## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Feasibility of Improving Identification of Familial Hypercholesterolaemia in General Practice: Intervention Development Study |
| **AUTHORS** | Qureshi, Nadeem; Weng, Stephen; Tranter, Jennifer; El-Kadiki, Alia; Kai, Joe |

## VERSION 1 - REVIEW

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| **REVIEWER** | Anthony Wierzbicki<br>Dept Metabolic Medicine/Chemical Pathology<br>Guy's & St Thomas Hospitals<br>London SE1 7EH, UK<br><br>Member ; NICE familial hypercholesterolaemia guidleien committee (CG71); Chair NICE Lipids & cardiovascular risk committee (CG181) |
| **REVIEW RETURNED** | 19-Mar-2016 |

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| **GENERAL COMMENTS** | This paper describes preliminary feasibility data for a trial to investigate strategies for idenifying patients in primary care with familial hypercholesterolaemia (FH). The study used 6 primary centres and potentially identified >800 patients with FH using a lipid criterion. However only 10-15% proceeded through the programme and only 7.5% were considered for referral for definitive diagnosis by secondary care. Clarification is required that genetic diagnosis was performed though it is implied in the wording.<br><br>Similarly FH is a disorder with lifelong choelsterol elevation. It is unclear how many patients more than one record of cholesterol measurement more than 1 or 5 years previously. Given the policy-bias (NHS health checks range 40-75) and female bias in recruitment ( see also Neil HA et al Int J Clin Pract 2008; 62: 1322 for general CVD screening) confounding by post-menopausal elevations in cholesterol is a common problem in FH screening yet this data is not provided.<br><br>The study involves the provision of training and support materials to primary care but the paper does not detail how much family history information was already available in the electronic care record (e..g family history of premature cardiovascular disease <60 years as per EMIS code) and how much of this was correct. This is a recurrent concern (see McManus RJ et al ; BMJ 324: 459 (2002)). Data is provided on post-study initiation screening for secondary factors (thyroid; diabetes; renal dysfunction) but data on patients excluded on the basis of prior results (1-2 years previously) is not provided.<br><br>Similarly it is a common clinical finding that patients with isolated high cholesterol or established young -onset cardiovascular disease |

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| | are simply treated with a statin (not necessarily high intensity high dose). In the latter case cholesterols measured in secondary care have often not been notified to primary care. Many FH cases lurk in this group in primary care or on cardiovascular risk registers and data of their potential numbers in this survey would be useful. The authors previously identified these groups in a previous publication when deriving a FH diagnostic technique (FAMCAT). |

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| **REVIEWER** | Gerald Watts<br>University of Western Australia |
| **REVIEW RETURNED** | 21-Mar-2016 |

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| **GENERAL COMMENTS** | A straightforward assessment employing descriptive statistics of the feasibility for an intended trial of improved detection of FH in general practice. Appropriate communication if within journal policy for publication, but rationale in line within MRC guidelines. Endpoints assessed fundamental, but critical proportion of returns on endpoints to warrant feasibility needs definition. How many practices will be required for the trial in question? and can design of trial be specified in text? A recent study has shown that SQL technology can be adapted to extract FH from suitable EMR very rapidly and should be referenced> Troeung et al Heart 2016. |

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| **REVIEWER** | Damon Bell<br>University of Western Australia, School of Medicine and Pharmacology. Cardiometabolic Service Royal Perth Hospital. Department of Biochemistry PathWest Fiona Stanley Hospital. Perth Western Australia. |
| **REVIEW RETURNED** | 26-Mar-2016 |

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| **GENERAL COMMENTS** | Qureshi et at have prepared a manuscript entitled “Feasibility of improving identification of familial hypercholesterolaemia in general practice: Intervention development study” for review as a research article. The authors are experienced and well published in this field. The manuscript is on a topic of importance and interest to readers of BMJ Open. It contains some novel aspects to try to identify people with FH, which is an area in great need of both further research and increased awareness. I look forward to reading the formal investigation and the further study to determine the experiences of both patients and health professionals form this pilot study. However, I have these points to raise;<br><br>1. With regard to the opportunistic software alerts, how often does the average person see their GP? Was waiting four months before performing a mail out enough time to test the effectiveness of this intervention?<br><br>2. Results page 10, figure 1. Please provide the total number of patients from the six practices, and the proportion of people meeting criteria for further investigation.<br><br>3. Results page 10 line 21. There were 207 packs provided opportunistically and 802 mailed, but only 831 participants. Please clarify. Were response rates different in individuals receiving these twice? |

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| | 4. Diagnosis rate page 11 line 16. Please expand on and clarify the comments regarding genetic testing. Was this performed on all people referred to the specialists? If so how was it performed, and were mutations identified in the definite FH individuals?<br><br>5. Proposed outcomes page 11 line 35. 3% of individuals did not have LDL-cholesterol concentrations documented, was this secondary to elevated triglycerides and the inability to calculate LDL via the Friedewald equation?<br><br>6. It would seem from the results that on average the triglyceride concentrations were above 2 mmol/L. Please provide information on the TG levels, and consider this in the context of the FAMCAT FH identification tool, as it may suggest some of these individuals may have familial combined hyperlipidaemia, or co existing hypertriglyceridaemia.<br><br>7. Strengths page 14, line 29. The authors comment that the eligibility criteria did not consider statin therapy, but I noted 26-32% of the cholesterol results allowing entry were from previous lipid measurements, was any information available to suspect levels of lipid lowering in these individuals (changes in cholesterol levels, prescription information)?<br><br>8. Authors could compare and contrast this method with those described by Troeung L et al. Heart 2016: A new electronic screening tool for identifying risk of familial hypercholesterolaemia in general practice. On line Feb 2016, and with Kirke et al, Systematic detection of FH in primary care. Heart Lung Circ 2015;24(3)250-256. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

Reviewer Name

Anthony Wierzbicki

Institution and Country

Dept Metabolic Medicine/Chemical Pathology
Guy's & St Thomas Hospitals
London SE1 7EH, UK

Please state any competing interests or state ‘None declared’:
Member ; NICE familial hypercholesterolaemia guideline committee (CG71); Chair NICE Lipids & cardiovascular risk committee (CG181)

A) This paper describes preliminary feasibility data for a trial to investigate strategies for idenifying patients in primary care with familial hypercholesterolaemia (FH). The study used 6 primary centres and potentially identified >800 patients with FH using a lipid criterion. However only 10-15% proceeded through the programme and only 7.5% were considered for referral for definitive diagnosis by secondary care.

Author response: We would like to thank the reviewer for their helpful review and insightful comments. The FAMCHOL study was a pragmatic feasibility study in real-time clinical practice. As such, there will

be practical issues with patients being recruited, GPs taking action to make referrals, and patients attending appointments within a relatively short time-frame. As highlighted in discussion (lines 315 to 319), we have over-sampled inner city disadvantaged populations with 4 of the 6 general practices recruited from deprived areas. This would account for the overall lower response and referral rates. Thus, this 15% response rate is heavily weighted by disadvantages populations (the one more affluent rural practice had a response rate of 26% as shown in Figure 1).

B) Clarification is required that genetic diagnosis was performed though it is implied in the wording.

Author response: Thank for raising this point that we have not explicitly stated how the diagnosis was made in secondary care. Genetic testing in the local area lipid clinic was not widely available. Thus, the patients in this study were diagnosed based on clinical criteria (i.e. using NICE Simon-Broome criteria). We have added clarification in the methods section (lines 200-201):

“Diagnosis of confirmed FH in secondary care was based on clinical criteria (i.e. NICE Simon-Broome criteria).”

C) Similarly FH is a disorder with lifelong cholesterol elevation. It is unclear how many patients more than one record of cholesterol measurement more than 1 or 5 years previously. Given the policy-bias (NHS health checks range 40-75) and female bias in recruitment ( see also Neil HA et al Int J Clin Pract 2008; 62: 1322 for general CVD screening) confounding by post-menopausal elevations in cholesterol is a common problem in FH screening yet this data is not provided.

Author response: We agree with the reviewer that there is a policy-bias for general CVD screening. As started in the participants sections (lines 152-155), the eligibility criteria for patients to be recruited in this study was a single cholesterol measurement above 7.5 mmol/L. Our search of electronic health records, identify patients with at least one episode of raised cholesterol to recruit into the study. We agree it is possible that some patients may have more than one elevated cholesterol level but this level of extraction was not necessary to recruit patients to the study. However, the bias highlighted by the reviewer is highly relevant and incorporated into Limitations section of the Discussion (lines 329-333):

“Additionally, recruitment of eligible patients to the study may have been influenced by health care policy and a gender bias in recruitment. The NHS vascular check programme screens 17 offers CVD risk assessment for age range of 40-75 years and previous evidence 18 have shown that women are more likely to join a general CVD screening programme than men.”

D) The study involves the provision of training and support materials to primary care but the paper does not detail how much family history information was already available in the electronic care record (e.g family history of premature cardiovascular disease <60 years as per EMIS code) and how much of this was correct. This is a recurrent concern (see McManus RJ et al ; BMJ 324: 459 (2002)). Data is provided on post-study initiation screening for secondary factors (thyroid; diabetes; renal dysfunction) but data on patients excluded on the basis of prior results (1-2 years previously) is not provided.

Author response: The reviewer raises a good point about family history in primary care records. We know from our previous research as highlighted in lines 117 to 119 (see reference 8: Dhiman P, Kai J, Horsfall L, Walters K, Qureshi N. Availability and Quality of Coronary Heart Disease Family History in Primary Care Medical Records: Implications for Cardiovascular Risk Assessment. PLoS ONE 2014; 9(1): e81998) that the availability of routinely available family history if extremely poor in primary care.

Thus, as part of the study procedure, the study pack contained a validated self-administered family history questionnaire to help facilitate the GP to conduct a detailed family history (lines 179-184). We agree that this is an important issue and in fact are already conducting a subsequent study analysis (which is due to be completed very soon) that investigates at the post-study changes in family history and other clinical relevant clinical characteristics (which will provide information on the proportion of patients with secondary factors diagnosed prior to study) using data readily available in electronic records. We have added more detail in the future research section of the discussion (lines 351 – 353):

"To improve future implementation, we are currently assessing the post-study changes in practitioner behaviour on relevant clinical outcomes such as family history and diagnosis of secondary causes, as well as, the qualitative experience of those patients and health care professionals who participated in this study, including patients who declined follow-up. [24]"

E) Similarly it is a common clinical finding that patients with isolated high cholesterol or established young -onset cardiovascular disease are simply treated with a statin (not necessarily high intensity high dose). In the latter case cholesterols measured in secondary care have often not been notified to primary care. Many FH cases lurk in this group in primary care or on cardiovascular risk registers and data of their potential numbers in this survey would be useful. The authors previously identified these groups in a previous publication when deriving a FH diagnostic technique (FAMCAT).

Author response: We agree with the reviewer that isolated cases of high cholesterols or established young onset CVD will likely be treated with statin. This was a pragmatic feasibility study to identify FH in primary care using NICE S-B criteria. These records were not linked to hospital data. In response to this study's findings we have developed a FH identification tool (FAMCAT) using national GP database linked to hospital (secondary care) data. This has already been published. We have added some additional details on how FAMCAT addresses the issue of statin usage and early onset CHD in the discussion (lines 359-363):

"For instance, our recently developed approach (Familial Hypercholesterolaemia Case Acertainment Tool) [27] from routinely data, held in primary care EHRs, takes into account patients already on statins, secondary causes of raised cholesterol, triglycerides, and premature CHD when identifying patients who may have FH."

Reviewer: 2

Reviewer Name

Gerald Watts

Institution and Country

University of Western Australia

Please state any competing interests or state 'None declared':
None

F) A straightforward assessment employing descriptive statistics of the feasibility for an intended trial of improved detection of FH in general practice. Appropriate communication if within journal policy for publication, but rationale in line within MRC guidelines.

Author response: We thank the reviewer for their positive review and acknowledgement that study falls within MRC guidelines for intervention development.

G) Endpoints assessed fundamental, but critical proportion of returns on endpoints to warrant feasibility needs definition. How many practices will be required for the trial in question? and can design of trial be specified in text?

Author response: We thank the reviewer for acknowledging the endpoints assessed are fundamental. We are currently calculating the sample size for a proposed cluster Randomised Controlled Trial in discussion with a Critical Trials Unit. To finalise the calculation we need further details on the discriminatory accuracy of Simon-Broome criteria. As of now, using the study parameters: 2.36% eligible patients from 6 six practices (reported on line 227) with 15% recruitment rate (reported on line 238) would require 762 patients total recruited to a two-armed study based on 80% power, 5% significance, and an intra-cluster coefficient of 0.03. The number of general practices required would depend on the practice size. We have added an additional statement to highlight the design of the future study as well as which parameters feed into it in the discussion (lines 365-367):

“The parameters derived in this study on eligibility, recruitment, and diagnosis will directly inform a future cluster randomised controlled trial in primary care.”

H) A recent study has shown that SQL technology can be adapted to extract FH from suitable EMR very rapidly and should be referenced> Troeung et al Heart 2016.

Author response: Thank for you for providing this reference we have added this reference (29) in the context of using a similar approach for a future trial (lines 369-372):

“Extraction of pseudo-anonymized data from electronic health records demonstrated in this and other related studies [29] can rapidly capture key trial outcome measures without burdening patients, for example with forms seeking detailed information which may reduce response rates. [30]”

Reviewer: 3

Reviewer Name

Damon Bell

Institution and Country

University of Western Australia, School of Medicine and Pharmacology. Cardiometabolic Service Royal Perth Hospital. Department of Biochemistry PathWest Fiona Stanley Hospital. Perth Western Australia.

Please state any competing interests or state ‘None declared’:
None declared.

G) Qureshi et at have prepared a manuscript entitled “Feasibility of improving identification of familial hypercholesterolaemia in general practice: Intervention development study” for review as a research article. The authors are experienced and well published in this field. The manuscript is on a topic of importance and interest to readers of BMJ Open. It contains some novel aspects to try to identify

people with FH, which is an area in great need of both further research and increased awareness. I look forward to reading the formal investigation and the further study to determine the experiences of both patients and health professionals form this pilot study. However, I have these points to raise;

Author response: We thank the reviewer for acknowledging the experience and strength of the team and that the topic addresses an important issue in a novel way.

1. With regard to the opportunistic software alerts, how often does the average person see their GP? Was waiting four months before performing a mail out enough time to test the effectiveness of this intervention?

Author response: Most recent data from UK general practice indicates that an average adult patient will see their GP no less than four times per person-year (for current data: https://data.gov.uk/dataset/trends_in_consultation_rates_in_general_practice). As a resource-limited feasibility study, it was not appropriate or practical to run opportunistic recruitment for an extended period of time. Within the time available, the opportunistic recruitment was run for 6 months, with postal recruitment offered after 4 months. Although small numbers recruited opportunistically, we still demonstrated higher response rate than postal invitation (shown in Figure 1: 19.8% opportunistic, 10.3% postal).

2. Results page 10, figure 1. Please provide the total number of patients from the six practices, and the proportion of people meeting criteria for further investigation.

Author response: This has been added to results (lines 227-228):

“Figure 1 outlines the study recruitment process and procedure for the 831 eligible patients (2.36% of total) identified at baseline from 35,438 patients, over 18 years, registered with the six general practices.”

3. Results page 10 line 21. There were 207 packs provided opportunistically and 802 mailed, but only 831 participants. Please clarify. Were response rates different in individuals receiving these twice?

Author response: The reviewer raises an interesting point. Due the pragmatic nature of this study, some patients will have received the packs both opportunistically and by postal invitation. For ethical reason, we could not access patient details on opportunistic invitation by GPs (only access patient details after consented). Hence, we were not able to identify which patients received study invitations by both recruitment methods. We have added this point as a limitation in the discussion (lines 322-325):

“Due the pragmatic nature of this study, some patients may have received the recruitment packs twice (opportunistic and postal). However, for ethical reasons, we could not identify patients given recruitment packs opportunistically who did not consent to participate in the study.”

4. Diagnosis rate page 11 line 16. Please expand on and clarify the comments regarding genetic testing. Was this performed on all people referred to the specialists? If so how was it performed, and were mutations identified in the definite FH individuals?

Author response: Further to response to Reviewer 1’s comment B, diagnosis of FH was primarily based on specialist clinical examination using NICE Simon-Broome criteria. During the period of the study there was limited access to genetic testing and this is incorporated in the study when available. In the Future Research section of the Discussion highlighted the importance of genetic confirmed diagnosis (lines 366-367):

"In any future trial, the diagnosis of FH should be based on both clinical assessment and genetic testing."

5. Proposed outcomes page 11 line 35. 3% of individuals did not have LDL-cholesterol concentrations documented, was this secondary to elevated triglycerides and the inability to calculate LDL via the Friedewald equation?

Author response: In these 4 patients with missing LDL, calculation of LDL could not be performed due to missing triglycerides entry in their electronic medical records.

6. It would seem from the results that on average the triglyceride concentrations were above 2 mmol/L. Please provide information on the TG levels, and consider this in the context of the FAMCAT FH identification tool, as it may suggest some of these individuals may have familial combined hyperlipidaemia, or co existing hypertriglyceridaemia.

Author response: The average triglycerides level was 2.04 mmol/L (SD 1.37). However, 15% of these values were missing or not documented in electronic health records at the time of the raised cholesterol recording. The reviewer also raises a good point that elevated triglycerides should be considered as a negative indicator of FH and this limitation has led to the development of our electronic FH identification tool FAMCAT. See response to comment E (Reviewer 1).

7. Strengths page 14, line 29. The authors comment that the eligibility criteria did not consider statin therapy, but I noted 26-32% of the cholesterol results allowing entry were from previous lipid measurements, was any information available to suspect levels of lipid lowering in these individuals (changes in cholesterol levels, prescription information)?

Author response: To identify patients for assessment, any patients with a previous recording of a cholesterol > 7.5mmol/L, irrespective of treatment at that time, were identified. As indicated in the limitations (lines 325-329), patients on statin and cholesterol levels below this threshold may have been missed by the electronic search. However, following this study, we plan to incorporate patients with lower cholesterols on statins in any future trial. Further, the impact of statins has been taken into account in our new FH identification tool (FAMCAT). See response to comment E (Reviewer 1)

8. Authors could compare and contrast this method with those described by Troeung L et al. Heart 2016: A new electronic screening tool for identifying risk of familial hypercholesterolaemia in general practice. On line Feb 2016, and with Kirke et al, Systematic detection of FH in primary care. Heart Lung Circ 2015;24(3)250-256.

Author response: Thank you for these suggested references. We have added both references to the paper (reference 28, line 359 and reference 29, line 370). We believe the methods of data extraction and capture used in these studies are extremely relevant to our approach. Also see comment H (Reviewer 2).

**VERSION 2 – REVIEW**

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| **REVIEWER** | Gerald Watts<br>UWA |
| **REVIEW RETURNED** | 26-Apr-2016 |

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| **GENERAL COMMENTS** | Well revised |

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| **REVIEWER** | Damon Bell<br>University of Western Australia, School of Medicine and Pharmacology, Roryal Perth Hospital. Perth Western Australia. |
| **REVIEW RETURNED** | 02-May-2016 |

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| **GENERAL COMMENTS** | The authors have adequately addressed the points I raised. |

# Correction: *Feasibility of improving identification of familial hypercholesterolaemia in general practice: intervention development study*

Qureshi N, Weng S, Tranter J, *et al*. Feasibility of improving identification of familial hypercholesterolaemia in general practice: intervention development study. *BMJ Open* 2016;6: e011734.

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This paper presents independent research funded by the National Institute for Health Research School for Primary Care Research (NIHR SPCR).

In addition, the following disclaimer should be included in this paper:
The views expressed are those of the author(s) and not necessarily those of the NIHR, the NHS or the Department of Health.



*BMJ Open* 2016;**6**:e011734corr1. doi:10.1136/bmjopen-2016-011734corr1