Design and rationale of the Ready to Reduce Risk (3R) Study: A randomised controlled trial of a group educational intervention with telephone and text messaging support to improve medication adherence for the primary prevention of cardiovascular disease

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Abstract

Background: Poor adherence to cardiovascular medications is associated with worse clinical outcomes. Evidence for effective education interventions that address medication adherence for the primary prevention of cardiovascular disease (CVD) are lacking. The 3R (Ready to Reduce Risk) Study aims to investigate whether a complex intervention, involving group education plus telephone and text messaging follow-up support, can improve medication adherence and reduce cardiovascular risk. This protocol paper details the design and rationale for the study.

Methods: An open, pragmatic, randomised controlled trial with 12 months follow-up. Participants were recruited from primary care and randomised on a 1:1 basis, stratified by sex and age, to either a control group (‘usual’ GP care) or an intervention group involving two group, facilitated education sessions with telephone and text messaging follow-up support, with a theoretical underpinning and using recognised behavioural change techniques. The primary outcome was medication adherence to statins. The primary measure is an objective, novel, urine-based biochemical measure of medication adherence. The Morisky 8-item Scale was also used to assess medication adherence. Secondary outcomes include changes in total cholesterol, blood pressure, high-density lipoprotein, TC:HDL ratio, body mass index, waist-to-hip ratio, waist circumference, smoking behaviour, physical activity, fruit and vegetable intake, patient activation level, quality of life, health status, health and medication beliefs and overall CVD risk score. Process outcomes relating to acceptability and feasibility of the 3R Intervention have also been considered.

Results: 212 participants were recruited between May 2015 and March 2017. The 12 month follow-up data collection clinics were completed in April 2018 and data analysis will commence once all study data has been collected and verified.

Discussion: This study will identify a potentially clinically useful and effective educational intervention for the primary prevention of CVD. Medication adherence to statins is being assessed using a novel urine assay as an objective measure, in conjunction with other validated measures.

Trial Registration: ISRCTN16863160

Keywords: medication adherence; cardiovascular disease; primary prevention; educational intervention; telephone support; text messaging support
**Introduction**

Globally, cardiovascular disease (CVD), including heart attacks and stroke, is the leading cause of death. An estimated 17.7 million people died from CVDs in 2015, representing 31% of all global death. [1] This is a significant burden on society. The overall CVD cost to the UK economy is approximately £19 billion. [2] However, it is estimated that 75% of all premature deaths from CVD are avoidable through effective reduction of modifiable risk factors.[3]

**Current International Guidance on CVD Risk Management for Primary Prevention**

Major international guidelines for the primary prevention of CVD provide the latest evidence-based guidance on lifestyle factors (exercise, diet, smoking, weight and alcohol) and lipid-lowering medication to reduce CVD risk.[4, 5][6, 7]. Despite some differences in the detail of the recommendations, there is a general consensus about the benefits of exercise, the cessation of smoking and the use of statins for people at high risk of CVD. [8]

The American Heart Association (AHA) recommends the prescribing of statins for the primary prevention of CVD in all patients with a serum LDL-C > 4.9 mmol/L, regardless of their CVD risk profile.[6] In contrast, the European Society of Cardiology (ESC) is more cautious and recommends that statins are more frequently required in those individuals with LDL-C levels raised to >4.9 mmol/L, but may not be necessary in those with a low CVD risk score [ESC SCORE Chart estimation <5%].[7] The latest NICE guidelines no longer use specific cholesterol targets as makers of CVD risk; instead, they advise atorvastatin 20 mg to be offered as primary prevention in patients < 85 years with a 10 year QRISK2 score of > 10%. [4] The QRISK2 is the updated version of the QRISK CVD risk calculator, that was developed and validated on a UK population and addresses risk issues such as ethnicity and social deprivation. [9]

In the UK, this guidance has been controversial; as such a low threshold for starting statins would mean that a 65 year old male would obtain a risk of 10% despite optimal BMI, optimal cholesterol and no comorbidities. [8] Also, a paper by Abramson et al [10] further fuelled the debate over the intolerable side-effects that are reported in 5-10% of patients. Consequently, in the UK, there has been a lot of negative media regarding the prescribing of statins which has resulted in many patients stopping statins.[11] Moreover, medication adherence to CVD-preventative drugs remains a problem in both secondary and primary CVD prevention.

**Medication Adherence and CVD Risk**

In patients with CVD, self-reported adherence to CVD medications for a common combination of aspirin, β-blocker, and a statin was shown to be less than 40% in both isolated and long-term follow-up surveys.[12] Moreover, despite the demonstrated safety and effectiveness of statins for CVD prevention, patient adherence to long-term statin treatment is poor.[13-15] In a recent study of a large cohort of Finnish patients (n=97,575), there was an approximately 30% increase in the risk of any CV events or death among primary prevention patients who adhered poorly to statins when they were compared with good adherers. [16] However, the evidence also suggests that the use of statins by patients is dynamic, and many patients after long periods of non-adherence will restart their treatment. This is strongly linked to clinical visits, implying that reiteration by GPs of the role statins play in reducing risk may be beneficial.[17]
With statin and antihypertensive treatments (the main medications used in primary CVD prevention) there are often multiple reasons for poor adherence to medication: forgetfulness, a negative attitude towards medication, frustration with poor therapeutic responses, preconceived beliefs regarding health and medication and a poor understanding of the pros and cons of a prescribed drug. In particular, there is a lack of understanding of the benefit of CVD prevention medication and a fear of drug-related adverse events.[18] The number of barriers to medication adherence stresses the importance of how risk and treatment options are communicated to patients by health professionals to promote behavioural change and engage people in self-management.

Poor medication adherence is one of the key reasons why overall CVD risk remains high despite patients being prescribed statins and provided with lifestyle advice by their GPs. Therefore, it is important that patient education addresses this issue and the many misconceptions to do with statins.

**Structured CVD Risk Education**

Structured education has been widely advocated as a cost-effective method of promoting self-management and behaviour change in individuals with chronic disease. [19] It is an alternative to one-to-one counselling and refers to group-based, patient-centred educational programmes that have a clear philosophy; a written curriculum that is underpinned by appropriate learning and health behaviour theories; an evidence base; and trained, quality assessed, educators.[20]

In the UK, the DESMOND programme for individuals with Type 2 diabetes has demonstrated that a structured education programme can be delivered within the NHS at a national level and promote behaviour change. [21] With the introduction of the NHS Health Checks and new treatment guidelines, there is a growing need for similar interventions to be developed, tested and implemented to provide a proper pathway for the management of CVD risk.

**Study Rationale**

This paper details the design and rationale of the Ready to Reduce Risk (3R) Study. This is a randomised controlled trial (RCT) to evaluate the effectiveness of a complex intervention (the 3R Education Programme with follow-up text messaging and telephone support) to improve medication adherence and reduce risk in the primary prevention of cardiovascular disease in high risk individuals.

**Methods**

The Consolidated Standards of Reporting Trials (CONSORT) checklist [22], in conjunction with the CONSORT-EHEALTH checklist [23], has been used to describe the design of this study to ensure that this trial protocol is well reported. [Multimedia Appendices 1 & 2]

**Study Design**

The study was an open, individual and pragmatic RCT recruiting from UK general practices (attached to a single study centre). Patients identified as being at high risk of CVD for primary prevention and already prescribed statins to reduce this risk were recruited. Participants were randomised to either the control group (‘usual’ GP care) or the intervention group (3R Group Education Programme plus follow-up telephone and text messaging...
support). For both the control and intervention participants, the GP was informed of a patient’s participation in the study but was not made aware of their group allocation. Both groups attended clinic visits at baseline and 12 months so outcome data could be collected at these time-points. [Figure 1]

Figure 1: Study Design
Participants & Recruitment

Eligibility Criteria for Participants

- Male or female aged 40-74 years old inclusive
- Prescribed statin medication for primary prevention of CVD that was still active, at least 12 months prior to enrolment
- Total cholesterol (TC) level ≥5.0 mmols/L at enrolment
- Ability to speak and read English to participate effectively in the group education programme
- Willing and able to attend education sessions and clinic visits
- Access to a mobile phone
- Willing and able to give informed consent
- Willing to allow GP to be notified of participation in the study
- No pre-existing CVD
- No inherited lipid disorder
- No established Type 1 or Type 2 diabetes
- No females who were pregnant (self-reported)
- No participation in another clinical intervention study in the 12 weeks prior to enrolment

As we expected there to be participants who had repeat prescriptions for statins but were not taking them as directed, a prescription was considered to be active - for the purpose of the study - if there had been at least two issues of the prescription within the previous two years. Participants with a TC ≥5 mmols/L at baseline were recruited, based on the assumption that these participants were more likely to be non-adherent to statin medication if their cholesterol levels were higher.

Method of Recruitment

Thirteen general practices from across Northamptonshire were identified to take part in the study. An automatic MIQUEST search (based on the eligibility criteria described above) was developed for the practices to download from a secure online site to generate a list of potential participants to be sent invitation packs. MIQUEST is a method which is used to extract data from different types of GP database systems, using a common query language to ensure consistency. Each invitation pack contained an invitation letter, a preliminary study information leaflet and a reply slip with prepaid envelope. Prior to the mailing of these packs, a clinical member of the practice staff screened the list to ensure the suitability of patients to take part.

Reply slips (from both positive and negative responders) were returned directly to the research team. All positive responders were contacted to verbally screen and confirm their eligibility for the study. Following this, eligible patients who were interested in taking part were booked to attend an initial data collection clinic. All participants were required to attend two data collection clinics: at baseline and at 12 months. The clinics were held in a suitable local venue, usually a community venue. Group clinics (of up to 8 participants at a time) were run by three trained study staff, including a qualified nurse. A full Patient Information Sheet (PIS) was sent with the clinic appointment letter. At the baseline clinic, written informed
consent for all participants was taken by a trained research before the collection of any data. All participants were made aware that they could withdraw from the study at any time.

Randomisation

Following confirmation of an eligible blood result for cholesterol, participants were randomised on a 1:1 basis, by a trained member of the 3R Team not involved with data collection using an online randomisation tool (Sealed Envelope Ltd). Participants were stratified by age (40-53 years and 54-74 years) and sex, before been randomly allocated to either the control or intervention group. If two people were taking part from the same household, they were automatically assigned to the same arm to prevent any contamination between groups taking place.

Following enrolment, blinding of participants was not possible, due to the open and pragmatic design of the study. However, some steps were taken to reduce bias: data were collected by research nurses not involved in any analysis, and GPs were not informed of a participant’s group allocation. Also, the analysis of the urine samples was conducted by lab staff blinded to the randomised groups.

Control Group

The control group continued with their ‘usual’ GP care with regard to lifestyle and medication advice for the primary prevention of CVD. To ensure that all participants had access to at least some basic knowledge about managing CVD risks, both groups were sent a British Heart Foundation (BHF) booklet—‘Keep Your Heart Healthy’—which contains general information about CVD risk prevention.

Intervention Group

Development of the 3R Education Programme and Follow-Up Support

The 3R (Ready to Reduce Risk) Programme was developed in line with the Medical Research Council’s (MRC’s) recommendations for the development of complex interventions. [24, 25]. Specific focus was given to supporting people to develop an increased sense of the role of their behaviours in their long term health and risk. In the absence of one unified model or construct, the concept of Patient Activation [26] and the Capability, Opportunity and Motivation (COM-B) model was employed as it encapsulates many theoretical components of behaviour change theory. [27] The behaviour change taxonomy was used to ensure accurate[28] reporting and to help identify the key active components of behaviour change interventions.

An experienced working group of health professionals, led by a psychologist, developed the intervention: based on the DESMOND philosophy of empowerment whereby participants are supported, rather than taught, to discover and work out knowledge to achieve their own health goals. [29] A number of different stages (including a literature search and focus groups with potential users) were used to explore and expand the original idea within the framework of the COM-B model. [27] This process informed the content, format and theoretical basis of the programme, and was used to draft a curriculum to provide a written structure for the 3R Programme and to identify the key component behaviours change techniques to be used. This was evaluated using an iterative process of testing with potential users, feedback and modification until the programme was considered ready for implementation. Educational,
mixed-media resources were also developed to support the delivery of the curriculum and to engage participants in the learning activities. In conjunction with the development of the education programme, a 2-day training programme led by an experienced psychologist was delivered to a group of 6 facilitators to ensure consistent delivery of the curriculum. The newly trained facilitators were given the opportunity to practise delivery of the programme before the start of the study.

In addition to the main education programme, follow-up support was developed to help sustain any potential, positive effects of the education. Continued support to maintain and promote positive health behavioural change has been shown to be effective when provided as brief telephone calls [30] and with text messaging. [31-34] After reviewing this literature, the best format for the delivery of the 3R follow-up support (text messages and phone calls) was decided. For the text messages, this process involved using content that had already been robustly developed and validated in the TEXTME study. [35] For the phone calls, a semi-structured script and 1 day training session (involving practise role-play scenarios) was developed, using the same framework that was used for the follow-up calls in the successful PREPARE study [30].

**Delivery of the 3R Education Programme & Follow-Up Support**

The intervention group were invited to attend the 3R Education Programme and receive the follow-up support (text messages and phone calls). They continued with their usual GP care and were sent a copy of the BHF booklet. Boxes 1, 2 and 3 detail the different components involved in the delivery of each of the three major elements of the intervention and identifies the behavioural control techniques (BCTs) [28] or ‘active components’ involved in each:

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**Box 1: 3R Education Programme**

<table>
<thead>
<tr>
<th><strong>3R Education</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Setting:</strong> Local venue (e.g. community hall)</td>
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<tr>
<td><strong>Format:</strong> Group education (∼8 per group; participants were allowed to take a partner or friend) facilitated by a written structured curriculum &amp; mixed-media educational resources (including a free pedometer).</td>
</tr>
<tr>
<td><strong>Frequency:</strong> 2 sessions</td>
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<tr>
<td><strong>Duration:</strong> ∼2 hours</td>
</tr>
<tr>
<td><strong>Facilitators:</strong> 2 trained facilitators (at least one was health care professional)</td>
</tr>
<tr>
<td><strong>Training:</strong> 2 day course, self-study &amp; practise run</td>
</tr>
<tr>
<td><strong>Monitoring:</strong> ad hoc filmed sessions</td>
</tr>
<tr>
<td><strong>Outline:</strong></td>
</tr>
<tr>
<td><strong>Session 1</strong></td>
</tr>
<tr>
<td>Explored understanding and beliefs to do with CVD risk and how to manage it; showed how to calculate ‘own’ risk score using the Joint British Societies (JBS3) calculator; raised awareness of factors that influence risk, how these affect the body and the role of medication; and explored beliefs around medication adherence.</td>
</tr>
<tr>
<td><strong>Session 2</strong></td>
</tr>
<tr>
<td>Increased knowledge &amp; awareness about how to have a healthier lifestyle to reduce CVD risk; introduced behavioural control techniques to support ‘activated’ participants.</td>
</tr>
<tr>
<td><strong>Theories/Models:</strong> COM-B Model; Patient Empowerment; Working Alliance; Patient Activation; Self-Regulation; Self-Determination; Cognitive Dissonance; Self-Efficacy.</td>
</tr>
<tr>
<td><strong>BCTs:</strong> Goal setting (outcome); Problem solving; Action planning; Self-monitoring of...</td>
</tr>
</tbody>
</table>
outcome(s) of behaviour; Social support (emotional); Social support (practical); Information about health consequences; Salience of consequences; Demonstration of behaviour; Pros and cons; Adding objects to the environment; Incompatible beliefs; Valued self-identity.

<table>
<thead>
<tr>
<th>Box 2: Follow-Up Support Phone Calls</th>
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<tbody>
<tr>
<td><strong>Follow-Up Phone Calls</strong></td>
</tr>
<tr>
<td><strong>Setting:</strong> Participants were called at home by a member of the 3R Study Team from a private office and designated study mobile.</td>
</tr>
<tr>
<td><strong>Format:</strong> Participants received individual calls facilitated by a semi-structured script and delivered using a patient-centred approach.</td>
</tr>
<tr>
<td><strong>Frequency:</strong> 2 calls at approximately 2 weeks and 6 months</td>
</tr>
<tr>
<td><strong>Duration:</strong> Approximately 10-20 minutes</td>
</tr>
<tr>
<td><strong>Facilitator:</strong> A trained member of the 3R Team who was experienced in calling research participants.</td>
</tr>
<tr>
<td><strong>Monitoring:</strong> Written records of the calls were documented by the facilitator, using a structured template.</td>
</tr>
<tr>
<td><strong>Outline:</strong> Participants were called at a convenient time and asked some questions about how they were ‘getting on’ following the 3R Education. The facilitators used open questions to elicit information about what had been going well and not so well, and participants were given the opportunity to discuss any pitfalls and ways to overcome these.</td>
</tr>
<tr>
<td><strong>Theories/Models:</strong> The theoretical basis was the same as the 3R Education Programme.</td>
</tr>
<tr>
<td><strong>BCTs:</strong> Goal setting (outcome); Problem solving; Action planning; Self-monitoring of outcome(s) of behaviour; Social support (emotional); Social support (practical); Information about health consequences; Pros and cons; Valued self-identity</td>
</tr>
</tbody>
</table>
Box 3: Text messaging Follow-Up Support

**Text Messaging**

**Setting:** One week post-education, participants received text messages to their own mobiles via an independent SMS Text service which is set-up to work from the secure, study contacts database.

**Format:** A series of automated, unidirectional text messages were sent, consisting of medication reminders (e.g. ‘Have you taken your tablets today?’), and motivational/support TEXTME© messages (e.g. ‘Walking up and down a flight of stairs several times is a great strengthening activity.’).

**Duration:** 44 weeks

**Frequency:**
- **Medication reminders:** Weeks 1 to 2 (7 texts); Weeks 3 to 4 (4 texts); Weeks 5-26 (1 text); Weeks 27 to 28 (7 texts); Weeks 29-30 (4 texts); Weeks 31-44 (1 text) [Sent at the same time each evening]
- **TEXTME messages:** Four texts per week [Sent on random week days at random times]

**Facilitator:** Texts were initiated and stopped manually by the 3R Team.

**Training:** Participants received a ‘3R Follow-On Support’ booklet and facilitators received training from their Clinical Research Service (who developed the study database) on how to manage the text messaging support via the database interface.

**Monitoring:** All texts sent were logged and monitored to identify any problems.

**Outline:** Participants could choose between a ‘Smokers’ and ‘Non-Smokers’ pathway for the type of texts that they received. A series of texts relating to healthy eating, physical activity, medication, general heart health and smoking (if chosen) were then delivered as per the 44 week schedule detailed above. Texts could be stopped at any time by the participant, by sending a text to a specified number.

**Theories/Models:** The theoretical basis of the TEXTME© messages is detailed in the protocol paper by Redfern et al (2014) [35]

**BCTs:** Reduce prompts/cues (for medications reminders); other BCTs associated with the TEXTME messages are detailed in Redfern et al (2014) [35]
Outcomes & Measures

Primary Outcome
The primary outcome was medication adherence to statins at 12 months. The primary measure was a urine-based biochemical measure involving a novel assay to test for statin and anti-hypertensive levels in urine samples. This method has already been used successfully to show poor adherence to anti-hypertensive medication pre-surgery. Participants were informed that urine samples would be collected to assess the levels of statins, and were asked to provide a first morning urine sample (in a standard urine collection tube) prior to clinic. Tandem Mass Spectrometry (LC-MS/MS) in targeted MRM (multiple reaction monitoring) mode was then used to detect the presence of statins, antihypertensives and their metabolites. This gives a direct and objective measure of short-term medication adherence (i.e. whether or not any statin medication had been taken the previous day).

In addition, the self-reported Morisky 8-item Medication Adherence Scale was completed at baseline and 12 months. This is an established and validated scale that is commonly used to measure adherence. At the end of the study, practices were asked to provide details for individual participants regarding both statin and antihypertensive (if applicable) prescriptions issued during the 12 months of the study. These data will provide useful supporting information about the pattern of patient medication adherence behaviour over the 12 month study period.

Secondary Outcomes
Secondary outcomes include adherence to antihypertensive medications and other anticipated potential effects of the intervention, including a change in overall CVD Risk Score measured by the QRISK®2 calculator as well as potential changes in the following individual CVD risk factors: total cholesterol (TC), high-density lipoprotein (HDL), TC:HDL ratio blood pressure (BP) and body mass index (BMI). Changes in behaviour and lifestyle were also observed for, using validated questionnaire measures: smoking, physical activity, fruit and vegetable intake, patient activation level, well-being, health status, health/medication beliefs and medication adherence to antihypertensives (for participants prescribed this treatment for high blood pressure). All outcome measures were collected at the baseline and 12 months clinics in line with standard operating procedures and good clinical practice guidelines. In addition, an adverse event check was carried out and recorded at the final visit, and whenever a participant was contacted for the purpose of the study to monitor health status during the course of the study. All study data collected were treated as confidential and kept securely. Study data were anonymised and participants were identified by an allocated study number.
Box 4: Data collection Schedule

<table>
<thead>
<tr>
<th>Demographic Data</th>
<th>Measure</th>
<th>Baseline</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender &amp; Age</td>
<td>Self-report</td>
<td>X</td>
<td>NA</td>
</tr>
<tr>
<td>Medical History</td>
<td>Self-report</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medication History</td>
<td>Self-report/GP database</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Measure</th>
<th>Baseline</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication Adherence to Statins</td>
<td>Urine test</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>Measure</th>
<th>Baseline</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD Risk Score (%)</td>
<td>QRISK®2 Calculator</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>TC; HDL; TC:HDL (mmol/L)</td>
<td>Blood sample</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>OMRON® Monitor</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Height (cm) &amp; weight (kg)</td>
<td>X (height &amp; weight)</td>
<td>X (weight only)</td>
</tr>
<tr>
<td>Smoking History</td>
<td>Self-report using QRISK®2 format</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Self-report: 15D (a generic, comprehensive, 15-dimensional, standardized measure of health-related quality of life) [40]</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Health Status</td>
<td>Self-report: EQ5D Questionnaire (a standardized, instrument for measuring generic health status)[41]</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>Self-report: International Physical Activity Questionnaire (short form) [42]</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Patient Activation</td>
<td>Self-report: Patient Activation Measure (a valid and reliable scale that reflects a developmental model of an individual’s readiness for health behaviour change) [43]</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medication/Health Beliefs</td>
<td>Self-report: Beliefs about Medicines Questionnaire (BMQ)[44] and the Brief Illness Perception Questionnaire (IPQ) [45]</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medication Adherence to Statins</td>
<td>Self-report: Morisky 8-item Medication Adherence Scale[37]</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Supporting Outcomes</th>
<th>Measurement</th>
<th>Duration of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription History</td>
<td>Record of repeat prescription issues for statins &amp; antihypertensives (if applicable) from the GP database</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>Self-report/observed from GP database</td>
<td>X</td>
</tr>
</tbody>
</table>
**Process Outcomes**

Process outcomes relating to participant acceptability and fidelity of the education intervention were also collected. Feedback data from evaluation forms, given out following the end of the education sessions, will be used to assess participant acceptability in conjunction with retention rates for the two sessions. Also, three sessions were filmed, with participants’ permission, to assess the fidelity of the delivered education sessions. Logs were kept to record the initiation, delivery and any terminations of text messages, and all made attempts at follow up support phone calls were recorded.

**Cost-Effectiveness Outcomes**

The protocol has been reviewed by a health economist to seek advice on cost effectiveness measures. If the intervention proves to be effective, additional funding will be sought to carry out a full cost effectiveness analysis.

**Sample Size**

The primary outcome measure is medication adherence to statins at 12 months. The sample size calculation has been based on the percentage of non-adherers using data from the INTERACT study.[31] To detect a difference in the proportion of medication adherers- of 16 percentage-points in the intervention group at 12 months compared to the ‘usual care’ control group (74% compared to 91%)- we required 84 participants per group, with 80% power and 5% significance. After allowing for a 20% dropout, 105 participants were required per group, making 210 participants in total. This minimum difference is based on a similar 16 percentage-point increase in adherence to cardiovascular preventative treatment observed in the INTERACT study [31] which used text messaging as the sole intervention. This was a six month follow-up study with a final control group adherence of 75%. We envisage similar adherence to medication at 12 months follow-up, following a multi-faceted intervention with continued follow-up support via text messaging and phone calls to sustain any initial intervention effect.

**Statistical Methods**

Baseline characteristics of the two groups will be summarised with means, standard deviations (SD), medians and ranges for continuous variables, and counts and percentages for categorical variables. Logistic regression will be used to assess the difference in medication adherence by group, adjusted for the stratification factors (sex and age) at 12 months. The primary outcome will be assessed at the 5% level with 95% CI. The primary analysis at 12 months will be based on complete data. The analysis of the secondary outcomes will be conducted in a similar manner using the appropriate model type: logistic regression for binary outcomes, linear for continuous and ordinal for ordinal outcomes.

Sensitivity analyses will be carried out on an intention-to-treat basis and a per-protocol basis to examine robustness of conclusions for missing data and attendance of the programme. To adhere to the intention-to-treat principle, missing outcome data will be imputed using multiple imputation. The imputation will be carried out using the command MI in Stata. We will also conduct analysis by adding the Morisky scale adherence data where urine adherence data are missing.
Ethics and Dissemination
The results of this study will be disseminated via the usual scientific forums: peer-reviewed publications and presentations at international conferences. At the local level, key stakeholders will be informed of the findings. The study has been administered by the Leicester Diabetes Centre, and is overseen by the NIHR Collaboration for Leadership in Applied Health Research and Care East Midlands (CLAHRC EM) Scientific Committee. Ethics approval was obtained from the NHS Health Research Authority East Midlands - Leicester South Research Ethics Committee (15/EM/0472) prior to the commencement of the study.

Results
Recruitment took place from May 2015 to March 2017 and a total of 212 participants have been enrolled and randomised. Follow-up clinic data collection finished in April 2018 and the analysis of the results will commence once all data has been collected and verified.

Discussion
This study aims to identify a potentially clinically useful and effective educational intervention to improve medication adherence to cardiovascular medications, for the primary prevention of CVD, to be delivered as an adjunct to primary care.

A recent systematic review looking at interventions to improve adherence to statin medication highlighted that multi-faceted interventions had small, positive effects on adherence but more methodologically rigorous trials are needed[46]. The 3R Study has followed CONSORT guidance [22,23]to ensure rigorous methods are used.

The 3R educational intervention was robustly developed in line with the MRC guidelines for complex interventions.[24,25] Moreover, a taxonomy of behaviour change techniques [28] was used to identify the key active components to ensure more precise reporting of the intervention and to aid future research in this field. Due to the complexity of the 3R intervention, there will have been unavoidable variations in how the intervention was delivered, such as the use of different facilitators and venue settings; however, all components of the intervention are monitored to ensure that, as far as possible, the intervention is delivered as per protocol. Process outcomes relating to patient acceptability and feasibility of the intervention have been addressed and a cost-effectiveness analysis will be carried out if the study proves successful.

Medication adherence is a challenging primary outcome to measure as no ‘gold standard’ measure exists. In the 3R Study, we have addressed this challenge by using a new and novel biochemical urine test as the primary measure [36]. Although this is an objective measure, it is essentially a ‘spot-check’ of medication adherence to statins, and, also, there is a bias as participants have to be informed that their urine is being tested for statins. Therefore, we have also used a self-reported validated questionnaire (the Morisky Scale) [37] and repeat prescription history as supporting outcome measures.

If successful, it is hoped that the 3R Education Programme can be implemented within the primary care framework to improve medication adherence to statins and other CVD medications, and to provide better support for GPs and people at risk of CVD.
Amendments
Significant changes to the original protocol:

- The original time windows for conducting follow-up phone calls were revised as these were too restrictive and not practical.
- The primary outcome measure was changed to the objective-based urine measure from the Morisky self-reported questionnaire measure. This was done following additional validation data for the urine measure which was not available at the start of the study.

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The TEXTME© Message Bank was developed and validated by the George Institute and was used under licence.

Conflicts of Interest
PG and PP were involved in the development of the urine assay test for the detection of statins and antihypertensives medications.

Abbreviations
3R Study Ready to Reduce Risk Study
AHA American Heart Association
BCT behavioural control technique
BHF British Heart Foundation
BMI body mass index
BMQ Beliefs about Medicines Questionnaire
BP blood pressure
CI confidence interval
CLARHC EM Collaboration for Leadership in Applied Health Research and Care East Midlands
COM-B Capability, Opportunity and Motivation
CONSORT Consolidated Standards of Reporting Trials
CVD cardiovascular disease
ESC European Society of Cardiology
Authors’ Contributions
KK conceived the original idea and is the chief investigator; KK, SR, LG, JB, HD led the overall design of the RCT; YD was responsible for the development of the intervention; JB drafted the manuscript; and all other authors (KK, SR, LG, HD, GW, PP, PG & MD) helped edit and review the manuscript.

Multimedia Appendix
Appendix 1: Checklist of items for reporting pragmatic trials
Appendix 2: Consort-Ehealth Checklist v1-6
References


