Evaluating alternative protocols for identifying and managing patients with familial hypercholesterolaemia: cost-effectiveness analysis with qualitative study

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SYNOPSIS

Title	Evaluating alternative protocols for identifying and managing patients with familial hypercholesterolaemia: cost-effectiveness analysis with qualitative study
Short title	Evaluating protocols for identifying and managing patients with FH
Chief Investigator	Professor Nadeem Qureshi
Objectives	- To evaluate the cost-effectiveness of alternative protocols for FH cascade testing using data from services in three UK regions, the literature, and linkage of national clinical databases. - To determine the yield of cases, treatment patterns, and short-and long-term outcomes for FH patients. - To qualitatively assess the acceptability of cascade testing approaches to individuals and families with potential and confirmed FH, and to health care providers, commissioners and other stakeholders.
Study Configuration	Multi-centre mixed methods study with evidence synthesis, database analysis, cost-effectiveness analysis and qualitative interviews
Setting	Primary and secondary care
Sample size estimate	Interviews will continue until saturation of themes in each set of patient, relative, provider, commissioner and stakeholder interviewee groups. No sample size calculation is required for the economic model development, evidence synthesis or database analysis.
Number of participants	Up to 72 participants will be recruited for the qualitative study
Eligibility criteria	Qualitative study interviews: - Able to give written informed consent - 18 years of age or over - Able to complete an interview in English - [For patients] Considered by their usual health care provider to be appropriate to recruit to the study.
Description of interventions	A single interview will be conducted with each participant. Participants will be offered the option of providing feedback by interview following reviewing their preliminaryinterview results.
Duration of study	Study duration – 36 months Individual participant duration – 3 months to 2 years (optional 2 years for providing feedback on the collated interview results)
Methods of analysis	Framework Analysis will be used for the analysis of the interview transcripts. Data from the NHS services, FH national databases and other databases, e.g. CPRD, will be used to develop economic models and to report characteristics of the data. A range of statistical analyses will be used to estimate parameters for the cost-effectiveness model. Standard cost-effectiveness modelling methods (decision trees and/or state transition models) will be used to estimate costs and health outcomes for alternative cascade protocols to inform decisions relating to cost-effectiveness. Value of information analysis will be conducted to inform future research prioritisation decisions.

ABBREVIATIONS

BHF	British Heart Foundation
CCG	Clinical Commissioning Group
CDC	Centre for Disease Control and Prevention
CHD	Coronary Heart Disease
CI	Chief Investigator (overall)
CPRD	Clinical Practice Research Datalink
CV	Curriculum Vitae
eDRIS	electronic Data Research and Innovation Service
FH	Familial Hypercholesterolaemia
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital Episode Statistics
HRA	Health Research Authority
ICER	Incremental Cost-Effectiveness Ratio
ICH	International Conference on Harmonisation
ISAC	Independent Scientific Advisory Committee
LDL	Low-Density Lipoprotein
MINAP	Myocardial Ischaemia National Audit Project
NACSA	National Adult Cardiac Surgery Audit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICOR	National Institute for Cardiovascular Outcomes Research
ONS	Office for National Statistics
PASS	Pro Active Software Solutions
PBPP	Public Benefit and Privacy Panel
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator at a local centre

PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QALY	Quality-Adjusted Life Year
RCGP	Royal College of General Practitioners
REC	Research Ethics Committee
R&D	Research and Development department
SB	Simon-Broome
UK	United Kingdom
UoN	University of Nottingham

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STUDY BACKGROUND INFORMATION AND RATIONALE

Familial Hypercholesterolaemia (FH) is the commonest autosomal dominant disorder with at least 1 in 500 individuals (0.2%) affected by the more common heterozygote form [1, 2]. However 80% of those with the condition are not currently identified [3].

Left untreated, individuals with FH have a dramatically higher risk of coronary heart disease (CHD), with a 100-fold increased mortality risk compared to the general population [4,5]. CHD in people with FH can be very effectively prevented by high intensity lipid lowering treatment, with a 48% reduction in CHD mortality [6]. Moreover, 50% of their first degree relatives and 25% of second degree relative will also have the condition and will benefit from intervention.

Improving the current low detection rate of FH is urgently needed. More effective cascade testing to identify affected relatives, especially younger relatives, and to initiate early statin treatment to lower LDL (low-density lipoprotein) cholesterol will prevent and reduce premature mortality, and long-term morbidity. Available service data highlight the major extent of the problem. National audits show only around 1 affected relative is identified for each index case [7].

Current national guidelines recommend the early identification and management of patients with FH. Despite recommendations in the 2008 NICE guidelines, a RCGP audit in 2010 indicates up to 80% of individuals with heterozygote FH are not identified, leading to unnecessary premature CHD in up to 256,000 individuals.

Identification in primary care remains poor and opportunistic. Processes in both primary and specialist care are neither systematic nor well documented, and strict criteria for genetic testing prevail. Subsequent cascade testing of relatives is also sub-optimal due partly to perceived barriers for specialists to approach relatives directly, particularly if they live in different geographies. Moreover, people with FH are mainly managed by specialist care, despite the potential for greater management in primary care.

Existing cost -effectiveness analyses (UK and internationally) have explored whether or not specific protocols for cascading are cost-effective [8,9,10,11]. However, commissioners and policy makers are uncertain about whether current cascade programmes represent the best value for money in practice [12,13]. They have questioned whether tighter criteria for cascading could offer better value for money, and whether service protocols could do more to maximise the number of relatives tested.

By using robust and multiple data sources, and modelling a wide range of possible protocols for cascade testing, this study will identify the most cost-effective protocol for cascade testing for familial hypercholesterolaemia in UK clinical practice and the NHS.

The study will use economic modelling to evaluate the cost-effectiveness of alternative cascade testing protocols. Parameters to inform these models will be derived from existing published literature and routinely available data in primary and specialist care. In this study we will collect data from 3 large regional FH services (Wessex, Scotland, Wales) with differing protocols for cascade testing.

The Welsh service, serving a population of 3.2 million since 2011 and co-funded by BHF, identifies new FH cases using modified Dutch Lipid Clinic referral criteria [16], including triglyceride levels. Several modalities of identification are used including specialist nurses accessing primary care records. Cascade testing to relatives is offered directly (initiated by

the clinic/medical professionals) and indirectly (initated by patients providing information to their family members).

The Wessex service, serving a population of 2.5 million, is one of the first British Heart Foundation (BHF) pilots (2014). Cases are identified through primary care based FH coordinators using modified NICE Simon-Broome referral criteria with higher LDL cholesterol threshold (>5.5) and takes account of triglyceride levels [14]. Cascade testing to relatives is usually through indirect contact.

The Scottish service protocol [15] serves a population of 5.5 million since 2008. GPs use NICE Simon-Broome criteria for referring suspected index cases either directly for genetic testing or through a network of 17 lipid clinics. Patients with genetically confirmed FH are referred to genetic services for cascade testing, initially contacting relatives indirectly, but more recently using indirect and direct approaches.

All 3 services have paediatric FH diagnosis protocols: Wessex and Scotland offer genetic tests from 10 years of age whilst the Welsh service offer testing from 8 years of age.

In exploring and identifying the most cost-effective protocols and care pathways, successful future and wider implementation will be dependent on their acceptability to a range of stakeholders. Exploration of the experiences, views and attitudes of patients and family members, primary care and specialist health providers, and service commissioners is thus needed.

STUDY OBJECTIVES AND PURPOSE

PURPOSE

The study will identify the most cost-effective and acceptable protocol for FH cascade testing based on best current evidence. In this cost-effectiveness model, aspects of the cascade protocol will be varied in different combinations to generate a series of protocols for comparison. Protocols will differ in terms of the criteria used to select individuals with FH from whom to cascade (e.g. Simon-Broome, Dutch Lipid Clinic referral criteria, cholesterol thresholds), methods of testing (genetic, LDL), direct or indirect contacting of relatives, how far to test family (1st, 2nd, 3rd degree relatives etc.) and extension of testing to relatives in other geographical areas.

PRIMARY OBJECTIVE

To evaluate the cost-effectiveness of alternative protocols for FH cascade testing using data from service protocols in three UK regions, the literature, and linkage of national clinical databases.

SECONDARY OBJECTIVES

1. To determine the yield of cases, treatment patterns, and short- and long-term outcomes for FH patients by analysis of routine service data and by new linkage of national FH, primary and secondary care datasets.

2. To qualitatively assess the acceptability of cascade testing approaches to individuals and families with potential and confirmed FH, and to health care providers, service commissioners and other stakeholders.

STUDY DESIGN

STUDY CONFIGURATION

The focus of this protocol is to detail the qualitative study and process of extraction of routine secondary care NHS data and established research databases to inform the development and parameterization of economic models for alternate protocols of FH cascade testing.

This is a multi-centre mixed methods study with evidence synthesis, database analysis, cost-effectiveness analysis, and qualitative interviews.

The setting is UK Primary (general practice) and Secondary Care.

STUDY MANAGEMENT

A core study management team of chief and co-investigators and employed staff will meet monthly, including local PPI representative, with PPI lead and Service leads joining by telephone. In the first 18 months, prior to each meeting, each dataset provider will confirm progress on data capture and linkage. There will also be an annual full meeting of the complete team.

External oversight will be provided by a study advisory group, including local PPI representative, BHF and Heart UK representatives, lipid specialist, health economist and the study chief investigator and work stream leads.

The Chief Investigator has overall responsibility for the study and shall oversee all study management.

The data custodian will be the Chief Investigator.

DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

Study duration: 36 months

Participant duration in qualitative study: 3 months for a single interview, or up to 2 years if optional consent is received to review a preliminary interview findings and provide feedback.

End of the Study

The end of the study will be the last interview/validation interview of the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS FOR QUALITATIVE STUDY

Recruitment

Understanding stakeholders' views and experiences, provides insight into why a protocol/care pathway, or its constituent components, may not be implemented or may have unanticipated consequences. Relevant qualitative exploration with stakeholders is thus important in identifying acceptability of approaches.

The objectives of the qualitative study are, to assess the acceptability of care pathway/protocols for FH identification, in particular, the cascade testing approaches used,

from the perspectives of patients, parents of affected children, other family members, health care providers, and health service commissioners.

Sampling frame

Patients

Purposeful samples of patients (FH index cases and relatives) will be identified and selected to participate from across two Welsh Health boards and up to two large counties of England. Participants will be sampled to include a spectrum of experience in relation to differing types of FH index and cascade testing provision (e.g. dual primary-secondary care, nurse specialist locality outreach, virtual and conventional lipid clinic, regional genetic service models). The estimated number of participants is 30-40 (approximately 15-20 index cases and 15-20 relatives). The index cases and relatives are all patients.

Patient participants will be recruited from primary and secondary care clinics in England and Wales. The initial approach will be from a member of the patient's usual care team in person during a clinic visit, or via an invitation letter and information sheet sent in the post. A reminder letter will be sent if initial interest in the study is lower than anticipated and not likely to meet the target recruitment.

Sampling will further seek appropriate diversity within each participant group. This will include, for example, socio-demographic range of index patients and relatives identified by cascade testing, with differing range of FH assessment and testing experiences (e.g. confirmed negative/genetically confirmed FH/declined testing; relative indirectly or directly approached for testing; contacted within or outside of area for testing; variation in number of relatives successfully or not successfully tested per index case); and diversity of health care provider (administrative, outreach/FH coordinator or nurse specialist, primary care, lipid or genetic specialist).

Staff: Health Care Providers

A purposeful sample of health care providers (estimated at 15-20) will be identified and selected to participate from across two Welsh Health boards and up to two large counties of England. Participants will be sampled to include a spectrum of experience in relation to differing types of FH index and cascade testing provision (e.g. dual primary-secondary care, nurse specialist locality outreach, virtual and conventional lipid clinic, regional genetic service models).

Staff: Service commissioners and other stakeholders

Up to a further 10-12 semi-structured telephone interviews will be undertaken with a purposeful sample of service commissioners and other stakeholders across the UK (CCGs, NHS England, Public Health England, Department of Health). These will discuss the emerging cascade testing approaches and those from patient, relative and provider interviews (above). This will be used to inform further exploration and discussion of the acceptability of cascade testing protocols for the NHS.

Staff (health care provider, service commissioner and other stakeholder) participants will be recruited from primary and secondary care, service commissioners and other stakeholders in England and Wales. The initial approach will be from the research team who will contact the service/department via email and follow up with a telephone call if necessary. A key member at the service/department may disseminate the email invitation and information sheet to further members of their team. A reminder email will be sent if initial interest is lower than anticipated.

The investigator or their nominee, e.g. from the research team or a member of the participant's usual care team, will inform the participant of all aspects pertaining to participation in the study.

Hospital interpreter and translation services will not be required for the interviews as all interviews will be undertaken in English as per the inclusion criteria.

It will be explained to the potential participant that entry into the study is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased.

Eligibility criteria

The eligibility criteria in this section relates to the qualitative study only

Inclusion criteria

Patients and health care providers, service commissioners and other stakeholders

- Able to give written informed consent
- 18 years of age or over
- Able to complete an interview in English
- [For patients] Considered by their usual health care provider to be appropriate to recruit to the study.

Exclusion criteria

Patients and health care providers, service commissioners and other stakeholders

- Unable to give written informed consent
- Under 18 years of age
- Unable to complete an interview in English
- [For patients] Considered by their usual health care provider to be inappropriate to recruit due to psycho-social reasons, or significant health reasons, e.g. terminal illness/diagnosis.

Expected duration of participant participation

Study participants will be participating in the study for one interview lasting up to 45 minutes. It is anticipated that participants will be involved in the study for up to 3 months from the date of providing consent to the end of the interview. Participants have the option to provide feedback on their preliminary interview findings should they wish to add anything or provide further information. In these cases, the participants may be involved in the study up to 2 years after invitation.

Participant Withdrawal

Participants may be withdrawn from the study either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Informed consent

Qualitative study

All participants will provide written informed consent. For telephone interviews, the consent form will be posted to the participant for completion and return prior to the interview. On receipt, the researcher will sign and date the consent form. The researcher will re-confirm consent verbally at the start of the interview.

The Consent Form will be signed and dated by the participant before they enter the study. The Investigator or nominated representative will explain the details of the study and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator or nominated representative will answer any questions that the participant has concerning study participation. Verbal informed consent will be collected from each participant before they take part in an interview and this will be recorded during the audio recording.

One copy of the consent form will be kept by the participant and one will be kept by the Investigator for the study master file. Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the study, continuing consent will be obtained using an amended Consent Form which will be signed by the participant.

STUDY REGIMEN FOR QUALITATIVE STUDY & ECONOMIC MODELLING

Qualitative study

Semi-structured interviews will follow topic guides that have been devised based on existing research and emerging findings from the economic model development, and discussions with our Patient and Public Involvement (PPI) and Study Steering Committee.

The interviews will explore participants' perceptions, views and concerns about cascade testing approaches they have experienced or been involved in delivering. This will include experienced or perceived acceptability, benefits, concerns or harms associated with cascade testing, including views on maximising number of relatives tested, and any different elements of proposed cascade testing protocols emerging from the other research work-streams.

Interviews will be up to 45 minutes, audio-recorded and transcribed verbatim; and will continue until saturation of themes in each set of patient, relative and health provider interviewee groups. This is anticipated to occur after up to 15-20 interviews in each set (45-60 in total) have been undertaken, or at 10-12 interviews for the commissioners and other stakeholders.

Semi-structured interviews will be conducted at participants' convenience:

- with patients and relatives interviewed by telephone, or face to face at their home or clinic site, according to their preference.
- with health care providers, service commissioners and other stakeholders by telephone.

Once all of the interviews are complete we would like to send a copy of the interview preliminary findings to all participants who wish to receive this. A sample of these may have

opted on the consent form to agree to a short telephone interview to discuss the findings. This telephone interview will be arranged by the researcher with the participant. Written notes will be made during the call.

Economic models
The primary objective involves developing an economic model that synthesises evidence on cascade testing, with evidence on the short- and long-term costs and benefits of identifying and managing FH cases. This will be based on anonymous data from a) differing cascade testing services operating in three geographical areas of the UK; and b) linking UK primary and secondary care datasets describing the management and outcomes of patients with FH alongside data from the peer-reviewed and grey literature.

The model will compare alternative cascade testing protocols to each other. The testing compared will differ by:

- criteria used to select individuals with FH from whom to cascade (e.g. Simon-Broome, Dutch Lipid Clinic referral criteria),
- methods of testing (genetic, LDL),
- direct or indirect contacting of relatives,
- how far to test family (1st, 2nd, 3rd degree relatives etc.)
- extension of testing to relatives in other regions.

The model will predict for each protocol:

- yield of FH relatives;
- reduction in long term cardiovascular events,
- survival and quality adjusted life years (QALYs) due to lipid lowering therapy initiation at different ages;
- short- and long-term costs incurred by the NHS and personal social services.

Routine NHS service databases
Data on yield of FH cases will be captured from routine service datasets in 3 areas: Wales, Wessex and Scotland. This rich evidence to estimate the impact of identifying and managing relatives with FH will enhance the precision and robustness of cost-effectiveness model parameters.

Access to the routine NHS service databases/data will be requested from the relevant NHS or university bodies with approval from the appropriate regulatory authorities (e.g. Health Research Authority, NHS ethics) and R&D offices.

Wales PASS (FH) data
The data required is held by the All Wales Medical Genetic Services within NHS Wales, hosted by Cardiff and Vale University Health Board. The FH data is held in PASS software. Access to use this data for research purposes is governed by ethics and R&D approvals at the Health Boards. PASS data will be anonymised by the PASS data guardian (Collaborator Kate Haralambos) and delivered to the research team at the University of Nottingham and the University of York. The anonymised data will be encrypted on site via TrueCrypt and transferred through secure file transfer protocol from Cardiff & Vale University Health Board to the University of Nottingham and to the University of York. The research teams will then store the dataset on secure University network drives, managed by IT services.

Wessex PASS (FH) data
University Hospital Southampton NHS Foundation Trust holds the data. The FH data is held in PASS software. The Wessex PASS database is held by Wessex Clinical Genetics Service. Access to use this data for research purposes is governed by ethics, HRA and R&D

approval. PASS data will be anonymised by the PASS data guardian/IT service/Wessex Clinical Genetics Service and delivered to the research team at the University of Nottingham and the University of York. The anonymised data will be encrypted on site via TrueCrypt and transferred through secure file transfer protocol from University Hospital Southampton NHS Foundation Trust University of Nottingham to University of York. The research teams will then transfer the dataset to secure University network drives, managed by IT services.

Data obtained from PASS software in Wales and Wessex will include the following variables where available:

- Type Client (Index/Relative)
- Age
- Age at death
- Gender (Unknown: Male: Female)
- Family number
- Database number (this field is automatically populated by the system)
- Reason does not participate
- Ethnicity
- *If relative:*
  - Method of contact of relative (unknown: direct: indirect)
  - Relationship to index case (parent, sib, child, 2nd degree relative, 3rd degree relative, unknown)
- Health Board/NHS Trust
- Height
- Weight
- BMI
- Date
- Previous CVD History & Age: MI/ACS, PTCA, CABG, Angina, Stroke/TIA, PVD, Other, Comment
- Clinical Signs of FH & location: Coneal Arcuas, Xanthelamas, Tendon Xanthomata, Comment
- Medical risk factors: Smoking (If YES selected, 'Cigarettes/Day?' appears. If NO selected, 'Age Stopped?' appears), Alcohol use, Blood pressure: (Systolic: Diastolic), Blood pressure date, Uses BP medication, IFG/TGT, Diabetes (If YES selected, 3 additional datafields appear: Type, Since, Treatment)
- Lipids: Currently on lipid treatment, Reason why patient not taking statin, Lipids [Date: Fasting: TC: HDL: Trig: LDL: Non-HDL: Glucose: Lipid medication: Apo A1: Apo B: Lp(a)]
- Genetic investigations: Date of sending, Genetic result and date
- Clinical investigations: Relative (Date of LDL-C measurement, LDL-C , FH status), Index (Simon Broome Criteria, Unknown, Possible SB, Definitive SB, Dutch Clinic Lipid Network score)
- Family history of raised cholesterol (level of cholesterol/LDL cholesterol; relative affected)
- Family history of CVD less than 60 (relative affected & age affected)
- Referrals: Date of referral, Comment

NHS Scotland FH data

The NHS Scotland FH genetic data, which has previously been linked to morbidity and mortality outcomes for service evaluation purposes, will be updated as part of this study and will contain data from over 4000 patients who have gone through genetic testing for FH in Scotland.

The Public Benefit and Privacy Panel (PBPP) is a governance structure of NHS Scotland. The panel, with its expertise in privacy, confidentiality and information governance reviews applications for access to NHS data for purposes other than direct care. Co-investigator Zosia Miedzybrodzka and her team will apply for permission from PBPP to use the linked data for the research described in this protocol and to have the linkage updated. eDRIS, (electronic Data Research and Innovation Service) which is part of the Information Services Division, NHS National Services Scotland, will prepare the updated linkage and transfer the pseudonymised linked FH dataset securely to the Grampian Data Safe Haven (DaSH) where it will be made available to the researcher team once all the appropriate permissions are in place.

DaSH, a joint University of Aberdeen and NHS Grampian facility, is one of eight Scottish Safe Havens recognised by PBPP; these facilities were set up to store and manage unconsented linked health data for research. As well as providing a secure computing environment DaSH has governance and data management procedures in place to reduce the risk to patient confidentiality. Only researchers named in the project permissions applications who have information governance training are allowed access to their pseudonymised data. Access is via a Virtual Private Network and is password protected. Researchers are made aware of the conditions of use of the safe haven and that there are penalties for breaches. Printing and internet access facilities are disabled in the safe haven desktop environment, researchers cannot remove data and any analyses outputs are checked by the safe haven Research Co-ordinators to ensure no individually identifiable information is removed.

In total, routine FH cascade testing service datasets will yield: retrospective data on 6408 cases & 1902 relatives from Scotland, Wales and Wessex with additional prospective data collection during study.

Linked FH study databases
The study team propose to evaluation treatment patterns and short- and long-term outcomes in FH patients, by linkage of national research databases. Data on cases managed in primary and secondary care will be linked to data on treatment patterns and cholesterol response.

Data from the following databases and registers will be included (where available):

- Simon-Broome FH disease registry
- National Institute for Cardiovascular Outcomes Research (NICOR) datasets
- Hospital Episode Statistics (HES) and Office for National Statistics (ONS) Mortality datasets
- Clinical Practice Research Datalink

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The databases will provide anonymised data for the economic model to the University of Nottingham and University of York. The providers issue a data sharing contract and material transfer agreement following their approval process for the data to be transferred or accessed. The data providers will conduct the linkages requested and deliver the anonymised data to the University of Nottingham and University of York research teams as described in the material transfer agreements.

Additional parameters will be identified by reviews of the literature and synthesis.

Criteria for terminating the study

Early termination of the study is unlikely, however should there be database access or transfer issues which cannot be resolved the data from the particular database will not be included in the final dataset. Where possible, e.g. for secondary care data held by the NHS, a replacement source/site will be sought.

ANALYSES of QUALITATIVE STUDY and DATABASES for ECONOMIC MODEL

Methods

Qualitative study

Data (transcribed verbatim from audiotaped interviews) will be organised using qualitative software, and analysed thematically. Coding and development of analysis will involve a minimum of two qualitative researchers, and include comparison of data within and between interviewee groups.

Data analysis will be carried out using Framework Analysis, an approach to thematic qualitative analysis that has been explicitly developed in the context of applied social science research. This method facilitates systematic and transparent data analysis, allowing the researcher to move between levels of abstraction while maintaining clear links to the original data. The approach allows the researcher to identify patterns or commonalities, as well as contradictions in and between participants' accounts, and explore and test explanations for those patterns. It is also open to external scrutiny and the systematic nature of the process means it can be replicated.

Data from each sample (patients, practitioners, commissioners) will first be analysed separately to produce a working report. A second stage of analysis will identify consensus and differences in views and perspectives between the stakeholder groups. This qualitative component focuses primarily on protocol implementation and is as such not seeking to elicit a deep understanding of lived experiences.

Framework analysis involves five distinctive stages:

1) familiarisation with the data: immersion in the raw data to gain an overview of the whole,
2) identifying a thematic framework: grounded in the research questions, identifying the key concepts and issues (both a priori informed by existing literature) and those emerging from the data of one or more individual respondents,
3) indexing: applying the framework to the transcripts, annotating the transcripts with identification codes referring to themes and sub-themes,
4) charting: extracting data from its original context, summarising and grouping it in chart form according to the thematic reference,
5) mapping and interpretation: reviewing the charts and research notes to compare and contrast, search for patterns and connections and provide explanations for the emerging findings.

Validate findings: To further refine and validate analysis, all participants will be invited to review and comment on summaries of preliminary findings to enable further opportunity to reflect on findings.

Economic models

Analysis of routine NHS databases
To generate the parameters necessary to populate the cascading process module of the economic model, routine service data collected in PASS and Scottish FH datasets will be analysed.

Data from these datasets will be used to predict the probability that an individual with specific demographic and clinical characteristics will have FH. This analysis will use data on all individuals with possible FH who received a genetic test in Scotland, Wales and Wessex to date. This analysis will use logistic regression to develop a predictive model to quantify the probability that an individual carries a monogenic mutation. This analysis will facilitate the comparison of different criteria by which index cases are selected for genetic testing and subsequent cascading. These criteria will range from broad (all index cases tested) through to tight criteria (only those with the highest probabilities of carrying the monogenic mutation are genetic tested).

Data will also be used to identify the potential number of relatives per index case, the actual number of relatives contacted and tested, and the characteristics of those relatives. The demographic and disease characteristics of the relatives will be used to generate predictions of their long-term outcomes. This data will also provide information on the extent of lipid lowering treatment use in relatives prior to FH diagnosis. This is important as it will impact upon the benefit of diagnosis.

Analysis of linked-FH databases
Data from the linked datasets of diagnosed FH patients identified in CRPD, and identified via the Simon-Broome registry will be analysed using a form of survival analysis called multi-state modelling [17,18]. Parametric survival models will be built to analyse and extrapolate rates of events. This will allow the full protocol followed by each patient, including treatment, non-fatal clinical events and deaths, to be described and for these data to inform estimates of long-term costs and QALYs. Estimates of the outcomes experienced by each patient will be conditioned upon their baseline demographic and clinical characteristics. Analysis of the Simon-Broome cohort of FH individuals followed up over a long time horizon will allow the sequence of adverse short and long-term consequences of FH to be accurately quantified for the first time.
The Simon-Broome dataset contains data from both the pre- and post-statin eras. These data will therefore be used to inform one scenario regarding the impact of diagnosis and treatment on outcomes.

Although the link between FH and elevated risk of coronary heart disease is well established, there is limited evidence regarding whether FH patients face an elevated risk of other cardiovascular diseases. In order to inform the selection of important events for inclusion within the model structure, an analysis comparing the rate of other cardiovascular events in FH patients with the rate in a matched cohort of the general population will be conducted from a large primary care dataset (CPRD).

Data from the literature

The analysis of databases described above will be supplemented by data from the literature where necessary to inform aspects of the model.

Model programming
A model will be developed to evaluate a wide range of protocol strategies, combining different criteria for genetic testing of the index case, use of different tests (genetic and/or LDL) and use of different methods to contact relatives (direct and indirect, contacting only

1st or also more distant relatives, inclusion of relatives in other geographical areas). The model will predict for each protocol: the yield of FH relatives; the reduction in long term cardiovascular events and extensions to survival and QALYs due to lipid lowering therapy initiation at different ages; and short- and long-term costs incurred by the NHS and personal social services. The ultimate output of the model will be the incremental cost-effectiveness ratios (ICERs) corresponding to the simultaneous comparison of all evaluated protocols. These results will be interpreted using a range of cost-effectiveness thresholds to identify a cost-effective FH protocol.

The results will be subject to deterministic and probabilistic sensitivity analysis. The deterministic sensitivity analyses will examine areas of parameter and structural uncertainty identified during the modelling process, including sensitivity analyses examining the impact of adherence, the approach used to model the impact of diagnosis and treatment on outcomes, and the impact of having a nationally co-ordinated programme compared to individual region-specific services as this will impact on the yield of relatives contacted and ultimately tested. Value of information analysis will be conducted to quantify the overall value of future research in this area, and the value of specific future research designs (e.g. a comparison of direct and indirect testing, improved data on treatment adherence and the link between adherence and outcomes).

Model review and validation
A series of established steps will be conducted to establish model validity [18]. The model outputs will be reviewed by the expert group who reviewed the conceptual model to establish face validity. This will take the form of a one-day meeting. At this meeting findings from the qualitative research will be reviewed to identify whether this has any implications for the feasibility of the protocols evaluated. Verification (technical validation) will be conducted using standard methods; cross-validation via comparison with other models will be conducted, as will external validation with other sources of data on outcomes in FH patients.

Sample size and justification

Qualitative study
Interviews will continue until saturation of themes in each set of patient, relative and health provider interviews. This is anticipated to occur after up to 15-20 interviews in each set have been undertaken and 10-12 interviews for the service commissioners and other stakeholders

Economic models
As this study is primarily aimed at developing new economic models for FH identification and management informed by evidence synthesis, using FH databases, and conducting qualitative interviews, no sample size calculation is required.

ADVERSE EVENTS

The occurrence of an adverse event as a result of participation within this study is not expected and no adverse event data will be collected.

ETHICAL AND REGULATORY ASPECTS

For the qualitative study, interviews may take place at participants' homes and other sites across the country. The researchers will follow the University of Nottingham Lone Working Policy when working off-site.

It is not anticipated that the interviews will raise any sensitive issues, however should this occur, the researcher will inform the Chief Investigator who will take appropriate action (e.g. inform the clinical care team if required).

ETHICS COMMITTEE AND REGULATORY APPROVALS

The study will not be initiated before the protocol, consent forms and participant information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

For databases, the researchers will follow all requirements set out by provider as described in the data sharing agreements (where available). Research will be conducted in accordance to information governance guidelines set forth by the respective Caldicott Guardian.

INFORMED CONSENT AND PARTICIPANT INFORMATION

For the qualitative study, the process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Study records.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care (for the patient participants), or loss of benefits to which the participant is otherwise entitled. No study-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Consent Form by the REC and use of the amended form (including for ongoing participants).

For the databases, the researchers will only access anonymised data with no identifiable information, thus no informed consent is needed.

RECORDS FOR QUALITATIVE STUDY

Study Forms

For the qualitative study, each participant will be assigned a study identity code number, for use on study forms, other study documents and the electronic database. The documents and database will use a study identifier which includes a site identifier starting from 01 and a participant number starting from 01. For example, 0101 or 0205.

Study forms will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth and Participant Study Number, to permit identification of all participants enrolled in the study, in case additional follow-up is required.
Study forms shall be restricted to those personnel approved by the Chief or local Investigator and recorded as such in the study records.

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Investigator shall sign a declaration ensuring accuracy of data recorded in the study forms.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, study records, field notes, interview transcriptions and audio records. A study form may also completely serve as its own source data. Only study staff shall have access to study documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The study forms and all source documents shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities.

DATA PROTECTION

All study staff and investigators will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The study forms will only collect the minimum required information for the purposes of the study. Study forms will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the study staff and investigators and any relevant regulatory authorities (see above). Computer held data including the study database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

For analysis, interview transcripts will be shared with the partner organisations (University of Southampton, University of York, Cardiff University and University Hospitals Southampton NHS Foundation Trust). Transcripts will have identifiable personal data removed and will only include participant identifier and the type of participant (index patient, family member, provider, commissioner or stakeholder). These will be shared in password protected files via email with the password telephoned to the relevant contact at each organisation separately.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for clinical study participants and study staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but study participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

STUDY CONDUCT

Study conduct may be subject to systems audit for inclusion of essential documents; permissions to conduct the study; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, timeliness of visits); accountability of study materials and equipment calibration logs.

STUDY DATA

Monitoring of study data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Study Coordinator/Academic Supervisor, or where required, a nominated designee of the Sponsor, shall carry out monitoring of study data as an ongoing activity.

Entries on study forms will be verified by inspection against the source data. A sample of study forms (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the study database will be checked. Where corrections are required these will carry a full audit trail and justification.

Study data and evidence of monitoring and systems audits will be made available for inspection by the REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The study documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all anonymised audio recordings, study databases and associated meta-data encryption codes.

DISCONTINUATION OF THE STUDY BY THE SPONSOR

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical or personal information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this study will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

In the UK, we are active current contributors to NICE guidelines for FH and will ensure the outputs of this cost-effectiveness analysis inform updated NICE guideline recommendations and quality standards.

We will also work with the International FH foundation, US CDC Office of Public Health Genomics and European collaborators, and our international advisers in Australia, USA and Europe to ensure our analysis informs international guidelines recognising potential differences between international settings.

We will ensure that findings are highlighted to the public, patients, and policymakers (NHS, Department of Health, Public Health England and NICE) in partnership with third sector voluntary organisations (Heart UK and British Heart Foundation - BHF).

We will support Heart UK to organise patient and health professional focus groups to help refine findings and produce digital dissemination strategies (e.g. involving website, email, Facebook, Twitter or similar).

Working closely with Heart UK and BHF we will disseminate learning from the study to NHS commissioners by:

- Networking with existing and potential FH service commissioners across England, e.g. national NHS commissioners workshop
- Presenting study findings in a way that makes sense to managerial and commissioning audiences, e.g. publish articles in NHS professional and health service commissioner journals
- Sharing learning of early implementers of FH services
- Scoping the possibility of producing a FH toolkit incorporating advice on FH service design and a revised costing template for FH services that is generalizable to the English NHS, based on CCG geographies.

As well as completing NIHR HTA monograph, standard dissemination strategies, of peer-reviewed open access primary care, public health, cardiovascular and genetic publications and conference presentation, will be further prioritised.

USER AND PUBLIC INVOLVEMENT

We have an established and experienced Familial Hypercholesterolaemia (FH) PPI group involved across our research processes from identifying questions to dissemination [3]. This includes working with nominated lay representative by Heart UK; local service user who has FH and have experienced cascade testing; and national PPI Co-Applicant William Rowlands, who has FH, was a member of the NICE FH Guideline Group [20] and is experienced in the development and dissemination of patient information resources.

Although it is 8 years since NICE guidelines for FH, our PPI group know there is minimal improvement in the identification of this condition. They consider current protocols are not working and that cascade testing could be improved. They strongly support direct contact with all relatives.

To assess the acceptability of testing protocols, our PPI group has highlighted the need for qualitative investigation with patients, health professionals and FH patient champions. With HeartUK and BHF, we continue to review current protocols and testing. We will ensure our PPI group continues to inform and be actively involved in the proposed work.

Patients and the public will be involved throughout this study, from design of the research through to management of the research, supporting developing participant information, contributing to the reporting of the research and in dissemination of the findings.

STUDY FINANCES

Funding source

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA).

Participant stipends and payments

Interview participants will offered an inconvenience allowance of a £20 gift voucher for their time. Travel expenses will be offered for any travel costs incurred for the interviews.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

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