: center;">Retention in randomised trials: development of best practice guidance</h3> <p style="text-align: center;">Valerie Brueton</p> <p style="text-align: center; font-size: small;">MRC Medical Research Council</p> | <h3>Background</h3> <ul style="list-style-type: none"> Loss to follow-up / drop out / non response In randomised trials this can lead to: <ul style="list-style-type: none"> Incomplete data primary and secondary outcomes e.g. weight, CD 4, BP Reduce power to detect a difference between the treatment and control group Different strategies used to improve retention Some evaluated others used ad hoc <p style="text-align: center; font-size: small;">MRC Medical Research Council</p> | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|------------------------|------------------|------------|---------------------------------------|----|---------------|---|----|------------------------------|--|---|---------------------------|---|---|-------------|----------------|---|-------------|---|---|-----------------|--------------------------------------|---|---|
| <h3>Methods</h3> <ul style="list-style-type: none"> Systematic review <ul style="list-style-type: none"> Establish effect of strategies to improve retention Included retention trials embedded within other trials Primary outcome of retention / response Qualitative study <ul style="list-style-type: none"> Explore retention strategies used in UK primary care trials In-depth interviews with 29 primary care trial personnel <p style="text-align: center; font-size: small;">MRC Medical Research Council</p> | <h3>Systematic review: data available</h3> <ul style="list-style-type: none"> 38 retention trials Embedded in diverse RCTs <ul style="list-style-type: none"> UK, Europe, USA, Australia Primary care, secondary care, community Treatment, screening, prevention, clinical management and social care Cancer, cardiovascular, dependency, depression, parenting, exercise etc. 34 outcome response to postal/electronic questionnaires, 4 retention of participants Although well conducted often not reported in sufficient detail or at all <p style="text-align: center; font-size: small;">MRC Medical Research Council</p> | | | | | | | | | | | | | | | | | | | | | | | | |
| <h3>Systematic review: results</h3> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Strategy</th> <th>Intervention evaluated</th> <th>Number of trials</th> </tr> </thead> <tbody> <tr> <td>Incentives</td> <td>Monetary, offers of, gifts, offers of</td> <td>11</td> </tr> <tr> <td>Communication</td> <td>Emails, texts, letter, post, telephone, reminders</td> <td>10</td> </tr> <tr> <td>Communication and incentives</td> <td>Monetary/non monetary incentives with postal questionnaire strategies, e.g. postage used</td> <td>4</td> </tr> <tr> <td>New questionnaire designs</td> <td>Shorter questionnaires, change in question order, relevance to condition being researched</td> <td>9</td> </tr> <tr> <td>Methodology</td> <td>Open vs. blind</td> <td>1</td> </tr> <tr> <td>Behavioural</td> <td>Motivational workshops vs. standard information</td> <td>2</td> </tr> <tr> <td>Case management</td> <td>Trial assistants to manage follow-up</td> <td>1</td> </tr> </tbody> </table> <p style="text-align: center; font-size: small;">MRC Medical Research Council</p> | Strategy | Intervention evaluated | Number of trials | Incentives | Monetary, offers of, gifts, offers of | 11 | Communication | Emails, texts, letter, post, telephone, reminders | 10 | Communication and incentives | Monetary/non monetary incentives with postal questionnaire strategies, e.g. postage used | 4 | New questionnaire designs | Shorter questionnaires, change in question order, relevance to condition being researched | 9 | Methodology | Open vs. blind | 1 | Behavioural | Motivational workshops vs. standard information | 2 | Case management | Trial assistants to manage follow-up | 1 | <h3>Incentives vs. no incentive: monetary</h3> <ul style="list-style-type: none"> 5 subgroups of incentives vs no incentive Large difference in effect by subgroup of incentive data not pooled  <p style="text-align: center; font-size: small;">MRC Medical Research Council</p> <ul style="list-style-type: none"> Monetary incentives better than no incentive to increase response to postal questionnaires (RR 1.18; 1.09 - 1.28, P < 0.0001) 3 trials (3166 participants) Qualitative study incentives used for postal questionnaires Ethics committees approve small amounts Response rate 60% expect 61 more questionnaires per 1000 sent |
| Strategy | Intervention evaluated | Number of trials | | | | | | | | | | | | | | | | | | | | | | | |
| Incentives | Monetary, offers of, gifts, offers of | 11 | | | | | | | | | | | | | | | | | | | | | | | |
| Communication | Emails, texts, letter, post, telephone, reminders | 10 | | | | | | | | | | | | | | | | | | | | | | | |
| Communication and incentives | Monetary/non monetary incentives with postal questionnaire strategies, e.g. postage used | 4 | | | | | | | | | | | | | | | | | | | | | | | |
| New questionnaire designs | Shorter questionnaires, change in question order, relevance to condition being researched | 9 | | | | | | | | | | | | | | | | | | | | | | | |
| Methodology | Open vs. blind | 1 | | | | | | | | | | | | | | | | | | | | | | | |
| Behavioural | Motivational workshops vs. standard information | 2 | | | | | | | | | | | | | | | | | | | | | | | |
| Case management | Trial assistants to manage follow-up | 1 | | | | | | | | | | | | | | | | | | | | | | | |

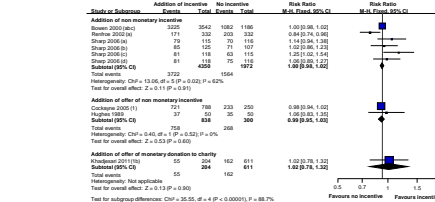
Incentive vs. no incentive: monetary



- Offer of monetary incentive / entry into prize draw is better than no offer for return of electronic questionnaires (RR 1.25; 1.14 - 1.38, P < 0.00001)
- 2 internet-based trials (3613 participants)
- Qualitative study offers of monetary incentives used unsure of effect
- Response rate 60%, 80 more questionnaires per 1000 sent

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Incentive vs no incentive: non-monetary



No good evidence that:

- A non-monetary incentive is better no incentive (RR=1.00, p=0.91) some heterogeneity (p=0.02) 6 trials (6322 participants)
- Offer of non-monetary incentive is better than no offer (RR=0.99, p=0.60) 2 trials (1138 participants)
- Offer of a donation to charity is better than no offer (RR=1.02, p=0.90) 1 trial (815 participants)

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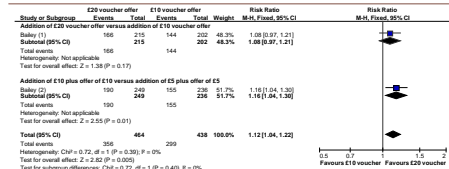
Non-monetary incentives

Qualitative study

- Gifts used for recruitment
- Seldom mentioned for retention
- Uncertainty about effectiveness
- Participants may think non-monetary incentives not good use of public money

MRC | Medical Research Council

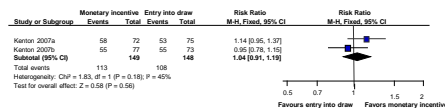
Higher value incentive vs. lower value



- Offer of higher value incentives are better than lower for return of a postal questionnaire plus biomedical specimen kit (RR 1.12; 1.04 - 1.22, p = 0.005) 2 trials (1138 participants)
- Irrespective of how given i.e. offered or split
- Response rate 60%, 44 more questionnaires per 1000 sent

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Addition of monetary incentive vs. offer of entry into a prize draw

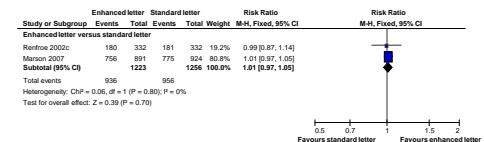


- No good evidence that giving a monetary incentive is better than an offer of entry into a prize draw on postal questionnaire response (RR=1.04; p=0.56) 2 trials (297 participants)
- Prize draw seldom used in primary care trials, thought may be more cost effective than giving an incentive

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Communication: enhanced letter vs standard

- Communication strategies so different analysed separately



- Results suggest there was no effect of an enhanced letter when compared to a standard letter on postal questionnaire response (RR=1.01; 0.97-1.05, p = 0.70) 2 trials (2479 participants)
- Qualitative study letters signed by trial managers
- Consistency of signatory rather than status thought important

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Questionnaires: relevance to condition

| Study or Subgroup | New questionnaires | | Standard questionnaires | | Risk Ratio | |
|---|--------------------|-------------|-------------------------|-------------|--------------------------|--------------------|
| | Events | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Questionnaires: relevance versus less relevant to condition | | | | | | |
| Mc Cambridge 2011 16a | 529 | 947 | 489 | 945 | 1.08 [0.99, 1.17] | |
| Mc Cambridge 2011 20a | 653 | 1263 | 208 | 488 | 1.08 [0.96, 1.21] | |
| Subtotal (95% CI) | 2280 | 4510 | 697 | 1433 | 1.07 [1.01, 1.14] | |
| Total events | 1182 | 2280 | 797 | 1433 | | |
| Heterogeneity: Chi ² = 0.06, I ² = 0.81; P = 0% Test for overall effect: Z = 2.12 (P = 0.03) | | | | | | |

- In research on reducing alcohol consumption, more relevant questionnaires (i.e. those relating to alcohol use) increased electronic questionnaire response (RR 1.07; 1.01 to 1.14, P = 0.03) 2 trials (3893 participants)

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Other retention strategies

No good evidence that

- Behavioural strategies are better than standard information (RR= 1.08, 0.93-1.24, p=0.31) 2 trials (273 participants)
 - Not used, negative about this strategy
- Intensive case management is better than standard follow-up (RR=1.00, 0.97-1.04, p=0.99) 1 trial (703 participants)
 - Elements used

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Other retention strategies

Some evidence that

- Open trial design is better than a blind trial design for postal questionnaires in fracture prevention trial (RR 1.37; 1.16 - 1.63, P = 0.0003) (538 participants)
 - Open trials used but not for retention in pc
 - Blinding to avoid bias but cannot be used in therapist led trials

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Factors contributing to loss to follow-up

- Age e.g. teenagers, young men, elderly, working mums
- No perceived benefit from trial participation e.g. weight loss
- Healthy volunteers
- Participants feel well
- Work environment room availability for flexible follow-up appointment times

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Best practice guidance for retention

- **Group 1**
Incentive strategies
- **Group 2**
Questionnaire strategies
- **Group 3**
Communication and other strategies

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Best practice guidance for retention

Group work development of best practice guidance for retention in trials

- Is the evidence convincing?
- Barriers to implementing results?
- In which setting would you use the strategy?
- With which population group?
- In which type of follow-up e.g. on line, postal, face to face?
- When to use the strategy?
- Negative strategies
- Any barriers to stop using these?
- Other strategies used that need evaluation?

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Appendix 8.3. Consensus workshop register

| | | | Role Tick as appropriate | | | | | | Area of research / disease area | List trial/s you work on |
|----|------|---------------|-----------------------------|---------------------------|------------------|----------------------------|-----------------------|----------------------------|------------------------------------|--------------------------------|
| | Name | Email address | Chief Investigator | Principal investigator | Trial manager | Trial research Nurse | Trial data manager | Other please specify | | |
| 1 | | | | | | | | | | |
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| 20 | | | | | | | | | | |

Appendix 9: Additional tables

9.1. Table of areas of overlap and difference between systematic reviews.

Appendix 9.1. Table of areas of overlap and difference between systematic reviews

| Review | Objective | Included studies | Setting | Searches | Number of eligible studies | Retention strategies identified | Meta-analysis yes / no | Effective strategies |
|------------------------|--|--|--|--|--|--|------------------------|--|
| Davis (2002) | To determine the effects of retention strategies on participant retention | Community based clinical trials | Community | Not reported | 21 RCTs that describe the use of strategies to improve retention | Study design Incentives Communication Staff training Trial management Marketing | No | - |
| Robinson (2007) | To identify and describe studies that use retention strategies to maximise in person follow-up | Studies that describe retention strategies for health care research and that include retention rates | Health care studies | PubMed; EMBASE; CENTRAL CINAHL; Cochrane Methodology Register Reference lists | 21 RCTs that describe the use of strategies to improve retention | Communication Marketing Incentives Trial management | No | - |
| Booker (2011) | To determine the effectiveness of retention strategies in population based cohort studies | Studies that evaluated retention methods in population based cohort studies | Population based | MEDLINE; EMBASE; CENTRAL; CINAHL DARE; PsycINFO; ISI; PsycABSTRACTS; AMED Health development agency literature Reference lists | 11 retention RCTs embedded in longitudinal cohort studies | Incentives Communication | No | - |
| Nakash (2006) | To identify effective methods to improve response to postal questions in health care research | Randomised trials of methods to improve response to postal questionnaires in clinical studies | All health care settings and disease areas | MEDLINE; EMBASE; CENTRAL; Cochrane database of systematic reviews ; PsycINFO National Research Register | 15 retention RCTs embedded in surveys and RCTs | Incentives Communication Questionnaire format | Yes | Reminders (OR 3.7: 2.3- 5.97) Shorter questionnaires (OR 1.35: 1.19-1.54) |

| Review | Objective | Included studies | Setting | Searches | Number of eligible studies | Retention strategies identified | Meta-analysis yes / no | Effective strategies |
|-----------------------|---|--|---|---|--|--|------------------------|--|
| Edwards (2009) | To identify effective strategies to increase response to postal and electronic questionnaires | Randomised trials of methods designed to increase response to postal and electronic questionnaires | All health care and non-health care research settings | MEDLINE; EMBASE; CENTRAL; PsycINFO; CINAHL; ERIC; PsycLit; Spectre; EconLit Dissertation abstracts Social Science and Science citation index Sociological Abstracts Index to Scientific and technical proceedings. Journal hand searches Contact with authors Reference lists | 513 retention trials embedded in surveys cohort studies and RCTs | Incentives Communication Questionnaire format | Yes | Postal response: Monetary incentives (OR 1.87; 1.73 - 2.04) Recorded delivery (OR 1.76; 1.43 - 2.18) Teaser on envelope (OR 3.08; 1.27 - 7.44) More interesting topic (OR 2.00; 1.32 - 3.04) Electronic response: Picture in an e-mail (OR 3.05; 1.84 - 5.06) Non-monetary incentives (OR 1.72; 1.09 - 2.72) |
| Brueton (2013) | To identify effective strategies to improve retention in randomised trials | Randomised trials of methods to improve retention in randomised trials and nested in randomised trials | All health care research settings | MEDLINE; EMBASE; CENTRAL; PsycINFO; CINAHL; ERIC; C2 Spectre; DARE, PreMEDLINE, Cochrane Methodology Register, Current Controlled Trials metaRegister, WHO trials platform, Society for Clinical Trials (SCT) conference proceedings, survey of all UK clinical trial research units. Contact with authors Reference lists | 38 retention trials embedded in randomised trials | Incentives Communication Questionnaire format Methodology Case management Behavioural | Yes | Postal questionnaires: Giving a monetary incentive (RR 1.18; 95% CI 1.09-1.28) Higher valued incentives (RR 1.12; 95% CI 1.04-1.22) Recorded delivery of questionnaires (RR 2.08; 95% CI 1.11-3.87). "Package" of postal communication strategies (RR 1.43; 95% CI 1.22-1.67). Open trial design (RR 1.37; 95% CI 1.16 -1.63). Electronic questionnaires: Offer of monetary incentive (RR 1.25; 95% CI 1.14-1.38) |

Appendix 10: Thesis protocol

10. Thesis protocol.

Appendix 10. Thesis protocol

Strategies to improve RCT retention

Background

Loss to follow-up occurs in randomised trials (RCTs) (Akl et al. 2009, Gravel et al. 2007, Wood et al. 2004) and can lead to incomplete data to accurately measure the primary outcome (Akl et al. 2009). This can cause bias and compromise the power of an RCT to detect the true difference between the control group and the intervention group. Loss to follow-up also has consequences for the internal validity and generalisability of the findings of RCTs (Fewtrell et al. 2008, Schulz et al. 2002).

Missing data as a result of loss to follow-up can be dealt with statistically. However, the risk of bias still remains (Hollis et al. 1999). Different strategies are used to try to retain participants in RCTs through optimal data return via questionnaires or compliance to follow-up procedures (Davis et al. 2002, Robinson et al. 2007). These strategies focus on motivating the study site (Leathem et al. 2009) and / or the participants to continue participating in RCTs once they have been recruited and randomised.

A number of systematic reviews have examined methods to improve the response to the postal and electronic questionnaires used in health care and other research contexts (Booker et al. 2011, Edwards et al. 2009, Nakash et al. 2006). Several effective strategies were found for example; incentives, communication and questionnaire strategies. These systematic reviews and meta-analyses include nested evaluations of strategies to improve retention in surveys, cohort studies and RCTs. However, we still do not know the spectrum of strategies that specifically improve retention in RCTs. It is important for researchers to know which retention strategies improve retention in the context of RCTs because participants may be lost to follow-up for different reasons to cohort studies and surveys and therefore the effective strategies may be different for RCTs. It is also unknown which retention strategies are commonly used in UK RCTs and the factors that improve retention in RCTs. Therefore, the overarching aim of this thesis is:

To establish the effectiveness and use of strategies to improve retention in RCTs, and to provide guidance for the future use of effective retention strategies in RCTs.

The specific objectives of this thesis are:

1. To identify the retention strategies that have been evaluated in RCTs.

2. To determine if the strategies that have been evaluated are used to improve retention in primary care RCTs.
3. To identify barriers to the use of strategies to improve retention in primary care RCTs.
4. To identify retention strategies for further evaluation.
5. To make recommendations for the use of effective strategies to improve retention in RCTs.

Methods

A mixed methods approach will be used to establish the effectiveness of retention strategies, explore their use, and develop best practice guidance for the future use of retention strategies in RCTs. These approaches will be:

1. A systematic review of the literature and meta-analysis to describe and quantify the effect of strategies to improve retention in RCTs.
2. A qualitative study using in-depth interviews with UK primary care RCT personnel to explore the strategies used to improve retention in primary care RCTs.
3. Consensus development workshops to develop best practice guidance for the future use of strategies to improve retention in RCTs based on the results of the systematic review and the qualitative study.

Systematic review methods

RCTs (i.e. host RCTs) from all disease areas and health care settings with embedded RCTs (i.e. retention RCTs) that have evaluated strategies to improve retention will be eligible for inclusion in the review. Retention RCTs will include at least one randomised comparison of one or more strategies to improve retention, or compare one or more strategies with no strategy. The strategies will be designed for use after participants have been recruited and randomised to either the intervention group or the control arm of a host RCT. Retention strategies in any combination directed toward the RCT clinician, researcher or participant will be included. Retention RCTs conducted in all languages will also be included. Cohort studies with embedded retention RCTs of strategies to improve retention will be excluded.

A search strategy will be designed to identify all published and unpublished RCTs that assessed strategies to improve retention in RCTs. The bibliographic databases to be searched are: MEDLINE, EMBASE, PsycINFO Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Methodology

Register CINAHL (Cumulative Index to Nursing and Allied Health) Campbell Collaboration's Social, Psychological, Educational and Criminological Trials Register (C2-SPECTR) Education Resource Information Centre (ERIC). Reference lists of published RCTs and RCT registers will also be searched for ongoing eligible retention RCTs.

Titles and abstracts generated from the searches will be screened for eligibility. Full text papers for potentially eligible retention RCTs will be obtained and screened for inclusion. Data will be extracted from eligible retention and host RCT publications and checked by another systematic reviewer. Summary data will be entered into Revman 5 for data analysis. The Cochrane risk of bias assessment tool will be used to assess the validity of each included retention RCT (Higgins et al. 2008).

For the data analysis, retention (i.e. 1- the proportion lost to follow-up) at the primary analysis point, as defined in each retention RCT, will be the primary outcome for the review. Risk ratios and their 95% confidence intervals will be calculated to determine the effect of strategies on retention. It is anticipated that most included retention RCTs will have randomised participants to either a control or intervention arm. In this case the unit of intervention will be the individual participant. For cluster randomised RCTs the unit of analysis will be the cluster. Heterogeneity will be measured by the χ^2 statistic at a significance level of 0.10 and the I^2 statistic (Higgins et al. 2003) and explored by subgroup analyses. Sensitivity analyses will be conducted if quasi RCTs are identified to assess the robustness of the results.

Although a variety of strategies may be used to improve retention, these may have been evaluated in different disease areas and care settings. It is not clear that these different strategies and settings will necessarily lead to differences in outcome. Therefore, risk ratios will initially be pooled using the fixed effect model, after heterogeneity is quantified and explored in subgroup analyses to determine if a pooled estimate is meaningful. If a sufficient number of retention RCTs is identified, reporting bias will be assessed using tests for funnel plot asymmetry (Egger et al. 1997, Sterne et al. 2008). If any heterogeneity cannot be explained or is excessive retention RCTs will not be pooled.

Qualitative study methods

In-depth interviews will be conducted with RCT personnel identified from a sampling frame of UK primary care RCTs published from 2000-2010. The RCTs to be included will be identified from: a) journals known to publish the results of primary care RCTs, b) the

Medical Research Council General Practice Research Framework (MRC GPRF) database of published primary care RCTs, and c) websites of primary care research units.

Ethics approval will be sought from University College London (UCL) ethics committee. Recruitment will be conducted by email and an information leaflet and a reply slip will be included in the invitation package to be sent to all researchers invited to participate.

Those that agree will be invited by email for an in-depth interview. After obtaining informed consent, participants will be interviewed using a predesigned topic guide. They will be asked about the strategies that they use to improve retention in primary care RCTs and about the use of strategies identified by the systematic review. The topic guide will be piloted and adjusted as needed. The interview topic guide will ask about: a) RCT personnel's experiences of loss to follow-up in RCTs, b) the factors that contribute to retention and loss to follow-up in RCTs, c) decision making about strategies to use to prevent or control loss to follow-up in RCTs. The impact of ethics committees on the use of incentive strategies to improve questionnaire response and the advantages and disadvantages of using strategies to increase follow-up will also be discussed.

The interviews will be recorded, transcribed verbatim and anonymised. Analysis will be carried out concurrently with the data collection, and emergent findings will be used to further refine the topic guide. Interviews will continue until no new experiences of the use of strategies or the barriers to the use of strategies emerge from the interviewees. It is expected that between 20 - 30 interviews will be conducted in total.

A thematic content analysis will be conducted based on the questions asked in the interview schedule. Interview transcripts will be read and re read to identify emerging categories and themes. A data review group will be convened to discuss emerging themes and to agree a coding scheme for the interview transcripts. Data will be coded using both pre-defined codes for strategies identified by the systematic review and codes for themes and other strategies that emerge from the transcripts. Themes around each category will be verified and confirmed by constant comparison and searching across all interviews for similar themes and categories for analysis (Pope C et al. 2000). ATLAS/Ti will be used to manage and retrieve the data for analysis.

Consensus development

To draw the results of these two studies together, the results of the qualitative study will be tabulated side by side with the results of the systematic review. Two best practice

guidance development workshops with trial personnel at a Clinical Trials Unit and an academic primary care research unit will be convened. The workshop attendees will be principal and chief investigators, trial managers, research nurses, trial statisticians and data managers. At each workshop the results of the systematic review and the qualitative study will be presented and where possible, recommendations for the future use of effective strategies to improve retention in RCTs will be agreed.

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