PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Detection and management of familial hypercholesterolaemia in primary care in Australia: protocol for a pragmatic cluster intervention study with pre-post intervention comparisons.
AUTHORS	Arnold-Reed, Diane; Brett, Tom; Troeung, Lakkhina; Vickery, Alistair; Garton-Smith, Jacquie; Bell, Damon; Pang, Jing; Grace, Tegan; Bulsara, Caroline; Li, Ian; Bulsara, Max; Watts, Gerald

VERSION 1 – REVIEW

REVIEWER	Nigel Stocks Discipline of General Practice, University or Adelaide, Australia
REVIEW RETURNED	08-Jun-2017

GENERAL COMMENTS	Perhaps I am being pedantic but I would like a clearly stated study objective or hypothesis. The primary and secondary outcomes are well defined and reading the text I understand what the authors are trying to achieve but a few sentences that just say ' the objective of this study is to determine if using the TARB-Ex extraction tool in general practice and facilitating GP/practice nurse review of patients .. I accept that pre/post intervention study has been chosen for pragmatic reasons but a more convincing methodology would have been a cluster RCT with usual care practices receiving education about FH and the need to intervene with cascade screening but not using TARB-Ex (for example). It wasn't clear to me if the economic evaluation would include the cost of additional investigations and final treatment of individuals? I think the study limitations of using a pre/post methodology should be added to the points already listed. It should also be acknowledged that patients in Australia can visit more than practice and duplication could occur. In addition a significant proportion of patients also move their residential address and practice in Australia every year, this may also affect the results and their interpretation. I note this study probably does not need to be registered as it is not an RCT. The authors acknowledge pharmaceutical company funding.

REVIEWER	Nadeem Qureshi University of Nottingham, UK Completing NIHR funded project to assess another Familial Hypercholesterolaemia tool in British General Practice
REVIEW RETURNED	19-Jun-2017

GENERAL COMMENTS	Related to step 1 the authors provided detailed information on the intervention (page 8-9). It is good to see in step 7 that the authors have included a nested qualitative study. SUGGESTED AREAS FOR IMPROVEMENT Page 9 (line 15): It would be useful to include in the protocol the basis of the complexity metrics. Is this based on specialist consensus opinion. Page 9 (line 47): Should the described tables be table 3 and 4 or tables 2 and 3? It would be helpful for qualitative research if all questions are open rather than initial closed. Page 10 (line 48): I wonder if this title is better phrased as 'expected extent of cascade testing from proposed sample size'. Page 10 (line 52): "Clarification that it could be between 66 and 125" could be rephrased as: "up to 50% of relatives diagnosed with FH: this could be between 66 and 125." Page 10-11 (data collection section): I wonder if this section is about data collection or outcome measures. Page 11 (line 13): What does the phrase "annotated attempts" mean? Page 11 (approximately line 15): It may be worth including health economic outcome measures here as well. AREAS FOR CLARIFICATION Page 9 (step 7): It is useful to recognise different methodologies (1 to 1 interviews and focus groups) will elicit different information related to the different interactions using the 2 approaches. Page 20 (line 51): When saying generate 125 more related cases, does this assume that all relatives are registered with the study general practices? Is this reasonable? In summary, I would support publication of this document with the minor amendments.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Nigel Stocks
Institution and Country: Discipline of General Practice, University or Adelaide, Australia

1. Perhaps I am being pedantic but I would like a clearly stated study objective or hypothesis. The primary and secondary outcomes are well defined and reading the text I understand what the authors are trying to achieve but a few sentences that just say ' the objective of this study is to determine if using the TARB-Ex extraction tool in general practice and facilitating GP/practice nurse review of patients ..
We have made the following changes to the methods and analysis section (Pg 7):
Objective: To trial a primary care-based MoC for FH.
Hypothesis: Electronic data extraction from patient records facilitates clinical review to improve the detection and management of FH in general practice.
2. I accept that pre/post intervention study has been chosen for pragmatic reasons but a more convincing methodology would have been a cluster RCT with usual care practices receiving education about FH and the need to intervene with cascade screening but not using TARB-Ex (for example).
We have added the following to the list of limitations (Pg 3).
• Our pragmatic approach using existing clinical infrastructure enhances feasibility and sustainability but pre-post intervention comparison is acknowledged as potential limitation.

3. It wasn't clear to me if the economic evaluation would include the cost of additional investigations and final treatment of individuals?
This is now more explicitly stated in the Data Analysis section (Pg 13):
Cost efficiency analysis: Costs collated from the start of the study to the endpoint at 12 months will be compared against historical costs sourced from tertiary centres for treating and managing FH cases. This will provide an indication of expenditures or savings from adopting the primary care based MoC.
4. I think the study limitations of using a pre/post methodology should be added to the points already listed. It should also be acknowledged that patients in Australia can visit more than practice and duplication could occur. In addition a significant proportion of patients also move their residential address and practice in Australia every year, this may also affect the results and their interpretation.

We have reworded the limitations to include the following (Pg 3):
• To the best of our knowledge this protocol is the first that focuses not just on early detection but also on the delivery of preventative care and management of FH in the primary care setting. It is trialled within the Australian context but builds on the consensus statements of the European Atherosclerosis Society1 and the International FH Foundation2 that FH care should ideally take place in the primary care setting.
• Our pragmatic approach using existing clinical infrastructure enhances feasibility and sustainability but pre-post intervention comparison is acknowledged as potential limitation.
• The GP and practice nurse (PN) team approach to phenotypic diagnosis and the cascade testing of FH relatives is likely to prove challenging initially from the GP/PN and patient perspective - length of follow-up to determine appropriate management of FH patients will be limited due to constraints of time and funding.
• There is potential for impact on the outcomes and interpretation as patients attending GP practices in Australia are not registered to a single practice - they may change residential address and be lost to follow-up or register at more than one practice with potential for duplication (or loss to follow-up if at a non-participating practice) however, this will be easily identified given the numbers of participants followed up.
• The potential for variability in compliance with medications (eg statins) and adherence to dietary and lifestyle advice across practices and between patients is acknowledged.

5. I note this study probably does not need to be registered as it is not an RCT. The authors acknowledge pharmaceutical company funding.
We have registered the study as it is a clinical study.
Australian New Zealand Clinical Trials Registry (ANZCTR) ID: 12616000630415.

Reviewer: 2
Reviewer Name: Nadeem Qureshi
Institution and Country: University of Nottingham, UK

SUGGESTED AREAS FOR IMPROVEMENT
1. Page 9 (line 15): It would be useful to include in the protocol the basis of the complexity metrics. Is this based on specialist consensus opinion.
This has been clarified in the text:
Step 5: Management and cascade testing. Management of patients is based on consensus opinion7 28 and is outlined in Figure 2.
2. Page 9 (line 47): Should the described tables be table 3 and 4 or tables 2 and 3? It would be helpful for qualitative research if all questions are open rather than initial closed.
The tables referred to are Tables 3 and 4. The initial questions in Tables 2, 3 and 4 have been amended as follows:
Discussion points Reason
How would you rate your current knowledge of FH?
Prompt if needed 1 (no knowledge) to 5 (extremely knowledgeable) Establishing extent of knowledge
How comfortable would you be with diagnosing FH?
Prompt if needed 1 (very uncertain) to 5 (extremely confident)
How confident would you feel managing a patient with FH?
Prompt if needed 1(very uncertain) to 5 (extremely confident)
Can you recall ever having a patient with FH previously?

3. Page 10 (line 48): I wonder if this title is better phrased as 'expected extent of cascade testing from proposed sample size'.
This has now been changed to: "Expected extent of cascade testing to inform proposed sample size:"
4. Page 10 (line 52):"Clarification that it could be between 66 and 125" could be rephrased as: "up to 50% of relatives diagnosed with FH: this could be between 66 and 125."
The text has now been changed to:
Expected extent of cascade testing to inform proposed sample size: Recruitment from 5 practices will generate an expected 66 index cases. It is expected that up to 50% of relatives will be diagnosed with FH31, potentially providing between 66 and 125 FH cases. However, it is acknowledged that not all relatives will be followed-up as they may not be patients of participating practices or may decline follow-up.

5. Page 10-11 (data collection section): I wonder if this section is about data collection or outcome measures.
This has been changed to "Outcome Measures"
6. Page 11 (line 13): What does the phrase "annotated attempts" mean?
This has been re-worded as follows: "Attempts recorded in notes to contact family members"
7. Page 11 (approximately line 15): It may be worth including health economic outcome measures here as well.
All outcome measures have now been included as follows:
Outcome Measures
Quantitative Data:

a) Number of known index cases of FH and new cases identified through TARB-Ex
b) Highest LDL-c measure ever
c) LDL-c measure closest to baseline
d) LDL-c measure closest to12-month follow-up
e) Statin type, dose and length of time prescribed over study period
f) Other CVD risk factors present
g) Attempts recorded in notes to contact family members
h) Number of family members with existing or new FH diagnosis or contacted
Cost Data:
a) Implementation and extraction of patient data using TARB-Ex
b) GP/PN time involved in manual screening of patient records
c) Personnel time/resources involved in recall of patients
d) GP/PN time (from billing schedules) involved in clinical screening of patient records
e) Patient management costs based on number of visits, length of visits for GP practice and specialist tertiary referrals over the course of the study.
f) Number and type of prescriptions issued
Qualitative Data:
Patient and clinical staff views will be assessed using items listed in Tables 2-5.

AREAS FOR CLARIFICATION
8. Page 9 (step 7):It is useful to recognise different methodologies (1 to 1 interviews and focus groups) will elicit different information related to the different interactions using the 2 approaches.
This is now included as follows: “The exact method will be guided by availability and preferences of the participants and it is acknowledged that the different methodologies used will elicit different information”
9. Page 20 (line 51): When saying generate 125 more related cases, does this assume that all relatives are registered with the study general practices? Is this reasonable?
This has been re-worded (see response to reviewer 2 #4)

VERSION 2 – REVIEW

REVIEWER	Nigel Stocks University of Adelaide, Australia
REVIEW RETURNED	28-Jul-2017

GENERAL COMMENTS	I have read the authors' letter and the revised paper. I am happy with their response to both reviewers comments and believe the paper can be published.

REVIEWER	Nadeem QURESHI University of Nottingham UK Funded similar research on FH identification through NIHR
REVIEW RETURNED	08-Aug-2017

GENERAL COMMENTS	The authors have completely answered my major queries, as listed in attached document (with my comments in CAPITALS) Only 1 suggested minor further amendment. On line 52 suggest rephrase to “…using items listed in Table 2-5 as interview prompts.”

	Overall, the protocol has substantially improved.