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Detection and management of familial hypercholesterolaemia in primary care in Australia: protocol for a pragmatic cluster intervention study with pre-post intervention comparisons

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ABSTRACT

Introduction Familial hypercholesterolaemia (FH), an autosomal dominant disorder of lipid metabolism, results in accelerated onset of atherosclerosis if left untreated. Lifelong treatment with diet, lifestyle modifications and statins enable a normal lifespan for most patients. Early diagnosis is critical. This protocol trials a primary care-based model of care (MoC) to improve detection and management of FH.

Methods and analysis Pragmatic cluster intervention study with pre-post intervention comparisons in Australian general practices. At study baseline, current FH detection practice is assessed. Medical records over 2 years are electronically scanned using a data extraction tool (TARB-Ex) to identify patients at increased risk. High-risk patients are clinically reviewed to provide definitive, phenotypic diagnosis using Dutch Lipid Clinic Network Criteria. Once an index family member with FH is identified, the primary care team undertake cascade testing of first-degree relatives to identify other patients with FH. Management guidance based on disease complexity is provided to the primary care team. Study follow-up to 12 months with TARB-Ex rerun to identify total number of new FH cases diagnosed over study period (via TARB-Ex, cascade testing and new cases presenting). At study conclusion, patient and clinical staff perceptions of enablers/barriers and suggested improvements to the approach will be examined. Resources at each stage will be traced to determine the economic implications of implementing the MoC and costed from health system perspective. Primary outcomes: increase in number of index cases clinically identified; reduction in low-density lipoprotein cholesterol of treated cases. Secondary outcomes: increase in the number of family cases detected/contacted; cost implications of the MoC.

Ethics and dissemination Study approval by The University of Notre Dame Australia Human Research Ethics Committee Protocol ID: 016067F. Registration: Australian New Zealand Clinical Trials Registry ID: 12616000630415. Information will be disseminated via research seminars, conference presentations, journal articles, media releases and community forums.

Trial registration number Australian New Zealand Clinical Trials Registry ID 12616000630415; Pre-results.

Strengths and limitations of this study

- To the best of our knowledge, this protocol is the first that focuses on early detection and on the delivery of preventative care and management of familial hypercholesterolaemia (FH) in the primary care setting. It is trialled within the Australian context but builds on the consensus statements of the European Atherosclerosis Society and the International FH Foundation 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 general practitioner (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 patients with FH 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.

INTRODUCTION

Familial hypercholesterolaemia (FH) is an autosomal dominant disorder of lipid metabolism resulting in excessively high plasma levels of cholesterol from birth. Left

untreated, it can result in premature coronary artery disease (CAD) due to accelerated onset of atherosclerosis.[1] For men with FH, the risk of developing CAD before age 50 years is 50% while for women it is 30% at age 60 years.[2 3] The accelerated development of atherosclerotic cardiovascular disease (CVD) by 20–40 years as a consequence of inheriting FH means that children and young adults have most to gain from early diagnosis and treatment.[4] It is estimated that between 1 in 500 and 1 in 200 persons have heterozygous FH yielding a worldwide population estimate of 20 million cases.[5] Of the estimated 45 000 with FH in Australia and New Zealand,[6] the vast majority remain undiagnosed and, among those diagnosed, most remain undertreated. However, lifelong treatment with diet and lifestyle modifications together with lipid lowering therapy can reduce the risk of CAD close to the non-FH population.[7] Early diagnosis is therefore critical.

The 2011 Australian FH Model of Care (MoC) primarily focused on specialist lipid clinics in tertiary centres to augment the development of clinical services for FH.[8] The need to develop a corresponding MoC suitable for the primary care setting is increasingly recognised,[8] especially in light of the vastly different disease demographics of patients attending primary and tertiary clinics (according to Bettering Evaluation and Care of Health (BEACH) data, 8.4% of primary care encounters are referred to medical specialists)[9] and the persisting low rates of FH detection and treatment in the Australian population.[8 10] Primary cares services are the first point of contact with the health system and over 85% of the Australian population attend a general practitioner (GP) at least once annually.[11] Thus, primary care teams are ideally placed to play a more active role in the detection and management of unsuspected cases of FH in the community, thereby contributing to addressing the gap that currently exists in the Australian health service.[8]

The key challenge for primary care is to develop a systematic and sustainable approach to detect index cases for FH in the community. Once this is achieved, the next step is to progress to family cascade testing. There is extensive evidence to show such an approach would be clinically[2 8 10] and financially[12–14] effective. The need to integrate the central role of primary care with specialist lipid services to optimise the detection and management of FH in the community is recognised.[15 16] The provision of a community-based MoC for FH involving a more comprehensive and focused education programme for GPs, practice nurses (PNs) and practice staff, improved communication with cardiologists and pathology providers as well as support from lipid specialists to help manage more difficult high-risk patients with FH and to improve cascade testing of relatives of index cases, has been suggested.[16]

In a regional Western Australian (WA) primary care setting, three different approaches for FH detection were successfully tested.[17] These included (1) a community pathology laboratory database (n=52 200); (2) a workplace-based occupational health assessment process (n=1079), and (3) a general practice patient database (n=41 100) to screen for increased CVD risk—a total population of 94 379. A total of 1316 individuals subsequently had a detailed clinical assessment for FH and 86 participants were identified with clinical FH. Those with Dutch Lipid Clinic Network Criteria (DLCNC)[2] scores >5 were offered referral to lipid specialist clinic for further review. Of the 59 individuals assessed by the lipid specialist who underwent DNA testing, 11 (18.6%) were identified to carry FH mutations.[17]

The study used the existing practice-based medical and nursing services in the regional primary care setting. The findings supported the potential development of an integrated screening programme capable of combining the use of pathology services (including interpretative comments on lipid profile) and the involvement of the primary care team in detection and management.[17] The engagement of local GPs and PNs in recalling and following up patients generated greater patient involvement in the screening process. The preferred model used a two-stage process where at-risk patients were identified through raised low-density lipoprotein cholesterol (LDL-c) concentrations that were subsequently flagged by the GP-PN team for review.

Bell *et al*[18] examined whether individuals with FH could be accurately identified in the primary care setting. They concluded that GPs were able to accurately identify individuals at high or low risk for FH using the DLCNC score,[2] thereby augmenting opportunistic FH detection in the community. In addition, by increasing education for the primary care team, the diagnostic accuracy of FH detection in primary care could be enhanced.

With this in mind, Troeung *et al*[19] designed an electronic data extraction tool (TARB-Ex) which enables routine clinical information to be extracted from general practice patient management software databases (Best Practice Software) and identifies patients at potential risk of FH for follow-up based on the DLCNC score. The extraction tool has shown its capacity to identify patients at increased risk of FH in the primary care setting, comparing favourably with a manual assessment of FH risk by the GP,[19] thus facilitating an innovative and time-saving approach to improve both detection and subsequent management.

The current protocol is an innovative primary care-based diagnostic approach using phenotypic criteria as per the DLCNC score rather than more expensive genetic testing. Close relatives of index cases will be targeted for cascade testing and appropriate treatment and lifestyle modifications instituted. Most of this work will be undertaken in the less expensive community setting of general practice. Lipid specialist assistance will be available for more difficult and complex cases but it is anticipated that most of the detection and management of FH will occur in the primary care sector. The MoC is thus both

pragmatic and feasible with potential for considerable immediate cost savings to the health sector.

METHODS AND ANALYSES

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.

Study design

A pragmatic, cluster intervention study with pre-post intervention comparisons.

Study setting

General practices in Australia. The study commenced in five practices in WA in July 2016.

Eligibility criteria

Patients aged 18+ years, able to provide informed consent.

Primary outcomes

1. increase in number of index cases clinically identified;
2. reduction in LDL-c of treated cases.

Secondary outcomes

1. increase in the number of family cases detected/contacted (including children);
2. cost implications of the method of care.

Study procedure

Community involvement

In June 2016, the investigation team worked with WA Consumer and Community Health Research Network[20] and included members of the FH Support Group[21] and FH Australasia Network[22] to organise a 'Community conversation' forum[23] prior to study commencement in WA. The aim of the forum was to reflect on aspects of the study protocol including the preferred approach to cascade testing of relatives.

Information sessions

Information sessions will be held at the start of each arm of the study for all participating practices. These will be convened as general sessions open to all participating GPs and PNs and supplemented by the investigation team undertaking location visits to each participating practice. The sessions will include background information on FH, the proposed method of care protocol, the process of consenting patients to participate, data to be collected during the research study and suggestions for cascade testing processes. The content for these sessions will be adapted from those previously undertaken.[24 25]

In addition, GPs and PNs will have the opportunity for one-on-one consultation with the GPs on the research team at each stage of the research protocol. This will allow for specific discussion of individual patients.

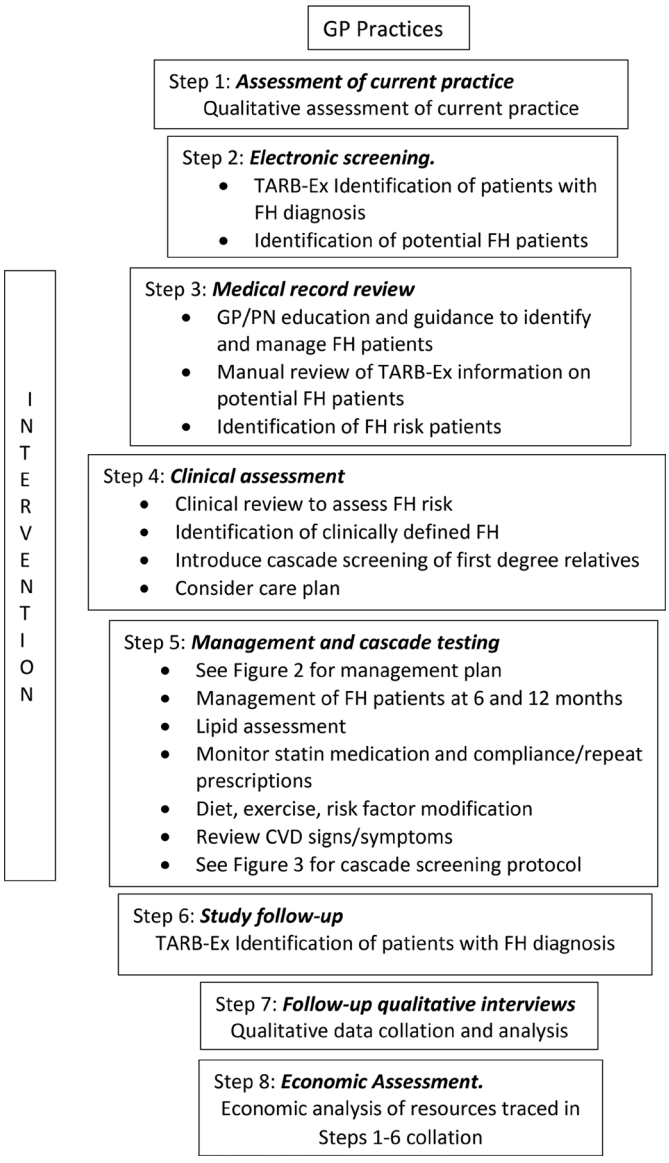

Figure 1 Steps involved in study protocol. CVD, cardiovascular disease; FH, familial hypercholesterolaemia; GP, general practitioner; PN, practice nurse.

Overall plan is outlined in figure 1 and timeline is outlined in table 1.

Step 1: assessment of current practice

Qualitative (open-ended) and semiquantitative (scaled) responses will be collected from GPs and PNs on current practice (table 2). This aims to establish a baseline of GP, PN and practice staff awareness and GP self-confidence in diagnosing and managing FH.

Step 2: electronic screening

Using a validated electronic data extraction method (TARB-Ex),[19] electronic medical records of all patients seen at the practice in the last 2 years with a recorded blood LDL-c will be screened for potential FH risk. TARB-Ex has an inbuilt standardising algorithm to nominally adjust cholesterol levels (see online supplementary information 1) of patients prescribed statins within

Table 1 Study timeline

	Activity
4 months	Employ additional staff, identify practices involved.
4 months	Study lead-in and set-up—staff commence, ethics applications, contact practices. Commence registry liaison.
4 months	*Steps 1–4 and 8 of study protocol* Baseline data extraction and qualitative information collection Commence training for GPs, PNs and practice staff. List at-risk patients for recall.
12 months	*Steps 5–8 of study protocol* Patients seen for management Monitor management/compliance and registry data. Relatives cascade tested/annotated attempts to contact family members. Time estimation and cost data sourced Qualitative information collected from practices
6 months	Study write-up Information dissemination

GP, general practitioner; PN, practice nurse.

1 week to 6 months of the date of highest recorded cholesterol measurement. Potential FH risk is established using a modified DLCNC score[2] and a list of at-risk patients generated. A list of all patients with an existing diagnosis of FH will also be extracted to establish baseline numbers of known FH cases at the practice.

Step 3: medical record review

As part of the intervention and in addition to the previously delivered information sessions, GP/PNs will receive enhanced guidance and training on the assessment and management of patients with FH via one-on-one and face-to-face practice meetings and referred to online information sessions.[24 25] In consultation with the clinical investigative team (TB, AV and GFW), the GP/PN team will then review the clinical records of potential FH risk patients (those with TARB-Ex DLCNC scores ≥5) identified in step 2 to determine if they are considered at high risk of FH and require clinical assessment. Other

Table 2 Preintervention discussion schedule for general practice staff

	Discussion points	Reason
1*	How would you rate your current knowledge of FH? Prompt if needed 1 (no knowledge) to 5 (extremely knowledgeable)	Establishing extent of knowledge
2	How comfortable would you be with diagnosing FH? Prompt if needed 1 (very uncertain) to 5 (extremely confident)	
3	How confident would you feel managing a patient with FH? Prompt if needed 1 (very uncertain) to 5 (extremely confident)	
4	Can you recall ever having a patient with FH previously?	
5	Before this study would you have considered a diagnosis of FH in patients with high cholesterol? Yes: ► How did you go about diagnosing the condition? ► Have you used any guidelines for managing FH (if so whichones?) ► How do you generally manage patient care in FH cases? (medication, lifestyle, and so on) ► Have you referred any patients onto a lipid specialist (if so who did you refer to and how?) ► Have you ever recommended patients contact family members for additional screening or investigation for FH, or followed up family members yourself? ► If yes how did you go about it? ► How did your patients feel about their families being contacted? No: ► Was that because you were previously unaware of FH?	Determining current management of FH
6	What would you usually do with a patient that presents with high cholesterol?	Determining current management of patients with hypercholesterolaemia

All prompt questions for general practitioner.
*Prompt question for practice nurse and practice manager.
FH, familial hypercholesterolaemia.

potential causes of hypercholesterolaemia (cholestasis, nephrotic syndrome, steroid use, hypothyroidism) also need to be considered in the decision. Clinical records of existing patients with FH identified in step 2 will also be reviewed by the GP/PN team in consultation with the clinical investigative team (TB, AV and GFW) to determine whether current treatment is optimal and/or if clinical reassessment is required.

Step 4: clinical assessment

The GP/PN will then recall the patients identified at risk of FH and likely to benefit from clinical assessment in order to update family and personal history, exclude possible secondary causes and assess adherence to cholesterol-lowering medications (if necessary). They will also undertake clinical examination to check for corneal arcus and tendon xanthomata. Information on family history and the importance of undertaking cascade testing of family members will also be flagged by the GP/PN. The diagnosis of FH will be based on the DLCNC score at clinical examination, and individuals with scores ≥6 will be regarded as having clinical FH. Consultation with the clinical investigative team (TB, AV and GFW) will be encouraged in confirming FH diagnoses. All newly diagnosed index cases will be consented into the study by the GP/PN. Patients with existing FH identified in step 1 will also be recalled and consented into the study. The general practice team will be encouraged to work with the Australian FH Registry[26 27] to record information on newly diagnosed patients as well as any existing patients with FH who are currently unknown to the FH Registry.

Step 5: management and cascade testing

Management of patients is based on consensus opinion[6 28] and is outlined in figure 2. Patients assessed as low-to-intermediate complexity FH will be managed by the GP/PN with additional specialist support if required. High-complexity cases will receive additional support from the specialist. Patients' lipid levels and cholesterol-lowering medication will be monitored (suggest every 3–6 months) as will other lifestyle factors. The GP/PN team will be responsible for cascade testing of FH relatives. Though we have provided guidelines,[28] this part of routine clinical practice is likely to prove challenging for research practices initially both from the GP/PN and patients' perspective. Additional support will be provided as required. In addition, GPs will be encouraged to consent into the study any new patients with FH they may identify as part of usual care.

Step 6: study follow-up

At the end of 12 months, TARB-Ex will be rerun to identify the total number of new FH cases diagnosed over the study period (including those identified through TARB-Ex, cascade-tested cases and new cases to the practice). Clinical records of all consented patients with FH detected will be reviewed and data on treatment and

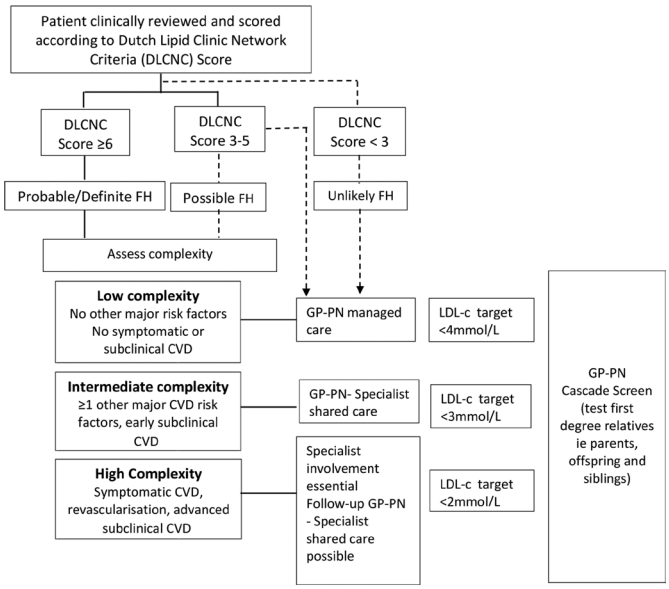

Figure 2 Suggested management plan derived from: (1) ref 28. (2) Brett, Watts, Garton-Smith, Bell, Vickery, Pang and Arnold-Reed (2015): Familial hypercholesterolaemia: challenges in primary care. Medicine Today 2015; 16(8): 20–26. CVD, cardiovascular disease; FH, familial hypercholesterolaemia; GP, general practitioner; LDL-c, low-density lipoprotein cholesterol; PN, practice nurse.

most recent LDL-c levels will be extracted from medical records to evaluate any change in LDL-c over the study period. All patients diagnosed with FH will be encouraged to have their information included in the Australian FH Registry.

Step 7: follow-up qualitative interviews

Patient, GP, PN and practice staff perceptions of the enablers and barriers and suggested improvements to using the approach in addressing FH will be examined (tables 3 and 4). This will be achieved using qualitative methodology which includes a triangulation of data collection methods including both semi-structured interviews (face-to-face and telephone) and focus groups (poststudy community feedback sessions). The exact method will be guided by the availability and preferences of the participants and it is acknowledged that the different methodologies used will elicit different information. For example, the preference potentially from a time perspective may be for GPs to complete a telephone interview. Conversely, in order to achieve a balance of individual perspectives, focus groups will be conducted among patient groups across practices. Specialist views on successes and failures on the overall process will also be elicited (table 5).

Step 8: economic assessment

The economic implications of implementing the MoC will be assessed. The costs of developing the TARB-Ex screening protocol have been identified in a previous paper.[19] In addition, labour costs of implementing the

Table 3 Discussion schedule for general practice staff postintervention

	Discussion points	Reason
Section A: Knowledge improvement		
1*	How would you rate your knowledge of familial hypercholesterolaemia? Prompt if needed 1 (no knowledge) to 5 (extremely knowledgeable)	Establishing extent of knowledge
2	How comfortable would you be with diagnosing FH? Prompt if needed 1 (very uncertain) to 5 (extremely confident)	
3	How confident would you feel managing a patient with FH? Prompt if needed 1 (very uncertain) to 5 (extremely confident)	
Section B: Effectiveness of proposed model of care for identification and management of FH		
4	In terms of the training you received for identification and treatment of FH, how did you feel about that process? Was it helpful or not? What did you like/dislike about it? What inclusion/exclusions, if any, would you like to see?	Establishing usefulness of training sessions with GP and staff
5	How do you feel about the follow-up care for FH? Do you feel it was beneficial to your patients? Why/why not? And did you find it beneficial? Why/why not?	Establishing effectiveness of introduced model of care
6	Did you need to contact the hospital lipid specialist? If yes, how well did the communication with them work? If not so well, was there anything you would like to see improve? If well, what were the elements that were particularly good?	Seeking out from participant any unique challenges within a practice setting that may create barriers and difficulties
Section C: Establishing effectiveness of screening process in identifying patients with FH		
7*	Did you feel the TARB-Ex tool was a useful add-on to your existing software? Was it easy for you and your staff to use? Can you give any examples of what worked well/not so well?	Establishing the practicality of the screening tool—*was it efficient?*
8	Did you feel that the screening process overall (TARB-Ex extraction and GP review of patient files) was helpful in detecting patients with FH? Was it an efficient process? Why/why not?	Establishing perceived effectiveness of the screening process—*did it work?*
9	What aspect of the overall screening process did you find the hardest? What area could improve?	Identifying potential improvement and increased efficiency
Section D: Establishing the effectiveness of family cascade testing for FH		
Preamble: part of the intervention required family members to be contacted and, if possible, tested for FH. I'd like to ask you a few questions around that process.		
10*	How did you go about contacting families and the cascade testing? What did you find easy or difficult about this process?	Establishing the effectiveness of the intervention within the practice—*was it practical?*
11*	Do you think that cascade testing benefited the families of those diagnosed with FH? If yes/no, why do you feel this way? Overall, did you see any increase in awareness within patients and their families regarding FH?	Establishing the perceived patient benefits of cascade testing and a family-based model of care—*did it work?*
12*	Did you encounter any examples of resistance to family screening?	
Section E: Overall intervention feedback		
13	Do you think you are likely to continue with this method of care in your practice? Why/why not?	Determining sustainability
14	Would you have any comments or suggestions that we have not mentioned about ways the process could work going forward?	

All prompt questions for the GP.
*Practice manager and practice nurse.
FH, familial hypercholesterolaemia; GP, general practitioner.

MoC including costs of training GPs and PNs in screening patients will be tracked at each practice. Furthermore, administrative data from each primary care practice will be sourced to identify the costs of managing patients with FH after they have been identified. Where FH cases are referred to specialist care, administrative data from the tertiary centres they were referred to will be sourced to identify the specialist costs associated with managing these

Table 4 Discussion schedule for patients postintervention

	Discussion points	Reason
	Preamble: I'd just like to thank you for your time. We have recently been part of introducing a new model of care for familial hypercholesterolaemia into the practice. I want to ask you a bit about FH and the approach to care you have been given.	
1	Approximately how long have you been attending *[practice name]*? Do you tend to see the same Dr or different GPs?	Trying to establish patient familiarity and comfort level with the practice
2	You were contacted recently to attend *[Dr or practice name]*, and based on your medical records you were investigated for FH *[confirm]* and then given a diagnosis of FH *[confirm]*.	Confirming diagnosis of FH
3	Were you clear as to why you were being contacted? How did you feel about that process?	Assessing clarity of communication
4	Were you able to ask questions? If you did ask questions, were your questions answered and were the answers satisfactory (enabling you to understand the condition?)	Evaluating impact of initial screening and contacting process on the patient
5	Can you describe what the health implications might be for someone who has been diagnosed with FH?	Evaluating if FH education has been integrated successfully from the GP to the patient
6	Your GP also suggested your family members be contacted to see if they could have FH. How do you feel about this? Did you consent to having family members contacted? Are your family members also patients of this practice?	Assessing the cascade testing procedures from patients' point of view
7	How did this process come about, did you contact them yourself or did the practice?	Assessing the most practical and efficient/preferred method of family contacting
8	Do you have anything else you would like to add in regard to this conversation about FH?	

FH, familial hypercholesterolaemia; GP, general practitioner.

patients. These costs can then be averaged to provide a mean cost per FH case.

Sample size calculation

Our sample size calculation is based on the number of patients needed to detect a statistically significant reduction in LDL-c at 12-month follow-up. Based on clinical audit data from three WA practices, the expected reduction in LDL-c for patients with FH receiving intensive statin treatment over 12 months is 2.83±1.15 mmol/L (n=13; Vickery, personal communication) versus 0.35 mmol/L in the control arm based on data from our previous study based on usual care.[29] This is an expected mean difference of 2.48 mmol/L. If we assume a more conservative mean difference of 2.0 mmol/L, we will need 41 patients with clinically diagnosed FH to adequately power our study at a 0.80 level with a type I error probability of 0.05 (two tailed).

Data from our pilot study[19] suggest the prevalence of FH in general practice is 1:412. Therefore, to detect 41 cases of clinically diagnosed FH, we will need to screen 16 892 patients.

To adjust for variation across five practices (clustering effect), we have applied a design effect inflation adjustment of 1.6 based on an assumed intraclass correlation coefficient for process variation in primary care of 0.15.[30] This estimates to a required total sample size of at least 27 027.

Pilot data[19] show that we are likely to have on average 5–8000 patients per practice who have been seen in the

Table 5 Discussion schedule for specialist staff postintervention

	Discussion points	Reason
1	Were you contacted by any of the GP teams? If yes, how well did the communication with them work? If not so well, was there anything you would like to see improve? If well, what were the elements that were particularly good?	Seeking out from participant any unique challenges within a practice setting that may create barriers and difficulties
2	How do you feel about the follow-up process worked? Do you feel it was beneficial? Why/why not?	Establishing effectiveness of introduced model of care

GP, general practitioner.

last 2 years. Hence, the study is adequately powered to achieve the primary outcome.

Expected extent of cascade testing to inform proposed sample size

Recruitment from five practices will generate an expected 66 index cases. It is expected that up to 50% of relatives will be diagnosed with FH,[31] 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.

Outcome measures

Quantitative data

- number of known index cases of FH and new cases identified through TARB-Ex;
- highest LDL-c measure ever;
- LDL-c measure closest to baseline;
- LDL-c measure closest to 12-month follow-up;
- statin type, dose and length of time prescribed over study period;
- other CVD risk factors present;
- attempts recorded in notes to contact family members;
- number of family members with existing or new FH diagnosis or contacted.

Cost data

- implementation and extraction of patient data using TARB-Ex;
- GP/PN time involved in manual screening of patient records;
- personnel time/resources involved in recall of patients;
- GP/PN time (from billing schedules) involved in clinical screening of patient records;
- patient management costs based on number of visits, length of visits for GP practice and specialist tertiary referrals over the course of the study;
- number and type of prescriptions issued.

Qualitative data

Patient and clinical staff views will be assessed using items listed in tables 2–5.

Data management

Data will be deidentified prior to records leaving the GP practice. Only deidentified data will be used by researchers. Audio recordings collected as part of the interviews and focus groups will be kept in secure, locked cabinets. No identifying patient information (eg, names, age) will be recorded during the interviews. Research data will be stored in a password-protected database on a secure server. This network to which the server belongs is protected by multiple firewalls to restrict outside, unauthorised access. Only aggregated, non-identifiable data will be produced in hard copy and this will be maintained in a 'restricted-access' locked cabinet located in a lockable office when not in direct use. Only specified research personnel will be permitted access to the data. As this is a clinical study, data will be retained for 15 years after publication.

Data analysis

Statistical methods

Analyses will be conducted using Stata V.13. Descriptive statistics will be used to outline the number of patients at each point of the study (screened, at risk, followed up and clinically diagnosed with FH). At 12 months, the number of new index cases and number of new family cases detected will be reported. FH prevalence will be calculated as the total number of index cases as a proportion of all active patients. The FH detection rate will be calculated as the number of new, clinically identified index cases at 12 months as a proportion of the number of at-risk patients identified through TARB-Ex at baseline. Change in LDL-c will be examined using multilevel mixed-effects modelling. LDL-c level at 12 months will be the dependent variable. Random effects included: GP (cluster effects) and time (repeated observations on the same individual). Analysis will also be adjusted for sex and age.

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.

Qualitative analysis

Qualitative analysis of interview data will be thematically analysed using QSR NVivo V.10. Thematic analysis allows for identification, analysis and detailed reporting of repeated themes within data.[32] Interviews will be audio-recorded and transcribed verbatim, then coded for key themes (words, sentences or phrases). An experienced qualitative researcher will be guiding the analysis. Two researchers will be analysing the data to increase reliability of coding and to enable a consensus regarding key themes and subthemes that emerge.

ETHICS AND DISSEMINATION

Ethics approval

The University of Notre Dame Australia Human Research Ethics Committee Protocol ID: 016067F. Australian New Zealand Clinical Trials Registry ID: 12616000630415.

Patient consent

The protocol involves the retrospective screening of patient records, clinical management of patients with FH and eliciting patient and clinic staff views on the method of care. It would not be practical to obtain consent from all patients whose results are to be electronically screened (steps 2 and 6). For patients screened, only deidentified aggregate data will be used for research analysis. For patients who are confirmed as having FH, management will be under GP care but patient-specific information

(steps 4 and 5) will be required for analysis. Consent to use this information will be obtained by the GP/PN. At consultation (step 4), the GP will inform the patient of the study. If the patient is confirmed as having FH, the GP will provide the patient with an information sheet and consent form. If the patients consent to be part of the study they will be considered index patients. If they do not consent they will not be followed up for research purposes, but this will not affect treatment received from their GP using study protocol. Step 4 will also provide the opportunity to initiate discussions with those who have consented to be part of the study for potential cascade testing of other family members should the individual patient be considered at high risk for FH. If the family member(s) identified are part of the same practice or seen by the same GP, they can also be considered as an index case and consented to be part of the study. If the new family member(s) identified are not part of the same practice/GP then they will be contacted by their GP (protocol outlined in Brett *et al*[28]) but will not be consented to the study.

GP, PN, practice managers and specialist consent

Steps 1 and 7 involve patient, GP, PN, practice staff and specialist staff perceptions of the success and/or barriers and suggested improvements to the approach. Informed consent will be obtained. The researcher will explain to the participants the purpose of the study and provide them with an information sheet. Consent will be written or verbally recorded.

Confidentiality

Patient medical records will not be removed from the clinic for research purposes. No identifying patient information (eg, names, age) will be recorded during the interviews.

Dissemination

Information will be disseminated via research seminars, conference presentations, journal articles and media releases. Community dissemination is envisaged through community advocacy groups involved in the community engagement at study set-up.

Access to data

The funders shall always be allowed to request full access to all deidentified data collected in the study in a deidentified form as long as this does not violate Australian legal requirements, including, but not limited to, the Privacy Act 1988,[33] for research, educational and registration purposes after the conclusion of the study. The funders may request an independent third party to undertake a second evaluation and analysis of data collected in the study.

Ethical considerations

From a patient management perspective, obtaining permission for cascade testing relatives will need to be considered and the protocol outlines suggestions of how this could be done.[28] Relatives who are not patients of the practice should be advised by the index case of their potential high FH risk and encouraged to have their LDL-c levels assessed at their local practice. If there is any uncertainty, Commonwealth and State Legislation, National Health and Medical Research Council guidelines and local health service protocols about disclosure of medical information without consent should be followed.

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Detection and management of familial hypercholesterolaemia in primary care in Australia: protocol for a pragmatic cluster intervention study with pre-post intervention comparisons

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