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Strategies for identifying familial hypercholesterolaemia in non-specialist clinical settings (Protocol)

Qureshi N, Weng SF, Tranter JA, Da Silva ML, Kai J, Leonardi-Bee J

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[Intervention Protocol]

Strategies for identifying familial hypercholesterolaemia in non-specialist clinical settings

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The purpose of this review is to assess the effectiveness of interventions to systematically improve identification of FH in non-specialist settings compared to usual care (incidental approaches to identify FH in non-specialist settings).

BACKGROUND

Description of the condition

Familial hypercholesterolaemia (FH) is an autosomal-dominant disease and has long been recognized as a cause of premature coronary heart disease (CHD) (Nordestgaard 2013). In the majority of people with FH, the disorder is caused by a mutation of the low-density lipoprotein (LDL) receptor gene which impairs the proper function of the receptor, thus resulting in very high levels of plasma cholesterol. This leads to early onset atherosclerosis, causing excess morbidity and mortality from CHD (Goldstein 1995). The majority of people have the heterozygous form of FH (Baumer 2009) with an estimated one in 500 people affected (Foody 2014). However, more contemporary data suggest that prevalence may be as high as one in 200, with over 30 million individuals affected worldwide (Benn 2012; Nordestgaard 2013; Weigman 2015). Based on predicted prevalence and the number of people currently diagnosed, it is reported that the majority of affected individuals remain undiagnosed (Demott 2008). The importance of early identification is to allow treatment prior to the appearance of CHD symptoms, since affected individuals have an estimated 100 fold-increase in CHD mortality compared to unaffected adults (Demott 2008; Nordestgaard 2013). It is estimated that half of the men with heterozygote FH will have developed CHD by 55 years of age and one third of women by 60 years of age (Marks 2003).

Several national guidelines on identifying and managing FH have been published (Goldberg 2011; Haralambos 2016; Harada-Shiba 2012; Hata 2002; Knowles 2015; NICE 2008; Nordestgaard 2013; Simon Broome Register Group 1991; Sullivan 2013; Williams 1993). In these guidelines confirmation of FH diagnoses involves assessment against one or more specified diagnostic criteria. These diagnostic criteria include:

- Simon Broome criteria (Simon Broome Register Group 1991). The criteria identify individuals with possible or definite FH as adults with total cholesterol > 7.5 mmol/L (LDL > 4.9 mmol/L) or children (less than 16 years of age) with total cholesterol over 6.7 mmol/L (LDL > 4.0 mmol/L), combined with a family history of premature heart disease or raised cholesterol or presence of tendinous xanthomata (or a combination of these) (NICE 2008; Qureshi 2009). This has been adopted in England and Wales following recommendations by the National Institute for Health and Care Excellence (NICE), following a review of non-randomised studies (NICE 2017).

- US MedPed criteria (Williams 1993). These use age-specific total cholesterol thresholds only and do not incorporate family history or clinical signs during an examination (Watts 2015).

- Dutch Lipid Clinic Network (DLCN) criteria (Defesche 2004; Reiner 2011; Watts 2011). In Europe, the European Atherosclerosis Society and the European Society of Cardiology recommend using the DLCN criteria (Reiner 2015; Nordestgaard 2013). The DLCN criteria combine five domains: family history, clinical history, physical examination (presence of tendinous xanthomata or arcus cornealis (or both)) and LDL-cholesterol levels. A scoring system then identifies individuals with a diagnosis of possible, probable or definite FH based on a scoring criteria (Austin 2004; Haase 2012; Nordestgaard 2013; Watts 2011).

- Wales has adopted a modified version of the DLCN criteria that includes triglyceride concentrations (Haralambos 2016).

- Japanese criteria (Harada-Shiba 2012). These criteria combine LDL levels (180 mg/dL or more), physical examination (presence of tendinous xanthoma or nodule xanthoma and family history (relatives in the 2nd degree) of FH or premature CAD (males younger than 55 years and females younger than 65 years). Individuals meeting two criteria are regarded as having FH, with the recommendation for further genetic testing. These supersede previous guidelines developed by the Japanese Atherosclerosis Society (Hata 2002).

Furthermore, most guidelines recommend that once individuals with FH have been diagnosed, they commence high-intensity statin therapy and identify other relatives with the condition (Goldberg 2011; Gidding 2015; NICE 2017; Nordestgaard 2013; Sullivan 2013).
Considering the possible assessment and referral pathway, individuals are initially assessed in primary care or another non-specialist setting. Primary care and non-specialist centres could be a general or family practice, an ambulatory or outpatient care centre, or a community health centre. Subsequent referral may occur to a specialist, such as lipidologists, endocrinologists, cardiologists, clinical nurse specialists or geneticists, depending on the organisational infrastructure. The specialist would then confirm the diagnosis (including, in many cases, genetic testing), initiate management and offer cascade screening to other relatives (Bell 2012; Bell 2013; Troeung 2016).

Description of the intervention

In non-specialised settings, the incidental identification of those who may be at risk of FH (usual care) may include the following strategies:

- assessment of FH opportunistically during an unrelated clinical consultation;
- assessment of FH as part of a routine health check or health screen;·
- assessment of FH when an individual raises concerns about their cholesterol or family history of heart disease.

However, FH remains under diagnosed and under treated, with up to 80% of individuals affected and resulting in major lost opportunities to prevent premature heart disease (Nordestgaard 2013; Qureshi 2009).
It has been suggested that a more systematic approach may help to identify more individuals in the non-specialist setting (Gidding 2015; Reiner 2015; Vallejo-Vaz 2015). These interventions could include: prospective population screening (Wald 2016); retrospective searches of health records (Gray 2008); proactive computer-generated reminders (Qureshi 2016); case-finding by health care practitioners and review of patient records (Green 2015); and pathology laboratories reporting back clinicians about patients who might have FH (Troeung 2016).

How the intervention might work

Prospective population screening programmes have been a successful strategy to target specific demographics of the population more likely to have a condition. For example, the UK National Health Service faecal occult blood test screening program for early detection of colorectal cancer targets the population by age (those aged 60 to 74 years) and has led to a 16% reduction in colorectal cancer mortality (Hewitson 2007).
Systematic searching of medical records (either manually or electronically) or pathology laboratory databases (Bell 2012; Gray 2008; Green 2015; Kirke 2015; Weng 2015) could identify individuals with relevant risk factors for FH, such as a history of raised cholesterol, premature heart disease, significant family history of CHD, and clinical signs.
An alert could be added to the medical records of individuals at risk to remind their doctor to check their cholesterol level. These reminders are an example of changing clinician behaviour using antecedent cues (Michie 2004). Agreement could be reached with local pathology laboratories contacting the primary care physician by telephone when a very high cholesterol result is processed (Bell 2014).

Why it is important to do this review

The WHO recognises the need to prevent and control cardiovascular disease (CVD), and that managing raised lipids is a key modifiable risk factor (WHO 2011). Internationally, it is recognised that a universal targeted approach to identify and manage heterozygote FH is a key priority to prevent CVD (Benn 2012; Nordestgaard 2013; Reiner 2015; Robinson 2013; Watts 2015). For successful identification of FH, case finding needs to extend beyond the specialist lipid clinic to non-specialists in primary care (NICE 2008) and other community non-health settings, such as occupational health services (Kirke 2015).

For people who are affected by FH, there is strong evidence for the benefits of early identification and treatment (Demott 2008; Marks 2003; NICE 2017). High-intensity lipid-lowering treatment is very effective with a 44% reduction in CHD mortality (Besseling 2016). However, evidence-based approaches to support guideline implementation are under developed (Grimshaw 1993; Michie 2004). Improving the current low detection rate of FH is urgently needed.

Moreover, identification of index cases will lead to the detection of affected but asymptomatic relatives, especially those at a younger age, resulting in early initiation of statin treatment to lower cholesterol with the recognised reduction in premature mortality, and long-term morbidity. As 50% of first degree relatives of people with confirmed FH will also have the condition, cascade screening by specialists has been shown to be a cost-effective approach (Marks 2003; Nherera 2011). This has also improved quality of life in those family members identified (van Maarle 2003).

To overcome existing gaps in care and reduce the preventable global burden of disease arising from FH, dissemination of current evidence to healthcare providers and policy makers is needed. This can inform the development of the most effective evidence-based guidelines to deliver optimal care for people with FH, thus enabling clinicians to expedite diagnosis and initiate effective treatment. Evidence on which strategies are effective for improving identification of FH is needed in order to prioritise primary healthcare resources and target those individuals at greater risk of developing premature CHD.

The review may also provide an exemplar for improving identification of other common monogenic disorders in the non-specialist primary care setting. Furthermore, the evidence may provide generic findings relevant to developing other pertinent interventions in this context.

OBJECTIVES

The purpose of this review is to assess the effectiveness of interventions to systematically improve identification of FH in non-specialist settings compared to usual care (incidental approaches to identify FH in non-specialist settings).

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs), cluster-RCTs and non-randomised study interventions (NRSI). Eligible NRSI are non-randomised controlled trials, prospective cohort studies, before-and-after studies, and interrupted-time-series (ITS) studies.

Due to the complex nature of the intervention and setting, we have included NRSI as we anticipate potential limitations in the availability of RCTs. NRSI evidence may highlight the need for research for high-quality RCTs. In addition, NRSI may yield evidence on outcomes for important study processes such as referrals or longer-term coronary outcomes which are unlikely to be available from RCTs.

Types of participants

Eligible participants of any age from the general population who access non-specialist clinical settings and other non-clinical community settings. Participants who are selected from specialist settings with expertise in lipid disorders will be excluded from the review. Participants who have a previous diagnosis of FH or other inherited lipid disorders will also be excluded. If the study contains both eligible and ineligible participants, the study will be included if the data on eligible participants can be extracted where at least 70% of the study contains eligible participants.

Definition of term 'non-specialist' can be found in an appendix (Appendix 1)

Types of interventions

Interventions that aim to systematically identify people with possible or definite FH, in non-specialist clinical settings in primary care and other community settings. Interventions which involve specialists delivering the interventions in a non-specialist setting (e.g. FH nurse specialists performing case findings) are also appropriate for inclusion.

A systematic intervention for identifying FH is defined as:

- prospective general population screening for FH using diagnostic criteria;
- retrospective electronic and manual health records search for participants who might have FH (i.e. based on elevated cholesterol levels, relevant family history, clinical characteristics, or combination of these factors);
- proactive computer-generated reminders for participants who might have FH (i.e. based on elevated cholesterol levels, past medical history, relevant family history, clinical characteristics, or combination of these factors);

- population based case-finding activities (i.e. healthcare practitioner reviewing patient records and contacting individuals; pathology laboratories reporting back high cholesterol levels).

These systematic strategies to identify individuals with possible or definite FH, will be compared with usual care, where participants will continue to receive their standard or current medical care (Reeves 2016). In this situation, usual care for FH identification in non-specialist primary care practice will be incidental and non-systematic during routine consultation with patients. This includes noting a raised cholesterol during consultation with individuals presenting with concerns about their personal or family history. Should usual care vary between geographical settings, a description of such will be provided.
Where possible, we will compare interventions to each other if the usual care strategies are similar between or within the studies.

Types of outcome measures

Primary outcomes

1. Diagnosis of definite FH at the end of study follow-up, defined by a positive genetic mutation test or clinical phenotype typical of FH (as defined by diagnostic criteria)
2. Diagnosis of possible and probable FH (as defined by diagnostic criteria) at the end of study follow-up
3. Adverse events at the end of study follow-up (e.g. drug adverse events, hospitalisations, all-cause mortality)

Definition of the terms definite FH and possible FH can be found in an appendix (Appendix 1).

Secondary outcomes

1. Cholesterol levels in participants diagnosed with FH (total cholesterol, LDL cholesterol) at the end of study follow-up, and from the date of FH diagnosis
2. Cardiovascular mortality and morbidity of FH participants at end of study follow-up (minimum of one year follow-up)
3. Lipid-lowering treatment prescribed to people with FH (including stratification of statin prescribing by high, medium, low potency at end of study)
4. Referral of FH participants at end of study follow-up to a specialist service
5. Adverse self-reported psychological effects at end of study follow-up (e.g. worry, anxiety, depression with a validated instrument)
6. Management errors (e.g. misdiagnosis, inappropriate statin prescribing, inappropriate referrals to specialists)

Where multiple measurements of the same outcome are reported at different follow-up times, we plan to report all measurements as per the categories below:

1. short-term (outcome reported closest to three months of end of study follow-up (range can include one to four months));
2. medium-term (outcome reported closest to six months of end of study follow-up (range can include five to nine months));
3. long-term (outcome reported closest to 12 months of end of study follow-up (range can include over 10 months)).

Search methods for identification of studies

We will search for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

We will identify relevant studies from the Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register using the term: hyperlipoproteinaemia.
The Inborn Errors of Metabolism Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated with each new issue of the Cochrane Library), and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS Inborn Error Review Series. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.
In addition to the above, we will conduct a search of the following databases combining free text terms and controlled vocabulary where applicable (Appendix 2):

- Cochrane Central Register of Controlled Trials (CENTRAL in the Cochrane Library (www.cochranelibrary.com) (all years);
- PubMed (Epub Ahead of print, In process & Other non-Indexed Citations only) (www.ncbi.nlm.nih.gov/pubmed) (1946 to present);
- MEDLINE (OvidSP, EpubAhead of Print, In-process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE) (1946 to present);
- Embase (OvidSP) (1974 to present);
- CINAHL (EBSCOHost) (1937 to present);
- ProQuest Dissertations & Theses Global ProQuest (www.proquest.com/) (1861 to present);
- Web of Science (CPCI-S) (1898 to present);
- SCOPUS (Elsevier) (1823 to present).

We will search the following trial databases and resources:

- ISRCTN registry (www.isrctn.com/) (all years);
- ClinicalTrials.gov (www.clinicaltrials.gov) (all years);
- WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp.en) (all years)

Searching other resources

Reference lists

We will check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant studies. We will contact the lead authors of the included studies to identify unpublished material and missing data or information regarding ongoing studies.

Handsearching

Search strategies for handsearching the following journals can be found in the appendices (Appendix 3).

- *Heart* (heart.bmj.com/) (all years)
- *Atherosclerosis* (www.atherosclerosis-journal.com/) (all years)
- *Journal of Clinical Lipidology* (www.lipidjournal.com/) (all years)
- *Current Opinion in Lipidology* (www.ovid.com/site/catalog/journals/439.jsp) (all years)
- *Journal of Inherited Metabolic Disease* (link.springer.com/journal/10545) (all years)

In addition, we will search the following prospective publication databases.

- HEART UK (heartuk.org.uk) (All years)
- the FH Foundation (thefhfoundation.org/) (all years)

We will also search the following relevant guideline developers.

- National Institute for Health and Care Excellence (www.nice.org.uk/ (all years)
- Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/) (all years)
- National Institute for Health and Care Excellence Clinical Knowledge Summaries (cks.nice.org.uk/) (all years)

We will also aim to identify any unpublished work by searching the abstract books of the following major cholesterol conferences.

- the Heart UK Annual Scientific Conference (heartuk.org.uk) (all years)
- the British Cardiovascular Society Conference (www.bcs.com) (all years)
- the European Atherosclerosis Society Conference (eas-society.org) (all years)

We will complement the searches by making contact with experts and researchers known to be active in the field in order to identify additional trials, including unpublished and ongoing studies.

Data collection and analysis

Selection of studies

We will select studies according to chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We will save the results from the searches in Endnote reference managing software (Endnote X5). Two authors (JT, MD) will independently screen the titles and abstracts of the identified studies to check for eligibility. We will then retrieve the full texts (were available) of the potentially eligible studies and two authors (JT, MD) will independently screen these. We will resolve any disagreements through discussion, or where necessary, with the assistance of a third author (JLB).

To guard against potential duplicate publication, we will link multiple reports using the same study participants. If any uncertainties arise concerning study eligibility for the review, we will correspond with the investigators of the study in question. If it is not possible to resolve any disagreements on whether to include a study without obtaining further information, we will categorize the study in the review as 'awaiting assessment' until the additional information is obtained from the study authors.

We will record details of studies excluded at the full text stage together with reasons for exclusion based on the inclusion criteria for the review.

Data extraction and management

Two authors will independently extract and record data from included studies following guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will use standard data extraction forms, based on the checklist from the Cystic Fibrosis and Genetics Disorders Group, which we will modify to allow relevant data to be captured from all the study designs which are eligible for inclusion in this review. Where possible we will pre-pilot the modified version of the data extraction form with a minimum of three studies with different study designs.

The data extraction form will include study characteristics such as study methodology, participant characteristics (including ethnic or cultural characteristics, geographical location), sample size, strategies and characteristics (including process and duration of intervention), primary and secondary outcome measures, FH diagnostic criteria and definitions of other outcomes, and analysis performed in the original trials.

For NRSI, we will extract additional data on confounding factors, the comparability of groups on confounding factors, methods used to control for confounding and on multiple effect estimates (both unadjusted and adjusted estimates) (Reeves 2011). Confounding factors need to be associated with both the intervention and the outcomes, thus are unlikely to be participant-level factors but population- or service-level factors. These may include, but are not limited to:

- type of health professional(s) delivering the intervention;
- size of the population being assessed;
- workload of the health professional(s)

We plan to resolve any discrepancies in data extraction through

discussion, or where necessary, through arbitration with a third author (JLB). One author (JT) will enter data into the Review Manager Software and a second author (SW) will verify the data (RevMan 2014).

Assessment of risk of bias in included studies

For all studies, two review authors (NQ and SW) will independently assess the risk of bias for each study; and if there is a disagreement, a third author (JLB) will check each assessment and discuss the outcome until consensus is achieved.

For RCTs, we will assess the risk of bias using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* according to the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other sources of bias (Higgins 2011c).

For NRSI, we will assess risk of bias for each outcome of interest in the study using the ROBINS-I tool developed by the Cochrane Non-Randomised Studies Methods Group (Sterne 2016). The tool considers seven domains: two domains of bias pre-intervention (bias due to confounding and bias in selection of participants into the study); one domain of bias at intervention (bias in the measurement of interventions); and four domains of bias post-intervention (bias due to departures from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result).

The authors will grade the methods used in each included study as either a high, low or unclear risk of bias. We will record all judgements in the 'Risk of bias' tables, together with the characteristics of each included study and we will prepare a 'Risk of bias' summary figure. We will contact relevant authors of studies published within the past 10 years for missing information or when further clarification is needed. We will document the outcomes of the correspondence in the review.

Measures of treatment effect

Where possible, we will report dichotomous outcomes using risk ratios (RR) together with 95% confidence intervals (95% CIs). For studies which have used randomisation, we will extract 2x2 data and estimate crude RRs; however, for studies without randomisation, we will extract RRs which have been adjusted for baseline differences or the ratio of the RR post-intervention compared to the RR for pre-intervention. Where studies report other adjusted measures of effect, e.g. odds ratios, we will extract these and report them separately.

Where possible, we will report continuous outcomes using mean differences (MD) together with 95% CIs. For studies which have used randomisation, we will extract raw data and estimate crude MDs; however, for studies without randomisation, we will extract MDs for the absolute change or the relative change, which have been adjusted for baseline differences.

For studies with a non-randomised study design, we will consider additional analysis on adjusting for baseline group differences, with appropriate regression analysis based on the form of the outcome variables (continuous or binary).

For studies which have used an ITS design, we will extract quantitative results from either a regression analysis with time trends before and after the intervention, adjusted for autocorrelation and any periodic changes, or from an ARIMA analysis. We will present the results for the outcomes as the change in level (immediate effect of the intervention) and the change in slope (longer-term effect of the intervention). If the results from a study using an ITS design are only reported as data points in a scanable graph or in a table, we will attempt to re-analyse the data by contacting study authors for permission to use their raw study data (Ramsay 2003).

Unit of analysis issues

We will consider whether any unit of analysis errors are made in the reported analysis for each study. For cluster-randomised studies, where the analysis may not adjust for the effect of clustering, if we identify a unit-of-analysis issue, we will attempt to correct the analysis by re-analysing the presented data. Or if there is insufficient information presented, we will contact the authors to obtain the necessary information or raw data. If we are not able to re-analyse the data taking into account clustering, we will report the uncorrected estimates without a measure of uncertainty (e.g. 95% CI).

For studies that have accounted for repeated measures we will report their study measures.

Dealing with missing data

Where important data are missing (e.g. standard deviations), we will contact the authors of studies published less than 10 years ago to request additional data. Where we are unable to retrieve missing data, we will conduct a sensitivity analysis to compare study outcomes grouped by how much data are missing: large amount (more than 30%); moderate amount (10% to 30%); low amount (less than 10%). We will then discuss the potential impact of the missing data on the findings of the review.

Assessment of heterogeneity

Clinical heterogeneity

We will consider clinical heterogeneity which can result from differences between studies in the characteristics of the populations, interventions and outcomes. We will fully discuss the influence of clinical heterogeneity on the observed effects.

Methodological heterogeneity

It is likely that we will identify heterogeneity as a result of bias from the different study designs included in the review. We will fully discuss the influence of methodological heterogeneity on the observed effects.

Statistical heterogeneity

We will quantify the proportion of variation in the meta-analyses due to clinical and methodological heterogeneity using I^2 (Higgins 2002). We will also visually examine the inconsistency of the 95% CIs within each meta-analysis. We will describe the proportion of variability due to heterogeneity using the following values described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d):

- 0% to 40%: might not be important;
- 30% to 60% may represent substantial heterogeneity;
- 75% to 100% considerable heterogeneity.

Due to the different designs of the included studies, we anticipate that we will identify moderate to high levels of heterogeneity within each meta-analysis; therefore, we will conduct a thorough examination of the heterogeneity to try to describe reasons for its presence.

Assessment of reporting biases

Where the meta-analyses contains more than 10 studies, funnel plots will be used to assess the potential effects of reporting biases. Where funnel plot asymmetry is apparent, the review authors will consider possible sources of asymmetry other than publication bias, for example based on domains of methodological quality, and conduct appropriate sensitivity analyses.

Data synthesis

We will initially summarise all included studies using narrative synthesis methods. This will involve the use of narrative text and tables to summarise data based on the type of intervention and according to setting, consider outcomes in the light of differences in study designs and address potential sources of bias, potential confounding factors and any further methodological limitations for each of the studies being reviewed, including how these may have impacted on the study findings. We will then provide a synthesised summary of the studies, including the range and size of any reported associations and important study characteristics.
Meta-analysis for RCTs and NRSI will be conducted separately. We will use random-effects models to conduct meta-analyses due to anticipated differences in the effectiveness of the intervention by type of intervention, setting, and populations.
We will be perform meta-analysis using the Review Manager (RevMan) software (RevMan 2014) or Stata version 14 (STATA 2015).

Subgroup analysis and investigation of heterogeneity

In each meta-analysis including at least five studies, the authors will perform subgroup analyses based on study-level variables, and will report a P value relating to the statistical test for differences between subgroups, where appropriate. We will consider the following characteristics:

- mode of diagnosis for FH (genetic or clinical);
- age of participant (under 10 years of age or 10 years of age and above);
- type of systematic intervention (prospective population screen, retrospective computer search, proactive computer reminders, population-based case finding);
- type of setting (primary medical care, employer-based clinics, community pharmacists).

We will undertake subgroup analyses using RevMan (RevMan 2014) or Stata version 14 (STATA 2015). We anticipate that due to the complexity of the intervention that most studies will include complex interventions and therefore we will group studies primarily based on similarities between outcome measures.

Sensitivity analysis

We will assess the impact of methodological quality on the results of the meta-analyses by re-analysing only those studies with a overall low risk of bias. We will compare the pooled effect size from this secondary analyses to the pooled effect size from the original analyses. We will report sensitivity analyses in table format within this review.

Summary of findings tables

The review authors will create 'summary of findings' table following the GRADE approach suggested in the *Cochrane Handbook for Systematic Review of Interventions* (Schünemann 2011a). This will state the participant population setting, intervention, comparison, and main outcome measures. In addition, the tables will present the quality rating of the evidence as 'high', 'moderate', 'low', or 'very low' using the following five GRADE considerations:

- risk of bias (serious or very serious);
- inconsistency (serious or very serious);
- indirectness (serious or very serious);
- imprecision (serious or very serious);
- publication bias (likely or very likely).

For NRSI we will also consider the following factors:

- size of effect (large or very large);
- confounding (either reduces the demonstrated effect or increases the effect if no effect was observed (yes or no)).

In GRADE, we will rate NRSI initially as low quality and downgrade or upgrade according to GRADE guidelines, if appropriate. We will present outcomes for these studies in separate tables from outcomes for the results of RCTs.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Glossary of terms

Term	Definition
Definite FH (Simon Broome criteria)	Adult = total cholesterol levels > 290 mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L) Child less than 16 years of age = total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L) Plus at least one of the two: 1. plus physical finding = tendinous xanthomas, or tendinous xanthomas in first or second-degree relative OR 2. DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation
Non-specialist	a person who is not an expert or does not have specialist subject knowledge
Possible FH (Simon Broome criteria)	Adult = total cholesterol levels > 290 mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L) Child = less than 16 years of age = total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L) Plus at least one of the two: 1. family history of at least one of the following: - myocardial infarction at 60 years or younger in first-degree relative OR - myocardial infarction at 50 years or younger in second-degree relative

(*Continued*)

	OR 2. family history of elevated total cholesterol: - > 290 mg/dL (7.5 mmol/L) in adult first- or second-degree relative OR - > 260 mg/dL (6.7 mmol/L) in child, brother or sister aged younger than 16 years

Appendix 2. Search methods - electronic searching

Database	Resource	Search dates	Strategy
CENTRAL, the Cochrane Library	**via the Cochrane Library:** (www.cochranelibrary.com/)	(All years)	#1.Hyperlipoproteinemia Type II [MeSH descriptor] #2. familial hypercholesterolaemia:ti,ab #3. Hyperlipoproteinemias [MeSH descriptor] #4. "hyperlipoproteinemia type IIb" #5. "hyperlipoproteinemia type 2 ti,ab" #6. "hyperlipoproteinemia type 2b ti,ab" #7. "hyperlipoproteinemia type 2a" #8. "hyperlipoproteinemia type IIa" #9. "Hyperlipidemia, Familial Combined" [MeSH descriptor] #10. "Hyperlipoproteinemia Type I" [MeSH descriptor] #11. " Hyperlipoproteinemia Type IV" [MeSH descriptor] #12. "lipoprotein lipase deficiency" #13. "inherited hypercholesterolaemia" #14. "inherited hypercholesterolemia" #15. "familial hyperchylomicron" #16 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
PubMed	(www.ncbi.nlm.nih.gov/pubmed)	(1946 to present)	#1.hypercholesterol*[Title/Abstract] #2.hyperlipoprotein* [Title Abstract] #3.familial hypercholesterolemia [Title Abstract] #4. familial hypercholesterolaemia [Title Abstract] #5. familial hyperlipoproteinemia (Title Abstract] #6. familial hyperlipoproteinaemia (Title Abstract] #7. familial hypercholesterolemia with hyperlipidemias [Title Abstract]

(*Continued*)

			#8. familial combined hyperlipidemia [Title Abstract] #9. hypertriglyceridemia, familial [Title Abstract] #10. hypertrigly* [Title Abstract] #11. hyperlipoproteinemia TYPE 2 [Title Abstract] #12. hyperlipoproteinemia TYPE 2A [Title Abstract] #13. hyperlipoproteinemia TYPE 2B [Title Abstract] #14. hyperlipoproteinaemia TYPE 2 [Title Abstract] #15. hyperlipoproteinaemia TYPE 2A [Title Abstract] #16. hyperlipoproteinaemia TYPE 2B [Title Abstract] #17. combined hyperlipidemia, familial [Title Abstract] #18. familial lipoprotein lipase deficiency [Title Abstract] #19.autosomal dominant hypercholesterolemia [Title Abstract] #20. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or#19) #21. general practice [Title Abstract] #22. primary health care [Title Abstract] #23. general Practitioner [Title Abstract] #24. GP [Title Abstract] #25. community [Title Abstract] #26. (#21 or #22 or #23 or #24 or #25) #27. detect* [Title Abstract] #28. diagnosis [Title Abstract] #29. diagnose* (Title Abstract] #30. laborator* [Title Abstract] #31. patholog* [Title Abstract] #32. database [Title Abstract] #33. record [Title Abstract] #34. screen* [Title Abstract] #35. mass screen [Title Abstract] #36. family [Title Abstract] #37. familial [Title Abstract] #38. audit [Title Abstract] #39. (#27 or #28 or #29 or #30 or #31 or # 32 or #33 or #34 or#35 or #36 or #37 or # 38) #40.(#20 and #26 and #39)

(*Continued*)

MEDLINE	**(OvidSP)**	(1946 to present)	1.((familial or inherited) adj2 hypercholesterol?emia$).tw. 2. Hyperlipoproteinemia Type II/ 3. (Hyperlipoprotein?emia$ adj (type II or type IIa or type IIb or type 2 or type 2a or type 2b)).tw 4. 1 or 2 or 3 5. general practice$.tw. 6. GP.tw. 7. (primary adj (health or care)).tw. 8. ((family or community) adj (medicine or practice)).tw. 9. Primary Health Care/ 10. exp General Practice/ 11. 5 or 6 or 7 or 8 or 9 or 10 12. ((((medical or health or patient$ or electronic) and record$ or database$ or data or audit or reminder$ or tool$)) or (diagnos$ or identif$ or detect$)).tw 13. 11 and 12 14. laborator$.tw. 15. Laboratories/ 16. pathолog$.tw. 17. Pathology/or Pathology, Clinical/ 18. 14 or 15 or 16 or 17 19. (record$ or database$ or data or audit or tool$ or daignos$ or identif$ or detetct$).tw 20. 18 and 19 21. screen .tw. 22. mass screening/ 23. 21 or 22 24. 23 and (11 or 18) 25. ((family or relative$) and test$).tw. 26. 13 or 20 or 24 or 25 27. 4 and 26
Embase	**(Ovid SP)**	(1974 to present)	1. HYPERLIPOPROTEINEMIA/ 2. Hypercholesterolaemia.mp. 3. Hypercholesterolaemia.tw. 4. Hyperlipoproteinemia.mp 5. hyperlipoproteinemia.tw. 6. familial hypercholesterolaemia/ 7. hypertriglycer$.tw. 8. hyperlipid$.tw. 9. lipoprotein lipase deficienc$.tw. 10. hyperlipoproteinemia Type 2.tw. 11. autosomal dominant hypercholesterol$.tw.

(*Continued*)

			12. familial hypertriglyceridemia$.tw. 13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 14. general practice.tw. 15. GP.tw. 16. primary health care.tw. 17. community.tw. 18. 14 or 15 or 16 or 17 19. laboratory.tw. 20. laboratories.tw. 21. screen.tw. 22. mass screening.tw. 23. detection.tw. 24. audit.tw. 25. record.tw. 26. 19 or 20 or 21 or 22 or 23 or 24 or 25 29 13 and 18 and 26
CINAHL	**(EBSCOHost)**	(1937 to present)	S1(MH "familial hypercholesterolemia" OR MH "hypertriglyceridemia" OR MH "hyperlipidemia" OR MH "hyperlipoproteinemia") S2 (TI "clinic" OR TI "clinical practice" OR TI "general practice" OR TI "gp" OR TI "general practitioner" OR TI "community" OR TI "primary care" OR TI "primary health care" OR TI "primary healthcare") S3 (TI "detection" OR TI "database" OR TI "laboratory" OR TI "audit" OR TI "screening" OR TI "mass screening" OR TI "records" OR TI "identification" OR TI "identity") S4 S1 AND S2 AND S3
ProQuest Dissertations & Theses	**(**www.proquest.com/**)**	(1861 to present)	ti(familial hypertriglyceridemia) OR ti(hypercholesteremia) OR ti(hyperlipidemia) OR ti(familial combined hyperlipidemia) AND ti(mass screening) OR ti(audit) OR ti (diagnosis) OR ti(identifying) OR ti(identify risk) OR ti(database) OR ti(detection) AND ti(general practice) OR ti(general practitioners) OR ti(clinical practice) OR ti(primary care) OR ti(primary health care) OR ti(community)
WEB OF SCIENCE	**(CPCI-S)**	(1898 to present)	#1 TS=((familial hypercholesterolaemia) OR TS=(familial hypercholesterolemia) OR TS= (hyperlipidaemia) OR TS= (hyperlipidemia) OR TS= (familial combined hyperlipidaemia) OR TS= (familial combined hyper-

(*Continued*)

			lipidemia) OR TS= (hyperlipoproteinaemia) OR TS= (hyperlipoproteinemia) Or TS=(familial hypertriglyceridemia) OR TS=(familial hypertriglyceridaemia)) #2 TI=((screen) OR TI =(mass screen) OR TI= (audit) OR TI= (detect*) OR TI= (identify) OR TI= (identification) OR TI= (record) OR TI= (diagnose) OR TI=(diagnosis)) #3 TI=((GP) OR TI= (general practice) OR TI = (general practitioner) OR TI=(primary health) OR TI= (primary health care) OR TI= (primary healthcare) OR TI = (laboratory) OR TI = (community)) #1 AND #2 AND #3
SCOPUS	**(Elsevier)**	(1823 to present)	familial PRE/1 hypercholesterolaemia OR hyperlipidemia OR hyperlipidaemia OR hyperlipoproteinemia OR hyperlipoproteinaemia OR hypertriglycerolaemia OR hypercholesterolaemia OR hypercholesterolemia AND mass PRE/1 screening OR diagnosis OR audit OR detect OR record OR database OR identify OR identification AND general practice OR general practitioner OR gp OR primary health care OR primary healthcare OR community OR laboratory OR clinic OR clinical practice
ISRCTN registry	(www.isrctn.com/)	(All years)	ADVANCED SEARCH *Search terms:* hypercholesterolaemia OR hypercholesterolemia OR hyperlipidemia OR Or hyperlipidaemia OR hyperlipoproteinaemia OR hyperlipoproteinemia OR hypertryglycerolaemia *Condition:* familial hypercholesterolaemia OR familial hypercholesterolemia
Clinical Trials.gov	(www.clinicaltrials.gov)	(All years)	ADVANCED SEARCH *Condition:* familial hypercholesterolemia *Study type:* All studies
WHO International Clinical Trials Registry Platform (ICTRP)	(www.who.int/ictrp.en)	(All years)	ADVANCED SEARCH Search 1: Title: hypercholesterolaemia AND Condition: familial hypercholesterolaemia Search 2: Title: hypercholesterolemia AND Condition: familial hypercholesterolemia

Appendix 3. Handsearching

Grey literature	Resource	Search dates	Strategy
HEART UK The FH Foundation	(heartuk.org.uk) (the fhfoundation.org/)	(All years)	familial hypercholesterolaemia OR familial hypercholesterolemia OR hyperlipidemia OR hyperlipidaemia OR inherited hypercholesterolaemia OR inherited hypercholesterolemia OR hyperlipoproteinaemia OR hyperlipoproteinemia
National Institute for Health and Care Excellence Scottish Intercollegiate Guidelines Network National Institute for Health and Care Excellence Clinical Knowledge Summaries	(www.nice.org.uk/) (www.sign.ac.uk) (cks.nice.org.uk/)	(All years)	familial hypercholesterolaemia OR familial hypercholesterolemia OR hyperlipidemia OR hyperlipidaemia OR inherited hypercholesterolaemia OR inherited hypercholesterolemia OR hyperlipoproteinaemia OR hyperlipoproteinemia
HEART UK Annual Scientific Conference(s) British Cardiovascular Society Conference(s) European Atherosclerosis Society Conference(s)	(heartuk.org.uk) (www.bcs.com) (www.eas-society.org)	(All years)	familial hypercholesterolaemia OR familial hypercholesterolemia OR hyperlipidemia OR hyperlipidaemia OR inherited hypercholesterolaemia OR inherited hypercholesterolemia OR hyperlipoproteinaemia OR hyperlipoproteinemia amilial hypercholesterolaemia OR autosomal dominant familial hypercholesterolemia
Jounals (reference lists): *Heart* *Atherosclerosis* *Journal of Clinical Lipidology* *Current Opinion in Lipidology* *Journal of Inherited Metabolic Disease*	(heart.bmj.com/) (www.atherosclerosis-journal.com) (www.lipidjournal.com/) (www.ovid.com/site/catlog/journals/439.jsp) (link.springer.com/journal/10545)	(All years)	familial hypercholesterolaemia OR familial hypercholesterolemia OR hyperlipidemia OR hyperlipidaemia OR inherited hypercholesterolaemia OR inherited hypercholesterolemia OR hyperlipoproteinaemia OR hyperlipoproteinemia

CONTRIBUTIONS OF AUTHORS

Roles and Responsibilities

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Review stage: (select studies for inclusion): NQ, JT, MD, J LB
Review stage: (data extraction): SW, JT, MD, J LB
Review stage: JT, MD (contact authors for additional information)
Review stage: (enter data into ReVMan) JT, SW
Review stage: (carry out analysis) NQ, SW, J LB
Review stage: (interpretation of data) NQ, SW, JK, J LB
Review stage: (writing the final review) NQ, JK, SW, J LB, JT, MD
Update stage: (update the review) NQ, SW, JT

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