Study Protocol

Study title:
Lipid-modifying therapy in children with familial hypercholesterolemia

Version 2.0
1 September 2024

Study Sponsor: University of Nottingham

Funder: This study is funded by the NIHR HTA [National Health Institute for Health and are Research Health Technology Assessment (Award ID NIHR134993)]. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

This document is the protocol for a mixed-methods study that contains 4 main data sources (study components) each with separate protocol approvals/data access agreements:

NHS HRA REC reference: 23/NE/0035	Estimating appropriate lipid lowering management in the United Kingdom paediatric hypercholesterolaemia register
CPRD RDG Protocol ID: 22-002278	Lipid-lowering therapy in young people with familial hypercholesterolaemia: A cohort study using primary and secondary care data to measure reductions in cholesterol, adherence, and safety
ALSPAC Reference (B Number): B3815	Cholesterol trajectories throughout childhood and associations with growth and carotid intima-media thickness
UoN FMHS REC reference: FMHS 253-0423	A questionnaire and interview study of healthcare professionals working in paediatric familial hypercholesterolaemia across the United Kingdom

NHS HRA REC	National Health Service Health Research Authority Research Ethics Committee
CPRD RDG	Clinical Practice Research Datalink Research Data Governance
ALSPAC	Avon Longitudinal Study of Parents and Children
UoN FMHS REC	University of Nottingham Faculty of Medicine and Health Sciences Research Ethics Committee

Table of contents

1 Study personnel and contact details

Sponsor: Contact name	University of Nottingham Ms Angela Shone Research and Innovation University of Nottingham Research and Innovation E-floor, Yang Fujia Building Jubilee Campus Wollaton Road Nottingham NG8 1BB
Study host organisation (Data Controller):	University of Nottingham
Co-Chief investigator	Laila J Tata Associate Professor, Epidemiologist Lifespan and Population Health, School of Medicine, Room B119, Clinical Sciences Building, City Hospital, Hucknall Road, Nottingham, NG5 1PB United Kingdom Phone: +44 (0) 115 823 1353 Email: Laila.tata@nottingham.ac.uk
Co-Chief investigator	Nadeem Qureshi Clinical Professor, General Practitioner Lifespan and Population Health, School of Medicine, Applied Health Research Building, University Park Nottingham, NG7 2RD Phone: +44 (0) 115 846 6900 Email: Nadeem.qureshi@nottingham.ac.uk
Study Co-applicants:	Manpreet Bains Beth Woods Alexis Lewellyn Yana Vinogradova Ralph Akyea Lorraine Priestley-Barnham Steve Humphries Joe Kai Manual Gomes Mark Fisher
Study Coordinating Centre:	School of Medicine Applied Health Research Building, University Park Nottingham, NG7 2RD

2 Summary of research

2.1 Plain English Summary of research

BACKGROUND: People with familial hypercholesterolaemia (FH) have raised cholesterol levels in their blood from birth. Cholesterol is a type of fat our bodies need but having raised levels over a long time causes heart disease, such as heart attacks. To prevent future heart disease, guidelines recommend starting cholesterol-reducing medication, usually statins, by age 10. However, there are still unanswered questions about what is the right age and cholesterol level at which to start statins to prevent heart disease later in life. Important considerations are: avoiding side effects, giving best value for money for the health service, and ensuring that treatment is acceptable for children/young people and their families.

We will answer these questions by:
1. Measuring health benefits and risks of starting cholesterol-reducing medication in childhood and adolescence ("Clinical effectiveness")
2. Exploring the "Acceptability" of this medication for children/young people, families and healthcare professionals
3. Assessing value for money, through calculating the costs and benefits of starting medications at various ages and the savings produced by preventing early heart disease ("Cost-effectiveness")

DESIGN & METHODS:
(1) "Clinical effectiveness": we will follow children/young people with FH over time, to confirm how well medications work in reducing cholesterol and measure any side effects. We will use a national FH patient register, records from general practices across the country and previous studies. Finally, we will identify average cholesterol levels from young people without FH, which will indicate how far cholesterol levels should be reduced with treatment in children/young people with FH.

(2) "Acceptability": Using questionnaires repeated over time, we will ask young people how regularly they take their medication. We will also arrange interviews to ask the views of children/young people with FH, their families and healthcare professionals about how acceptable it is to start medication early, and the information families need to support their ongoing treatment.

(3) "Cost-effectiveness": We will find out the costs of starting cholesterol-reducing medication and how often children/young people are seen by doctors and nurses. Using the study findings above and information on how cholesterol affects later risk of heart disease, we can calculate the value for money of starting treatment at different ages and cholesterol levels.

2.2 Scientific abstract of research

BACKGROUND: Around 1 in 250 people have familial hypercholesterolaemia (FH) with raised low density lipoprotein-cholesterol (LDL-C) from birth, increasing the risk of premature cardiovascular disease. National guidance recommends starting lipid-lowering treatment (LLT) at age 10 years, yet evidence for the age and LDL-C thresholds at which to initiate LLT is limited, leading to an NIHR HTA commissioned call for the RESEARCH QUESTIONS:

What is the clinical and cost-effectiveness of LLT in children with FH in the UK? How are these affected by the age of commencing treatment and different thresholds of LDL-C for commencing treatment?

OBJECTIVES to answer research questions:

1. Estimate absolute and relative reductions in LDL-C, and in cumulative LDL-C, achieved in current practice with LLT, and whether these vary by age and LDL-C at initiation of LLT

2. Estimate the incidence of side-effects and adverse events associated with LLT

3. Estimate LLT adherence at different ages and characterise reasons for variations in adherence

4. Understand the views of children and young people (CYP), their families and healthcare professionals, on information needs for starting LLT at different ages, and how these influence treatment acceptability, monitoring, and adherence

5. Estimate the impact of initiating LLT at different ages on the costs of managing FH over the short-term in CYP

6. Estimate long-term health outcomes and NHS costs of starting LLT at different ages and LDL-C thresholds to identify a cost-effective approach to management

DESIGN & METHODS:
Obj 1-2: We will update the national Paediatric FH Register (PFHR) with new recruitment, retrospective clinical data and 3.5 years of prospective data, increasing the current 613 patients to over 1,300. We will also identify FH patients in the Clinical Practice Research Datalink (CPRD), and conduct evidence reviews for any remaining gaps. The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort will provide average age-specific LDL-C levels across childhood in the general population that could be used as target LDL-C levels for treatment in FH.

Obj 3-4: Repeated questionnaires sent to CYP on the PFHR will characterise LLT adherence over time, inform healthcare utilisation (for Obj 5), and inform sampling for qualitative interviews (Obj 4). Interviewing 40 CYP with FH and their families and 30 healthcare professionals will inform LLT acceptability and information needed to support monitoring.

Obj 5-6: We will estimate the healthcare costs of managing FH in CYP and the impact of initiating LLT. Synthesising information compiled across the study, we will develop a new cost-effectiveness model estimating long-term reductions in cardiovascular disease risk given observed LDL-C reductions in childhood. The model will compare the benefit-risk, short- and long-term health outcomes and costs of starting LLT at different ages and LDL-C thresholds.

PROJECT TIMELINE: CPRD/ALSPAC analyses [3-12mths]; PFHR and questionnaire analyses [9-54]; Systematic and pragmatic evidence reviews [6-12 & 36-42]; Interview analyses [10-30]; Estimate costs [39-44]; Build cost-effectiveness model [45-56]

IMPACT & DISSEMINATION: We will establish 2 new patient/stakeholder groups for this study bringing direct experience of FH (CYP Advisory Group (CYPAG) and Parent and Carer Advisory Group (PCAG)). In partnership with these groups, charities including HEART UK, and health care professionals involved in FH care, we will widely disseminate findings with presentations and publications for various audiences. Impact will include updating national FH guidelines and informing commissioners and policymakers on service configuration.

3 Acronyms and summary of terms

ALSPAC	Avon Longitudinal Study of Parents and Children
BHF	British Heart Foundation
BMI	Body Mass Index
CIMT	Carotid Intima-Media Thickness
Co-app	Co-applicant

CPRD	Clinical Practice Research Datalink (GP database)
CVD	Cardiovascular Disease
CYP	Children and Young People
CYPAG	Children and Young Peoples' Advisory Group
FH	Familial Hypercholesterolaemia
GMSA	Genomic Medicine Service Alliance
GP	General Practitioner/General Practice
HEART UK	Hyperlipidaemia Education & Atherosclerosis Research Trust UK
HCP	Heathcare Professional
LDL-C	Low Density Lipoprotein Cholesterol
LLT	Lipid Lowering Treatment/Therapy
NHS	National Health Service
NIHR HTA	National Institute for Health and Care Research Health Technology Assessment
PCAG	Parent and Carer Advisory Group *(parents or adult carers/family members)*
PFHR	Paediatric Familial Hypercholesterolaemia Register *(also called The Register)*
PPIE	Patient and Public Involvement and Engagement
QALY	Quality-adjusted life year
REDCap	Research Electronic Data Capture
SD	Standard Deviation
The Register	Referring to the Paediatric Familial Hypercholesterolaemia Register (PFHR)
TWA LDL-C	Time-Weighted Average Low Density Lipoprotein-Cholesterol

4 Background

Heterozygous familial hypercholesterolaemia (FH) is characterised by raised low density lipoprotein-cholesterol (LDL-C) from birth, which increases the risk of premature cardiovascular disease (CVD) as early as people's mid-thirties.[1] Early identification and treatment has shown to be effective.[2,3]

The National Institute for Health and Care Research Heath Technology Assessment (NIHR HTA) have commissioned a call to address a specific evidence gap for the use of lipid-lowering treatment/therapy (LLT) medications in the clinical treatment of children with FH. Current NICE recommendations are to initiate LLT by 10 years of age[4,5] based on: Reviews of studies on statins (the most common type of LLT) demonstrating they reduce LDL-C and are safe (based on up to around 1 year of follow-up data);[2] Observational evidence that treating children with FH reduces their long-term cardiovascular disease (CVD) risk;[6] Estimates of the impact of raised LDL-C over time on CVD risk;[3] and Clinical consensus.[4,5]

The 2019 NICE FH guideline development group recognised the need for more robust evidence on the age and LDL-C at which LLT should be started in children and young people (CYP).[4] Although there are no current longitudinal data with long enough follow-up to provide a direct observation of the association between starting LLT in childhood and CVD onset in adulthood, the commissioned call offers the opportunity to look at other approaches. Statin treatment in adults has a good safety record, however, there are no long-term monitoring studies of safety in children, with the longest studies usually not extending past two years. Monitoring of follow-up lipid concentration levels, growth rates, progression through puberty, and information on any major side effects is of importance throughout childhood. Although the results of short trials are reassuring, many clinicians are still reluctant to prescribe statins at an early age because of the lack of long-term data.

With around 1 in 250 children in the UK[7] having the common heterozygote form, FH is as common as type-2 diabetes. However, over 80% of these individuals remain undiagnosed. To tackle this, the National Health Service (NHS) long term plan proposes to identify 25% of predicted FH individuals by 2024.[8] This will lead to more CYP being diagnosed with the condition, hence the need for clear evidence-based guidance on when to initiate LLT.

5 Research questions (core study aim) and objectives 1 to 6

What is the clinical and cost-effectiveness of LLT in children with FH in the UK? How are these affected by the age of commencing treatment and different thresholds of serum LDL-C for treatment initiation?

To answer these questions the **objectives** are to:

1. Estimate **absolute and relative reductions in LDL-C, and in cumulative LDL-C, achieved in current practice with LLT**, and whether these vary by age and LDL-C at initiation of LLT

2. Estimate the **incidence of side-effects and adverse events** associated with LLT

3. **Estimate LLT adherence** at different ages and **characterise reasons for variations** in adherence

4. **Understand the views of children and young people, their families and healthcare professionals, on information needs** for starting LLT at different ages, and how these influence **treatment acceptability, monitoring, and adherence**

5. Estimate the impact of initiating LLT at different ages on the **costs of managing FH** over the short-term in children and young people

6. Estimate long-term health outcomes and NHS costs of starting LLT at different ages and LDL-C thresholds to identify a **cost-effective approach to management**

5.1 Study design and rationale:

Objectives will be met using a **mixed methods study design, building on existing established longitudinal cohort data sources:**

- **The Paediatric FH Register (PFHR)**[9,10] (section 6.1 on page 11)
- **Children with FH from the Clinical Practice Research Datalink (CPRD) general practice (GP) database**[11] (section 6.2 on page 15)
- **Children from the general (non-FH) population from the Avon Longitudinal Study of Parents and Children (ALSPAC)**[12] (section 6.3 on page 15)

Further detail to characterise adherence and healthcare use will be obtained from **questionnaires sent to PFHR-registered patients**. Questionnaires will provide a framework for sampling **patients/families for qualitative interviews** that will further elucidate views, experiences, and information needs.

Questionnaires sent to healthcare professionals (HCP) and qualitative interviews (section 6.4 on page 15) will also be used to describe adherence monitoring and healthcare use. Questionnaires will provide a framework for sampling HCPs for qualitative interviews that will further their elucidate views and experiences of working with the paediatric FH population, and their views on information needs for this patient group and their families.

We will estimate **long-term cost-effectiveness with a decision model parameterised by the above estimates**. **Systematic and pragmatic evidence reviews** will be conducted to address possible evidence gaps and provide alternative evidence sources for the economic model. Patient and public involvement and engagement (PPIE) will be incorporated via the study **Children and Young People's Advisory Group (CYPAG) and Parent and Carer Advisory Group (PCAG)**. These groups will be involved in co-development of the methodology and outputs at each stage of the research.

Risks and benefits of initiating treatment at different ages and LDL-C threshold levels are most efficiently and appropriately addressed by our mixed-methods study design, rather than a randomised controlled trial. NICE already recommend LLT initiation from age 10.[4] A trial designed to observe the

effects of LLT initiation starting at various ages and LDL-C thresholds would be prohibitively resource intensive and require multiple arms and decades of follow-up to observe rare CVD outcomes (e.g., Of 203 CYP with FH treated in childhood re-contacted after 20-years, only one experienced a CVD event[6]). Furthermore, there are no robust surrogate outcomes that can be measured in childhood. Greater Carotid Intima-Media Thickness (CIMT) has been shown in children with FH compared with unaffected siblings[13] and a small reduction in CIMT has been shown in short-term trials of statins,[14] however, routine CIMT measurement is not currently recommended as its clinical prognostic utility, independent of LDL-C and other risk factors, is not yet established in FH nor in the general population.[15,16]

Our study will yield a more nationally representative sample of CYP diagnosed with FH than previously available, to best inform future implementation of our findings across the country. Robust non-trial evidence (including mendelian randomisation studies) shows that reducing LDL-C earlier in life and maintaining optimal levels is an effective strategy to prevent CVD.[17]

As well as assessing **LDL-C reduction in current practice with LLT**, we will estimate the **reduction in cumulative LDL-C across childhood and adolescence**. Accruing evidence indicates that cumulative exposure to LDL-C during adulthood increases later CVD risk despite an individual's current (adult) LDL-C level.[17] A recent study of 4 pooled US cohorts replicated these findings when considering LDL-C exposure from early adulthood.[18] Furthermore, paediatric FH specialists involved in the PFHR have highlighted that "normal" age-specific LDL-C levels in CYP are not known. Our established PPIE group raised concerns about how low LDL-C can be safely reduced, given that cholesterol is important for growth and neurodevelopment. NICE guidelines do not provide treatment targets for CYP due to a lack of evidence, however, recommended targets based on clinical consensus are available from the UK's cholesterol charity, the Hyperlipidaemia Education & Atherosclerosis Research Trust UK (HEART UK)[5] and the European Atherosclerosis Society.[15] Our study will explore the achievement of age-specific LDL-C levels after LLT initiation ("**treatment targets**") based on (i) recommended targets of 30-50% reduction or <3.5mmol/l,[5,15] and (ii) population-expected levels at different ages across childhood/adolescence in the general (non-FH) population, the latter estimated using the ALSPAC cohort.[12]

Short term trials (up to 2 years) have shown **side-effects of LLTs** in children are rare[2] and early data from the PFHR showed no evidence of statin toxicity.[10] We will use data from the PFHR, the CPRD and evidence reviews to characterise longer-term safety and growth in CYP with FH.

LLT Adherence from adolescence to adulthood is critical to achieving stable LDL-C reductions. Adherence studies using self-reports and medical record reviews indicate poor long-term adherence; as low as 20% at around 10 years after initiation.[19,20] Other than in short trials, studies have not examined adherence to LLT longitudinally across childhood. We will estimate and characterise this using new data items that we will add to the PFHR, repeated questionnaires sent to PFHR-registered patients to obtain direct-patient report, and HCP questionnaires. We will also use CPRD to measure a proxy for adherence using longitudinal maintenance of LLT prescribing. Whilst this cannot directly measure individual patient adherence, repeat prescription patterns can be used to measure gaps in medication maintenance (periods of non-adherence) or discontinuation, providing an objective proxy for measuring changes in adherence over time.[21–23]

Our established PPIE group in FH and new engagement with the Nottingham CYPAG emphasised the need to explore barriers to continuing LLT, particularly across life transitions into adolescence and adulthood. They indicated we need to capture CYP's understanding of safety and relative benefits of LLT, as there can be scepticism around statin use and CVD risk. We will use qualitative interviews to **understand the views of CYP, their families and HCPs.**

Our PPIE groups and FH clinical specialists have emphasised the importance of understanding typical NHS healthcare utilisation (e.g., number of appointments/blood tests) on starting LLT, hence **costs of**

managing FH. This information will be collated using the patient and HCP questionnaires, because outpatient secondary care appointments are expected to be the largest cost driver[24] and these are not consistently recorded in the CPRD GP database.

As children only experience benefits of LLT later in life, the **cost-effectiveness of managing FH in CYP** and impact on the NHS of LLT from early childhood is not clear-cut. Our recent NIHR HTA study on FH cascade screening showed the cost-effectiveness of diagnosing children depended on the frequency of monitoring if children were treated and on the link between early life LDL-C reductions and CVD risk.[25] An **economic model will be developed to assess the cost-effective approach to management**.

6 Research methods: Protocol for each data source (study component)

6.1 The Paediatric Familial Hypercholesterolaemia Register (PFHR)

NHS HRA REC reference: 23/NE/0035

See full protocol in section 14 **(**APPENDIX: Full Protocol for NHS HRA REC reference: 23/NE/0035**)**

Existing Register size and representativeness: The PFHR was established in 2012 with the primary aim of monitoring LLT safety nationally, and feeding back to clinics on routine care.[9,10] Up to and including 2019, there are 613 patients registered on the PFHR from across 39 clinical sites in England. Using a secure web-based portal, the Register captures routine clinical and demographic data from specialist clinics seeing patients with paediatric FH. Children treated with LLT and those without LLT treatment are both well-represented on the PFHR.[10] Age, gender and lipid profiles are similar to those reported in other child FH populations,[26] and 75% are of white ethnicity (compared with 86% of the national UK population). The mean age of diagnosis is 9 years (Standard deviation (SD) 4) with a mean follow-up of 2.9 years (SD 1.8) and 57% initiating LLT at some point (mean age of initiation is 11 years, SD 3). The Register has been dormant since 2019 due to lack of funding.

6.1.1 Protocol summary for re-instating the Register

This study will reinstate the Register and collect up to 3.5 further years of follow-up data, by consenting new paediatric FH patients and collecting both retrospective and prospective clinical follow-up data using routinely recorded information from clinic appointments. **Clinical data collection will maintain collection of the original Register data items with the addition of data items on LLT adherence, reasons for non-adherence, and patient-reported side-effects/intolerance**. New patient registration across all clinics will be promoted with a focus on funding recruitment and data entry time from clinical case notes at key clinical sites. These sites are in areas based on larger concentration of case numbers, socioeconomically, ethnically, and geographically diverse populations, and underserved urban communities (Manchester, Bristol, Harefield, Wessex, Nottingham, all 5 sites in South Wales, London).

Clinical data collection will use REDCap (Research Electronic Data Capture https://www.project-redcap.org/), a secure web application, for the PFHR electronic database accessible by study-approved clinicians who see individuals diagnosed with FH in childhood and adolescence. Clinicians (or a nominated staff member) will be 1) approved for recruiting, consenting, and registering patients for clinical data collection, 2) provided with a username and password for entry of clinical data at registration and clinical follow-ups.

Site-specific monthly data monitoring will be conducted. Monthly targets for cohort recruitment at key clinical sites will consist of current paediatric FH patients being seen in these sites who are not yet registered on the PFHR (recruitment with retrospective longitudinal data entry and prospective follow-

up) and newly presenting paediatric FH cases (prospective recruitment and follow-up). An **Internal Pilot**, starting month 8 of the project, will be carried out over the first year of recruitment with monthly monitoring of recruitment data on total case numbers, data completeness on cholesterol and LLT, and representativeness of ethnic diversity.

In recognition of the need to ensure robust information on the clinical management of FH and the use of LLT including benefits and risks from both clinical practitioner and patient perspectives, **two new elements will be added to the PFHR: patient questionnaires and interviews**. Patients who consent to PFHR clinical data collection can additionally express an interested in being contacted for involvement in further research. Those patients who agree to being contacted for further research will be invited to participate in **questionnaire data collection (4 repeated questionnaires per participant at baseline, 8, 16, 24 months) and/or semi-structured interview data collection**.

Questionnaires will capture greater detail and a direct patient-reported indication of changes in LLT adherence and side-effects/intolerance over time as well as healthcare utilisation experience. To measure changes in adherence over time, the Medication Adherence Report Scale,[27] a previously validated tool, will be used within the questionnaire at each timepoint.

Interviews will seek to understand the perceived acceptability, benefits, concerns or harms associated with starting LLT and how these may impact adherence, considering the variation in the ages participants started LLT. Interviews will also cover treatment and monitoring experiences and views on service provision and access, and how these could be improved. Questionnaires and interviews will inform information needs for patients and families.

Target recruitment is increasing the Register to 1,374 paediatric FH patients with clinical data entry, 500 participants for questionnaires and 40 participants for interviews. Clinical, questionnaire and interview consent forms and data collected will be securely stored at the University of Nottingham.

6.1.2 Eligibility criteria for the Register

Individuals who have been diagnosed with FH before the age of 18 years and have been seen and followed-up in an NHS clinical setting for management of their FH during childhood (i.e., under age 18) are eligible for clinical data collection. Individuals with FH who are age 16 years or older and parents/guardians of individuals with FH who are under age 16 are eligible for questionnaire and interview data collection.

6.1.3 Inclusion criteria

- Age 0 years to 25 years (upper age limit can change in future based on data availability)
  - Case recruitment is prioritised to the following:
    - a clinical or genetic diagnosis of FH (excluding confirmed homozygous, compound heterozygous/digenic FH)
    - age 7 years or older with a baseline cholesterol measurement (ideally at diagnosis) and planned clinical follow-up [based on current NICE guidelines for starting LLT by age 10, these children will have the opportunity to start LLT over the study duration]
    - at least 1 available LDL-C measurement before age 16 years
    - for cases on LLT, date treatment started and the pre-treatment LDL-C measurement
- Ability of participant with FH to provide informed consent at age 16 years or older
- Ability of participant's parent/guardian to provide informed consent for participants with FH under age 16 years
- Ability of participant with FH to provide informed assent at age 5-15 years for clinical data collection
- Attending a clinical site for their FH that has been approved for study recruitment

6.1.4 Exclusion criteria

None beyond limits of eligibility and inclusion criteria other than the following language restrictions:

- To facilitate completion by non-English speaking CYP and/or parents/guardians, study materials can be translated into the 4 commonest non-English languages in the UK and telephone support for patient information sheets and completion of completion of consent forms and questionnaires will be available through LanguageLine UK. However, this may still result in some language restrictions which could exclude some potential participants.

6.1.5 Recruitment and consent procedure

Patients are recruited for clinical data collection by clinicians (or a nominated staff member who will usually be a clinical member of staff with experience of working with the patient group) at NHS clinical sites seeing individuals diagnosed with FH during childhood across England and Wales. The clinician or nominee will inform the participant and/or their parent/guardian, of all aspects pertaining to participation in the study. The clinical setting is chosen for base recruitment as data collection is from clinical records and consultations with health professionals. Patients or their parents/guardians are initially approached for recruitment during or between clinic visits, via email, telephone, text message or post, based on accepted recruitment practices and patient-contact methods within the clinical site. Clinical teams also have the option of using trained NHS research volunteers who will be approved by the site PI to assist in recruiting participants. The research volunteers will have lived experience of FH in their family or undergo training paediatric FH from the study team which includes clinical professionals working in paediatric FH. It is possible for patients or parents/guardians to approach their clinicians with interest in participating in the study; their clinical team will need to have been approved for data collection prior to recruitment.

Patients aged 16 years and over or parents/guardians of younger patients are recruited for questionnaire data collection if they express an interest in being contacted for participation in further research when they enrol for clinical data collection. The study team at the University of Nottingham will directly contact individuals who express an interest in further research to invite them to participate in questionnaire data collection.

Patients aged 16 years and over or parents/guardians of younger patients are recruited for semi-structured interviews if they express an interest in being contacted for participation in further research when they enrol for clinical data collection and based on a sampling framework that uses clinical and questionnaire data to obtain diversity based on sociodemographic, geographical, and FH-related characteristics (adherence, side-effects, healthcare service use). Participants with FH aged 16 years or over will have the choice to be interviewed alone or with their parent/guardian. Parents/guardians will have the choice to be interviewed alone or with their child who has FH (i.e., child on the clinical Register), if the child is age 11-15 years.

Informed consent for clinical data collection will be obtained as follows:

- Informed consent by the individual with FH if they are age 16 years or older
- Informed consent by a parent/guardian if the individual with FH is under age 16 years
- Informed assent by the individual with FH if they are under age 16 years (in conjunction with parent/guardian consent)
- Informed consent by the individual with FH who has previously provided informed assent when they reach 16 years of age

Informed consent for questionnaire data collection will be obtained as follows:

- Informed consent by the individual with FH if they are age 16 years or older
- Informed consent by a parent/guardian if the individual with FH is under age 16 years

Informed consent for semi-structured interviews will be obtained as follows:

- Informed consent by the individual with FH if they are age 16 years or older
- Informed consent by a parent/guardian if they participate in an interview with their child with FH who is age 16 years or older (in conjunction with their child's consent)
- Informed consent by a parent/guardian if the individual with FH is under age 16 years
- Informed assent by the individual with FH if they are age 11-15 years and participate in an interview with their parent/guardian (in conjunction with parent/guardian consent)

Participant information sheets, consent forms and assent forms are in paper or electronic format. Electronic format will be via the REDCap secure web application. Where individuals require languages other than English, paper copies will be available in the next 4 commonest languages in the UK.

Should there be any amendments to the final protocol that might affect a participant's participation in the study, continuing consent/assent will be obtained using amended consent/assent forms which will be signed by the participant.

6.1.6 Participant commitment and data collection

Commitment for clinical data collection requires consent/assent on one occasion by the participant individual with FH and/or their parent/guardian. The clinical data collection period does not require any time commitment from the participant as data collection is done by clinical sites. Data collection will use routinely recorded information obtained during the course of clinical care from specialist clinic appointments. The REDCap secure web application will be used for clinical data entry to the PFHR.

Commitment for questionnaire data collection by the participant with FH and/or their parent/guardian is 2-3 years (based on time to return questionnaires), completing questionnaires on 4 different occasions, aimed at baseline, 8,16, and 24 months. Questionnaire data will be collected using REDCap web-based software or paper questionnaires.

Commitment for interview data collection by the participant with FH and/or their parent/guardian is one interview of up to 1 hour. Interviews will be conducted via telephone or Microsoft Teams and will be recorded using a handheld digital audio recorder. For interviews conducted online using Microsoft Teams, the transcription utility will be used to transcribe the interview without the use of audio-visual recording; the audio recording will be retained as a backup for listening to any sections of the interview where the text transcription file is unclear.

6.1.7 Participant withdrawal

Participants with FH aged 16 years and older or parents/guardians of a participant who is under age 16 may withdraw from further data collection. The participants will be made aware from the outset that this will not affect their current or future healthcare. Participants will be made aware (via information sheets and consent forms) that should they withdraw, the data collected to date cannot be erased from any research where it has already been used. As consent for the Register's clinical, questionnaire and interview data collection are separate, it will be possible for participants to withdraw from one aspect of the study whilst maintaining participation in another (e.g., withdrawal from interview but still participate in clinical data collection).

Clinical site staff participating in clinical data collection may not withdraw a participant without the consent of the participant or their parent/guardian.

6.2 The Clinical Practice Research Database (CPRD) paediatric FH cohort

CPRD RDG Protocol ID: 22-002278
The CPRD will be used as a secondary source of data to assess LLT treatment and potential side-effects in children with FH, as well as medication adherence. This provides detailed longitudinal electronic health records from primary care with linkages to hospital admissions (but no access to specialist lipid clinic records). The general population in CPRD is highly representative of the sociodemographic distribution across the UK.[11] Our current unpublished research using CYP in the general population shows good national representation across socioeconomic and ethnic groups. Our June 2021 feasibility assessment of all CYP with diagnostic codes for FH in the CPRD GOLD database (which contains ~27% of the CPRD general population) showed they had a mean diagnosis age of 11 years, mean active follow-up 9 years, 64% were prescribed statins before age 18, and the mean number of LDL-C measures was 3, with almost half (42%) having prospective clinical records into adulthood. Using the whole of CPRD (GOLD and Aurum), we estimate at least 2,000 CYP with coded FH and another 1,600 with the clinical phenotype (based on our assessment of statin prescribing and hypercholesterolaemia coding). CPRD has reasonably complete information for these patients' gender, socioeconomic group, ethnicity, body mass index (BMI), however, it lacks the level of information on potential confounders that are available from the PFHR.

6.3 The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort for deriving average cholesterol across childhood in the general (non-FH) population

ALSPAC Reference (B Number): B3815

The ALSPAC cohort will provide data for estimating average levels of LDL-C across childhood in the general (non-FH) population, a critical gap identified by clinical specialists and the NICE guidelines[4] that needs addressing to inform FH treatment initiation and effective and safe target levels to which LDL-C should be reduced in CYP. ALSPAC is a longstanding cohort of children born in Avon in 1991-2 with repeated health and lifestyle measures into adulthood.[12] It is internationally unique in having repeated cholesterol and growth measures from birth to early adulthood. Cholesterol, growth and puberty measures are available at age 8,16,18 and 25 years (~7,000 CYP and ~2,000 with additional cholesterol near birth) as well as socioeconomic measurements, ethnicity and lifestyle factors that may be potential confounders. There are currently no other general-population British paediatric cohorts with such longitudinal measures.

6.4 Questionnaire and interview study with healthcare professionals working in paediatric FH

UoN FMHS REC reference: FMHS 253-0423

6.4.1 Protocol summary

Currently, treatment of paediatric FH remains secondary and tertiary care led. This study will collect questionnaire and interview data from HCPs currently involved in the clinical diagnosis and follow-up management of CYP with FH, in centres throughout the UK. It will provide data on and insight into current treatment practices in contemporary FH management in CYP, from lifestyle management to LLT, and from diagnosis to transfer to adult services. It will provide information on variation in clinical practice (routine practice/criteria on decisions to initiate LLT, treatment targets, adherence monitoring, starting dose, changing dose, and type/frequency of specialist healthcare provision) and the factors that influence this. Information will be used to describe the current clinical landscape and as variables in the PFHR analyses of clinical and cost-effectiveness, to account for clinical variation across sites in factors such as treatment targets.

There are no available estimates of the number of HCPs working in paediatric FH in the UK. Based on the existing PFHR clinical network and informal professional networks organised by the UK cholesterol charity HEART UK, we estimate 50-100 HCPs will complete questionnaires and we will interview 30 HCPs.

6.4.2 Eligibility criteria

Healthcare professionals involved in the clinical care of CYP with FH within the UK NHS (i.e., paediatric FH care) are eligible to participate. Participants may be from any clinical specialty/job role and may also work in adult care, but some of their role must be with paediatric FH patients.

6.4.3 Inclusion criteria

- Healthcare professionals involved in the clinical care of CYP with FH within the UK NHS (i.e., some involvement in paediatric FH care)
- Participants should be currently working in their clinical role or have worked in this role within the past 10 years

6.4.4 Exclusion criteria

- Not meeting inclusion criteria

6.4.1 Recruitment and consent procedure

Due to the diversity and complexity of HCPs working in paediatric FH, including dieticians, pharmacists, specialist nurses and physicians from a broad range of specialities, no formalised method of contact via NHS communication channels exists. Recruitment will utilise professional networks and contacts. The study will be advertised in the newsletter of HEART UK and through the linked Lipid Intelligence Network, which brings together different types of professionals with an interest in blood lipids. It will also be advertised to the Lipid Interest Group (a shared learning group open to nurse specialists and allied professionals) and at the HEART UK conference in July 2023. HCPs contributing the to PFHR and contacts of those participating in the PFHR network will be approached.

Questionnaire recruitment: HCPs will be invited (via above methods) to fill in an online questionnaire on their insight/ views on factors that influence diagnosis, and initiating and maintaining LLT in CYP. Questionnaire participants can express an interest in being contacted for further research and may be invited for follow up interviews to gain further narrative information on current practice and its determinants.

Semi-structured interview recruitment: Health professionals who provide the paediatric FH service will be purposely sampled to participate in semi-structured interviews. It is envisaged this group will comprise paediatric cardiologists, lipidologists, metabolic medicine specialists, endocrinologists, nutritionists, and specialist genetic or FH nurses covering diverse healthcare settings. Some will have completed the online questionnaire and indicated an interest in being interviewed, but others may be recruited directly for interviews. Therefore, our sampling approach will combine both convenience (self-selecting individuals opting to take part or be contacted, and subsequent completion of eligibility) and purposeful approaches. We will purposefully invite individuals representing specific criteria, to ensure we capture a range of perceptions and experiences:

- Large and small clinical sites
- Services led by different specialities (e.g., paediatrics, metabolic medicine, cardiology)

- Services using and not using specific clinical protocols
- Different types and grades of HCP
- Geographic location of site

Informed consent for questionnaire and/or interview data collection: Potential participants will require online access to complete the consent form or it can be completed via posted paper form or telephone. Consent forms will be signed and dated by the individual before any relevant data are collected. Electronic formats will be via the REDCap secure web application.

Should there be any subsequent amendment to the final protocol that might affect a participant's participation in the study, continuing consent will be obtained using amended consent forms which will be signed by the participant.

6.4.1 Participant commitment and data collection

Questionnaire data collection: Following provision of consent, participant individuals will complete one self-administered questionnaire, comprising a mix of closed and open-ended questions, using the REDCap web application, paper questionnaire or questionnaire administered via telephone with the researcher using the REDCap web application.

Semi-structured interviews: Following provision of consent, participants will undergo an interview of up to 1 hour conducted via telephone or online using Microsoft Teams (or in-person if telephone or online methods are not practical). All interviews will be recorded using a handheld digital audio recorder. For interviews conducted online using Microsoft Teams, the transcription utility will be used to transcribe the interview without the use of audio-visual recording; the audio recording will be retained as a backup for listening to any sections of interview where the text transcription file is unclear.

6.4.1 Participant withdrawal

Participants will be free to withdraw (i.e., to stop completing the questionnaire or stop the interview) at any time without giving a reason. In addition, the research team may discontinue a participant's participation from the study at any time they consider it necessary for any reason including:

- Withdrawal of consent
- Incomplete/unusable data

When a participant withdraws from further participation, any information already obtained will be retained and may still be used in the final study analyses (this will be made clear in information sheets and consent forms).

7 Analysis

7.1 Objective 1: Estimate absolute and relative reductions in LDL-C, and in cumulative LDL-C, achieved in current practice with LLT, and whether these vary by age and LDL-C at initiation of LLT

Methods: We will evaluate the effectiveness of initiating LLT at different ages and LDL-C thresholds (at baseline) on LDL-C levels measured at **routine follow-up visits recorded in the PFHR** (and **secondarily in the CPRD FH population**). We will:

(a) estimate absolute and % reductions in LDL-C from pre-treatment levels, which will then be incorporated into the economic model,

(b) estimate cumulative LDL-C and time-weighted average (TWA) LDL-C, the latter providing an estimate of average LDL-C burden over childhood and adolescence,

(c) evaluate achievement of treatment targets, using expert-consensus recommendations for FH[5,15] and average age-specific LDL-C levels in the general (non-FH) population (derived from CYP in the ALSPAC cohort),

(d) address potential evidence gaps by updating our current systematic review of statin trials in children with FH[2] to include all LLT and a new pragmatic review of high-quality observational evidence.

Analysis (a): **Absolute (mmol/L) and % reductions in LDL-C** from pre-treatment levels associated with age and LDL-C at LLT initiation will be estimated using a linear mixed-effects model. A multi-level structure will be used to account for children being grouped at clinical sites, with site as a random effect.

LDL-C changes in those exposed to LLT will be compared with changes in those never exposed or unexposed up to a certain age, measured as the difference between the earliest and later follow-ups. We will use inverse probability of treatment weighting techniques[28,29] to balance exposed and unexposed groups according to both baseline and time-varying measured confounders: family history of CVD and/or FH in family, gender, genetic testing, body mass index (BMI), ethnicity, other health conditions, reasons for not being on LLT or non-adherence, process factors such as attendance frequency, and socioeconomic deprivation (using post-code linkage to index of multiple deprivation).

We will primarily estimate intention-to-treat effects, i.e. the effect of prescribing LLT to children with FH on LDL-C levels.[30] We will then estimate per-protocol effects, which corresponds to the effect of continuously taking LLT during the following period. Potential treatment non-adherence and loss to follow-up will be accounted for via censoring weights.[30] Missing data in both the LDL-C outcomes and confounders will be addressed using multiple imputation.

We will conduct sensitivity analyses to assess the extent to which the effects of age and LDL-C at initiation are robust to potential unmeasured confounding. We will adopt the E-value approach,[31] which essentially explores how strong (association with both LLT initiation and LDL-C outcomes) the unmeasured confounders need to be to change the study conclusions. These analyses will be informed by discussions with clinical specialists and PPIE groups, and the HCP questionnaire.

This will be a descriptive analysis with the ultimate aim to derive effectiveness estimates that will feed into the cost-effectiveness model, where uncertainty will be fully propagated.[32] However, initial assessment, based on pre- and post-puberty in current PFHR data shows children initiating LLT before age 12 years achieved a mean reduction in LDL-C of 2.199 after initial mean levels of 6.115 (pooled SD=2.51) and those initiating LLT at 12 or older achieved a mean reduction in LDL-C of 1.748 after initial mean levels of 5.570 (pooled SD=1.53). Demonstrating this difference at 90% power and 0.05 significance level with a 60-40 allocation ratio (as in the current Register) would require 560 children initiating LLT before age 12 and 376 initiating LLT at 12 or older, which is within our planned recruitment target.

Secondary analyses:

- In the PFHR, we will also assess total cholesterol, HDL-C, triglycerides, and non-HDL changes
- Using the CPRD (primary care database), we will repeat LDL-C analyses in the larger sample of FH patients who may also represent a more diverse population.

Analysis (b): **Cumulative LDL-C** (cholesterol burden) will be calculated as area under the age trajectory of LDL-C between age 8 and 18 years using a linear mixed-effects model, following methods described by our collaborator Zhang.[18,33] LDL-C trajectories of CYP with current exposure to LLT will be compared with those never exposed or unexposed up to a certain age. We will also calculate **TWA LDL-C** (cumulative LDL-C divided by time) as a measure of average LDL-C burden. We will use the same approach as in analysis (a) to model associations with age and LDL-C at LLT initiation and to address potential confounding. Building on the current PFHR and 3.5-year prospective follow-up, we expect to have at least 4 LDL-C measures available on most CYP. Since we will have representation

across all ages, we will also create models where we impute un-observed LDL-C using previously described methods.[34]

Analysis (c): **Achievement of treatment LDL-C targets** before and after puberty, and at age 18 will be estimated using logistic regression, assessing confounding and other biases as in analysis (a). We will evaluate by age and LDL-C threshold at LLT initiation, the achievement of (i) recommended targets of 30-50% reduction or <3.5mmol/l[5,15] and (ii) general (non-FH) population expected LDL-C levels obtained from analyses of the ALSPAC cohort data.

Using the ALSPAC cohort, we will derive population-expected LDL-C levels across childhood and adolescence using longitudinal measures on approximately 7,000 non-FH children to estimate LDL-C trajectories with a linear mixed-effects model of LDL-C against age. To describe how LDL-C trajectories vary by gender, ethnicity, and key growth and health measures such as weight-for-age, weight-for-height z-scores, fat-free mass and blood pressure, we will fit models with and without interaction terms between age splines and these factors.[33] This variation will be used in our models of target LDL-C (e.g., trajectory variation between boys and girls). Our protocol for this was approved by ALSPAC in June 2021.

Analysis (d): A **systematic review and a pragmatic review** will address potential evidence gaps for the economic model. Effect estimates of LLT effectiveness (and safety for objective 2) will be pooled using meta-analysis where appropriate. Our 2019 Cochrane review of statin trials in children with FH[14] identified only short-term LDL-C reduction and safety (median follow-up in trials 5.5 months). We will update this systematic review with any new randomised control trial evidence and expand it to include ezetimibe given its increasing use.[48] Due to a lack of long-term trial evidence, a **pragmatic review of high-quality observational studies with data on longer-term effectiveness and safety** will be conducted. It will prioritise high-quality registry and cohort evidence (defined by risk of bias criteria e.g., ROBINS-I), followed by long-term extension studies as relevant to inform the economic model. Eligible outcomes will include changes in LDL-C, growth and maturation, CVD and safety outcomes.

Outputs

- Parameters for economic model (Objective 6): absolute and % LDL-C reductions according to age and LDL-C thresholds at LLT initiation
- Identify how cumulative LDL-C up to age 18 is affected by age and LDL-C thresholds at LLT initiation
- Identify how achievement of LDL-C treatment targets is affected by age and LDL-C thresholds at LLT initiation

7.2 Objective 2: Estimate the incidence of side-effects and adverse events associated with LLT

Methods: The following data sources will be used to assess LLT safety (side-effects, adverse events, growth and development effects):

1. **PFHR** data captures adverse events through blood tests (raised level of creatine kinase, aspartate and alanine transaminase), documenting clinical features (e.g., rhabdomyolysis), and newly added data items on patient-reported side-effects such as muscle weakness or pain symptoms. Weight, height and age at first menstruation will be assessed as measures of growth and development.

2. **CPRD** data on hospital admissions or general practice attendance will be used to assess side-effects and adverse events. We will use post-marketing side-effects reported for each LLT type (e.g., headache, dizziness, unusual weakness, sleep problems). CPRD will provide a large sample to assess adverse events (e.g., rhabdomyolysis) as these will be extremely rare according to current evidence in adults.[35] Safety across childhood and into early adulthood will be assessed (with 42% of children with FH having CPRD records into adulthood).

3. Potential gaps will be addressed by the **systematic and pragmatic reviews**, as described in objective 1, that will include short and longer-term rare or serious side-effects of LLT including ezetimibe.

Analysis: Among children on LLT, liver enzyme (transaminases) measures >2.5 times the upper limit of normal before and after puberty will be described according to LLT type (of statin and more rarely used medications such as ezetimibe) and dose. Logistic regression models will be used to adjust for clinical and sociodemographic factors.

Age at first menstruation, weight-for-age and weight-for-height z-scores (BMI in adolescents) according to LLT exposure (type, dose, age at initiation) will be modelled using generalized estimating equations/growth models adjusting for clinical and sociodemographic factors.

Incidence rates of side-effects and adverse events will be described according to LLT exposure (type, dose, age at initiation) and Poisson regression will be used to adjust for clinical and sociodemographic factors.

Outputs

- Incidence of side-effects and adverse events
- Effects of LLT on growth and development
- Parameters for economic model (Objective 6): LLT adverse event rates

7.3 Objective 3: Estimate LLT adherence at different ages and characterise reasons for variations in adherence

Methods: We will measure adherence and characteristics related to variation in adherence using:

(a) Adherence captured at **routine follow-up visits recorded in the PFHR.** Based on discussions with our clinical specialist collaborators and Nottingham CYPAG and our PPIE group, these items will indicate recent adherence and reasons for sub-optimal adherence.[36]

(b) **Patient questionnaires at baseline, 8, 16, 24 months** to obtain changes in adherence over time incorporating the Medication Adherence Report Scale.[27] The study CYPAG and PCAG will support interpretation of the questionnaire results.

(c) **Repeat prescription information from CPRD records of CYP with FH** as an adherence proxy

Analysis (a) and (b): Following descriptive analysis, generalized estimating equations for repeated measures analysis will be used to examine associations of high adherence (versus low/moderate) with age, gender, ethnicity, deprivation, frequency of LDL-C testing and clinic visits, age and LDL-C level at LLT initiation, reasons for sub-optimal adherence, reported side-effects and family history of CVD.

Analysis (c): Using electronic LLT prescriptions, we will calculate the number of days individuals are prescribed compared with periods of active general practice registration. Missing information on prescription duration or dose will be imputed using prior published methods.[21,23] We will calculate a prescription possession ratio (PPR) over specified periods of time (e.g., annual PPR (%)= total days prescribed LLT/days of GP registration over 1 year).[21,23] We will estimate how the PPR is associated with current age and age at first LLT prescription, gender, deprivation and ethnicity. We will model factors associated with time to discontinuation using Cox regression, similar to an approach used in a US study on LLT prescribing in young people[22] and estimate the proportion of children maintaining LLT prescriptions into adulthood.

Outputs

- Patterns of medication adherence and characterisation of low/high adherence by age
- Factors associated with non-adherence triangulated between the Register, patient-questionnaires and CPRD

- Parameter for economic model (Objective 6): proportion of young people with FH who remain on treatment at age 18

7.4 Objective 4: Understand the views of children and young people, their families and healthcare professionals, on information needs for starting LLT at different ages, and how these influence treatment acceptability, monitoring, and adherence

Methods: We will use data from the qualitative semi-structured interviews with CYP, their parents/families and HCPs involved in the treatment and monitoring of young people with FH.

Analysis: Interview audio data will be transcribed verbatim. Data will be analysed using the framework approach, which is a hierarchical, matrix-based method developed for applied research.[37] The framework will enable us to map thematic differences/similarities within and between groups, such as by age at LLT initiation or adherence. Data will be coded both according to a priori themes and inductively. Initial readings will facilitate familiarisation and will lead to the generation of codes. Further analysis will result in more substantive themes and sub-themes (the analytical framework). Data will then be indexed according to the analytical framework. A sub-sample of data will be double coded to ensure validity of interpretations. We will also incorporate respondent validation whereby young people and parents will be invited to check initial accuracy of transcripts, add to them after a period of reflection, and review whether mapped themes are a reasonable reflection of their data. Finally, themes will be discussed and agreed between the research team, allowing clarification of the final framework that will then be applied across all transcripts.

The collected qualitative data will complement and clarify the quantitative findings by helping to identify common themes, and possible explanations.

Outputs

- Identification of barriers and facilitators to treatment adherence – considering the role of age at initiation, access to care/monitoring and triangulation with questionnaire findings (e.g., accounting for differences according to demographics)
- Identification and description of the information needs for starting LLT at different ages and how these maybe met
- Triangulation of findings from questionnaire and interviews with children, young people, parents and healthcare professionals to propose recommendations for how to best implement health service provision for treatment initiation and monitoring.

7.5 Objective 5: Estimate the impact of initiating LLT at different ages on the costs of managing FH over the short-term in children and young people

Method: To inform the cost-effectiveness model (Objective 6), we will estimate NHS costs of managing CYP with FH and the effect of starting LLT on costs using data on healthcare use (e.g., outpatient appointments, GP visits) **collected from PFHR patient questionnaires and HCP questionnaires,** as the preferred option for capturing most FH secondary care and a common method used in trials.[24]

Analysis: Using information on resources required during appointments (e.g. personnel, duration, tests) collected via the PFHR patient questionnaires and HCP questionnaires and national unit costs,[38] we will calculate total healthcare costs per individual. We will estimate the impact of starting LLT on NHS costs over time, accounting for potential confounders. Our analysis approach to confounding and missing data will be similar to that described in Objective 1(a), using an appropriate model to accommodate the typically skewed cost data (e.g., generalised linear models).[39]

Outputs

- Estimates of the use of NHS services by CYP with FH and their related costs
- Estimates of the effect of starting LLT on NHS costs related to service use

7.6 Objective 6: Estimate long-term health outcomes and NHS costs of starting LLT at different ages and LDL-C thresholds to identify a cost-effective approach to management

Method: To identify the cost-effective approach to initiating LLT at a range of ages and LDL-C thresholds, we will develop a new cost-effectiveness model. A decision model is required to estimate long-term reductions in CVD risk (which cannot be observed without decades of follow-up), given observed shorter-term LDL-C reductions. We will take the NHS perspective and express health outcomes primarily in quality-adjusted life years (QALYs). We will collaborate with the CYPAG, PCAG and clinical specialists to capture outcomes that matter to patients, families, clinicians, and healthcare commissioners. The cost-effectiveness analysis will be conducted and reported in accordance with current methodological guidance for cost-effectiveness analysis.[40]

Analysis: The model structure will be based on our model developed to analyse the cost-effectiveness of alternative cascade screening protocols for FH.[25] We will link LDL-C to CVD risk based on the well-established concept that LDL-C increases CVD risk and this effect increases over time.[17] Hence, the same LDL-C reductions over longer periods (from earlier LLT initiation) result in greater CVD risk reductions and more CVD events avoided. We will account for the impact of adherence in terms of its impact on LDL-C reductions from LLT (which are inherent to the estimates from the PFHR and CPRD data analyses) and via the proportion of CYP who continue LLT use into adulthood (estimated in Objective 3).

Decision options: We will evaluate a range of options for age and LDL-C at LLT initiation, highlighting combinations with major policy and clinical evidence, e.g., starting LLT at age 10 if LDL-C >3.5 mmol/L (as recommended by the European Atherosclerosis Society and the HEART UK Consensus Statement)[5,15] compared with starting later or at lower or higher LDL-C thresholds.

We anticipate our model will comprise two modules:

Module (a) will quantify LDL-C, safety (i.e., adverse events, impact on health-related quality of life), costs during childhood/adolescence, and the likelihood of remaining on LLT into adulthood.

Module (b) will estimate long-term CVD consequences of raised LDL-C, potential long-term LLT side-effects, and the impact of CVD and LLT side-effects on health-related quality of life, life expectancy, QALYs and NHS costs, over individuals' expected lifetime.

Module inputs: Data sources for the main inputs to (a) and (b) are tabulated below. Depending on whether data allows and the results from Objectives 1-3 and 5 analyses, individual inputs may be conditioned on pre-treatment LDL-C and age at LLT initiation. When multiple evidence sources are relevant, we will consider synthesising these or presenting alternative scenarios, depending on heterogeneity, quality, and relevance of the evidence.

Inputs for Module (a) on CYP outcomes:

Parameter	Source
Effect of LLT on LDL-C over time (proportional reduction)	• PFHR and CPRD analysis results (Obj. 1) • Systematic and pragmatic reviews (Obj. 1)
Proportion of young people remaining on treatment at age 18	• CPRD data analysis results (Obj. 3)
Cost of LLT	• PFHR data on the type of LLT prescribed (Obj. 1)

	• Unit costs according to Drug Tariff
NHS costs of managing CYP with FH depending on whether they are treated with LLT or not	• NHS costs results based on data from patient and healthcare professional questionnaires (Obj. 5)
LLT adverse event rates and consequences	• LLT adverse event rates from PFHR and CPRD analysis results (Obj. 2) • Systematic and pragmatic reviews (Obj. 2) • Literature informing impact of adverse events on health-related quality of life
Health-related quality of life	• UK general population data (given that in our preparatory PPI work, advocates indicated that LLT initiation is not expected to significantly affect health-related quality of life, beyond the impact of potential LLT-associated adverse events)

We selected data sources for Module (b) given our recently completed study on FH.[25] This represents the most up to date and UK-relevant evidence on long-term outcomes in adult patients with FH and aligns, as far as possible, with cost-effectiveness analyses that informed the NICE FH guideline. The effect size between LDL-C over time and CVD risk later in life is a key driver of long-term benefits from treatment and requires follow-up beyond the reach of the PFHR follow-up that is possible in this 5-year study. A pragmatic review will be conducted to identify high-quality evidence, such as large individual patient data meta-analyses, that quantifies the impact of high LDL-C from childhood/early adulthood on later CVD morbidity and mortality.

Inputs for Module (b) on outcomes in adulthood:

Parameter	Source
Relationship between LDL-C over time and CVD risk later in life	Pragmatic review of studies evaluating the impact of high LDL-C from childhood/early adulthood on long-term CVD risk
Risk of CVD in adulthood	Risk equations from our previous work on a UK cohort of patients with FH (N=2,135, median follow-up 4.8 years)
Risk of non-cardiovascular death	General population statistics
Mortality risk following a first non-fatal cardiovascular event	Risk equations from our previous work, based on the risk observed in patients with FH and UK general-population study
Costs of LLT and of routine FH management	Current clinical guidelines for adults and expert advice
Costs of care post-cardiovascular events	Costs from an analysis of UK routine data of patients with coronary disease
Health-related quality of life prior to cardiovascular events	UK general population norms
Health-related quality of life post cardiovascular events	UK general population norms, adjusted for the impact of cardiovascular events based on previous cost-effectiveness analyses to inform NICE guidelines

Uncertainty: The model will reflect the parameter uncertainty in the module inputs via probabilistic sensitivity analysis. We will conduct extensive scenario analyses to the key assumptions. Examples include using estimates of effect of LLT on LDL-C from CPRD analysis rather than those obtained from PFHR in Objective 1, calculating NHS management costs based on clinical guideline recommendations rather than those estimated in Objective 5, using alternative relationships between LDL-C and long-term CVD risk identified by the pragmatic review.

Output

- Comparative cost-effectiveness of alternative policy options, interpreted considering the evidence base developed and identified across other previous objectives

8 User and Public Involvement

A study-specific Children and Young People's Advisory Group (CYPAG) and Parent and Carer Advisory Group (PCAG) will provide regular PPIE input across all study aspects via meetings and written/verbal input on design and feedback for study materials between meetings. A PPIE Strategic Adviser with expertise of working directly with children and young people and a PPIE Administrator are on the Study Management Group to ensure the responsibilities and contributions of the CYPAG and

PCAG are appropriately integrated into the development and outputs of the study. PPIE over 5 years has been appropriately funded in accordance with NIHR good practice for involving patients and will follow the Nottingham University Hospitals PPIE Standard Operating Procedure under guidance of the PPIE Strategic Adviser.

9 Dissemination and outputs

As members of key FH working groups, such as the National Genomic Medicine Service Alliance (GMSA) FH oversight committee and the NHSE FH Expert Advisory Group, we have a natural channel to inform national FH policy and engage key stakeholders. We will work closely with cholesterol charity HEART UK to advertise the study, provide regular public updates and progress newsletters, and disseminate learning from the study to NHS commissioners and policymakers. We will work with international colleagues in Australia and the USA to ensure our findings also inform international guidelines.

In addition to informing policymakers and patient advocates, all tiers of the study will be widely disseminated through peer-reviewed publications and conferences for scientific audiences. At 4-5 years of recruitment, a national summary report of the Register data will be disseminated to clinical sites. At 5 years, a project report will be submitted to the NIHR HTA.

10 Plan of investigation

<u>Clinical Effectiveness, Safety and Adherence</u>
Analysis of ALSPAC & CPRD databases (3-12 months)
Training clinical staff on PFHR data entry (6-12 months)
PFHR database retrospective data collection (8-18 m) & preliminary analysis (12-32 m)
PFHR database prospective data collection (8-48 m) & main analysis (retrosp+prosp data) (18-54 m)
Evidence reviews (6-12 m) & updated searches and analyses (36-42 m)

<u>Questionnaires & Qualitative Studies</u>
Design of CYP/parent & HCP questionnaires (0-4 m)
Distribute & analyse HCP questionnaire (8-12 m)
Distribute & analyse baseline CYP/parent questionnaires (8-18 m), follow-up questionnaires (14-42m)
Recruit & interview HCP (8-20 m) & analyse (10-24 m)
Recruit & interview CYP/parents (14-26 m) & analyse (16-30 m)

<u>Cost-effectiveness Analysis</u>
Analysis of healthcare service use (including NHS costs), generate results & reports (39-44 m)
Economic model design and parameterisation plan (45-50 m)
Build economic model in software (51-56 m) & integrate PFHR & CPRD results (54-56 m)

<u>Generate reports and publications</u>
Qualitative study (28-32 m), Clinical effectiveness (13-56 m) Cost-effectiveness (57-58 m)
Integration of final report (59-60 m)

11 Project management

The project will be led from and sponsored by the University of Nottingham. The study is managed at the University of Nottingham by the Study Management Group. The Chief Investigators (Qureshi & Tata) are Co-Chairs of the Study Management Group, and have operational responsibility for project implementation, management, financial tracking and overall delivery, supported by an experienced Project Manager.

Clinical Effectiveness studies will be led by Tata. Preparation of questionnaires and collation of cohorts will be led by Tata & Qureshi. Analysis of databases and questionnaires will be led by Tata and study statistician (Vinogradova). Qualitative study will be led by Bains, supported by Kai, Qureshi & Tata. Economic studies will be led by Woods. Evidence reviews will be led by Llewellyn. These studies will be informed by Public Co-applicant Fisher and two PPIE groups (CYPAG & PCAG). Core study meetings (co-applicants) will take place monthly, with six-monthly meetings of the wider study team (including key clinical specialists and HEART UK), and six-monthly meetings of the External Study Steering Committee (SCC) and the Data Monitoring Ethics Committee (DMEC).

12 Ethical & Regulatory issues

There are no interventions, separate clinical visits nor measurements required for participation in PFHR study, beyond the patient's usual NHS clinical follow-up. Participation in the study involves consent for the patient's NHS clinical care information to be collected by the patient's clinical team for the Register with the option for the patient or their parent/guardian to fill out questionnaires of self-reported information about their experience of FH, and the option of participating in an interview about their experience of FH.

Patients will be provided with contact details for the Study Management Team to discuss any concerns relating to participation and will be directed to discuss any personal clinical concerns with their clinical care team.

Filling out questionnaires and participating in interviews will involve questions about FH symptoms, FH treatment and treatment medications, and potential adverse events or side-effects related to LLT. Participation therefore has the potential to raise queries, uncertainty, or anxiety about FH as well as increasing understanding about the condition. All participant-facing materials will be designed with and approved by stakeholders in FH including healthcare professionals and people with lived experience of FH to ensure they are appropriate for use with minimal ethical risks. This process will involve patient and health professional representatives on the Study Management Group, PCAG and CYPAG.

13 References

1. Humphries SE, Cooper JA, Seed M, Capps N, Durrington PN, Jones B, McDowell IFW, Soran H, Neil HAW. Coronary heart disease mortality in treated familial hypercholesterolaemia: Update of the UK Simon Broome FH register. *Atherosclerosis*. 2018;274:41-46. doi:10.1016/j.atherosclerosis.2018.04.040

2. Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Tonstad S, Wiegman A, Drogari E, Ramaswami U. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst Rev*. 2019;2019(11). doi:10.1002/14651858.CD006401.pub5

3. Vuorio A, Docherty KF, Humphries SE, Kuoppala J, Kovanen PT. Statin treatment of children with familial hypercholesterolemia – Trying to balance incomplete evidence of long-term safety and clinical accountability: Are we approaching a consensus? *Atherosclerosis*. 2013;226(2):315-320. doi:10.1016/j.atherosclerosis.2012.10.032

4. NICE Clinical guideline 71 (CG71): Familial hypercholesterolaemia: identification and management. NICE 2019. Accessed August 20, 2023. https://www.nice.org.uk/guidance/cg71

5. Ramaswami U, Humphries SE, Priestley-Barnham L, Green P, Wald DS, Capps N, Anderson M, Dale P, Morris AA. Current management of children and young people with heterozygous familial hypercholesterolaemia - HEART UK statement of care. *Atherosclerosis*. 2019;290:1-8. doi:10.1016/j.atherosclerosis.2019.09.005

6. Luirink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, de Groot E, Kastelein JJP, Hutten BA. 20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia. *New England Journal of Medicine*. 2019;381(16):1547-1556. doi:10.1056/NEJMoa1816454

7. Akioyamen LE, Genest J, Shan SD, Reel RL, Albaum JM, Chu A, Tu JV. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. *BMJ Open*. 2017;7(9):e016461. doi:10.1136/bmjopen-2017-016461

8. NHS. The NHS Long Term Plan. Published online September 2019. Accessed October 23, 2022. https://www.longtermplan.nhs.uk/publication/nhs-long-term-plan/

9. Ramaswami U, Cooper J, Humphries SE. The UK Paediatric Familial Hypercholesterolaemia Register: preliminary data. *Archives of Disease in Childhood*. 2017;102(3):255-260. doi:10.1136/archdischild-2015-308570

10. Humphries SE, Cooper J, Dale P, Ramaswami U. The UK Paediatric Familial Hypercholesterolaemia Register: Statin-related safety and 1-year growth data. *Journal of Clinical Lipidology*. 2018;12(1):25-32. doi:10.1016/j.jacl.2017.11.005

11. Wolf A, Dedman D, Campbell J, Booth H, Lunn D, Chapman J, Myles P. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *Int J Epidemiol*. doi:10.1093/ije/dyz034

12. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Molloy L, Ness A, Ring S, Davey Smith G. Cohort Profile: The 'Children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol*. 2013;42(1):111-127. doi:10.1093/ije/dys064

13. Wiegman A, de Groot E, Hutten BA, Rodenburg J, Gort J, Bakker HD, Sijbrands EJG, Kastelein JJP. Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia. *Lancet*. 2004;363(9406):369-370. doi:10.1016/S0140-6736(04)15467-6

14. Wiegman A, Hutten BA, de Groot E, Rodenburg J, Bakker HD, Büller HR, Sijbrands EJG, Kastelein JJP. Efficacy and Safety of Statin Therapy in Children With Familial Hypercholesterolemia: A Randomized Controlled Trial. *JAMA*. 2004;292(3):331. doi:10.1001/jama.292.3.331

15. Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, Ose L, Averna M, Boileau C, Borén J, Bruckert E, Catapano AL, Defesche JC, Descamps OS, Hegele RA, Hovingh GK, Humphries SE, Kovanen PT, Kuivenhoven JA, Masana L, Nordestgaard BG, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AFH, Steinhagen- Thiessen E, Stroes ES, Taskinen MR, Tybjærg-Hansen A, Wiklund O. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J*. 2015;36(36):2425-2437. doi:10.1093/eurheartj/ehv157

16. Zhang Y, Guallar E, Qiao Y, Wasserman BA. Is Carotid Intima-Media Thickness as Predictive as Other Noninvasive Techniques for the Detection of Coronary Artery Disease? *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2014;34(7):1341-1345. doi:10.1161/ATVBAHA.113.302075

17. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Borén J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen MR, Tokgözoğlu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A

consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38(32):2459-2472. doi:10.1093/eurheartj/ehx144

18. Zhang Y, Pletcher MJ, Vittinghoff E, Clemons AM, Jacobs DR Jr, Allen NB, Alonso A, Bellows BK, Oelsner EC, Zeki Al Hazzouri A, Kazi DS, de Ferranti SD, Moran AE. Association Between Cumulative Low-Density Lipoprotein Cholesterol Exposure During Young Adulthood and Middle Age and Risk of Cardiovascular Events. *JAMA Cardiology*. Published online September 22, 2021. doi:10.1001/jamacardio.2021.3508

19. Langslet G, Johansen AK, Bogsrud MP, Narverud I, Risstad H, Retterstøl K, Holven KB. Thirty percent of children and young adults with familial hypercholesterolemia treated with statins have adherence issues. *American Journal of Preventive Cardiology*. 2021;6:100180. doi:10.1016/j.ajpc.2021.100180

20. Braamskamp MJAM, Kusters DM, Avis HJ, Smets EMA, Wijburg FA, Kastelein JJP, Wiegman A, Hutten BA. Long-Term Statin Treatment in Children with Familial Hypercholesterolemia: More Insight into Tolerability and Adherence. *Paediatr Drugs*. 2015;17(2):159-166. doi:10.1007/s40272-014-0116-y

21. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiology and Drug Safety*. 2006;15(8):565-574. doi:10.1002/pds.1230

22. Joyce NR, Wellenius GA, Eaton CB, Trivedi AN, Zachariah JP. Patterns and predictors of medication adherence to lipid-lowering therapy in children aged 8 to 20 years. *J Clin Lipidol*. 2016;10(4):824-832.e2. doi:10.1016/j.jacl.2016.03.002

23. Taylor A, Chen LC, Smith MD. Adherence to inhaled corticosteroids by asthmatic patients: measurement and modelling. *Int J Clin Pharm*. 2014;36(1):112-119. doi:10.1007/s11096-013-9862-0

24. Franklin M, Thorn J. Self-reported and routinely collected electronic healthcare resource-use data for trial-based economic evaluations: the current state of play in England and considerations for the future. *BMC Medical Research Methodology*. 2019;19(1):8. doi:10.1186/s12874-018-0649-9

25. Evaluating alternative protocols for identifying and managing patients with familial hypercholesterolaemia: cost-effectiveness analysis with qualitative study - NIHR Funding and Awards. Accessed August 20, 2023. https://fundingawards.nihr.ac.uk/award/15/134/02

26. Bogsrud MP, Langslet G, Wium C, Johansen D, Svilaas A, Holven KB. Treatment goal attainment in children with familial hypercholesterolemia: A cohort study of 302 children in Norway. *Journal of Clinical Lipidology*. 2018;12(2):375-382. doi:10.1016/j.jacl.2017.11.009

27. Chan AHY, Horne R, Hankins M, Chisari C. The Medication Adherence Report Scale: A measurement tool for eliciting patients' reports of nonadherence. *Br J Clin Pharmacol*. 2020;86(7):1281-1288. doi:10.1111/bcp.14193

28. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34(28):3661-3679. doi:10.1002/sim.6607

29. Hernán MA, Robins JM. Causal Inference: What If. :311.

30. Hernán MA, Alonso A, Logan R, Grodstein F, Michels KB, Stampfer MJ, Willett WC, Manson JE, Robins JM. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology*. 2008;19(6):766-779. doi:10.1097/EDE.0b013e3181875e61

31. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med*. 2017;167(4):268-274. doi:10.7326/M16-2607

32. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *Journal of Health Economics*. 1999;18(3):341-364. doi:10.1016/S0167-6296(98)00039-3

33. Zhang Y, Woo JG, Urbina EM, Jacobs DR Jr, Moran AE, de Ferranti SD. Low-Density Lipoprotein Cholesterol Trajectories and Prevalence of High Low-Density Lipoprotein Cholesterol Consistent With Heterozygous Familial Hypercholesterolemia in US Children. *JAMA Pediatrics*. 2021;175(10):1071-1074. doi:10.1001/jamapediatrics.2021.2046

34. Zeki Al Hazzouri A, Vittinghoff E, Zhang Y, Pletcher MJ, Moran AE, Bibbins-Domingo K, Golden SH, Yaffe K. Use of a pooled cohort to impute cardiovascular disease risk factors across the adult life course. *International Journal of Epidemiology*. 2019;48(3):1004-1013. doi:10.1093/ije/dyy264

35. Newman Connie B., Preiss David, Tobert Jonathan A., Jacobson Terry A., Page Robert L., Goldstein Larry B., Chin Clifford, Tannock Lisa R., Miller Michael, Raghuveer Geetha, Duell P. Barton, Brinton Eliot A., Pollak Amy, Braun Lynne T., Welty Francine K., null null. Statin Safety and Associated Adverse Events: A Scientific Statement From the American Heart Association. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2019;39(2):e38-e81. doi:10.1161/ATV.0000000000000073

36. Stirratt MJ, Dunbar-Jacob J, Crane HM, Simoni JM, Czajkowski S, Hilliard ME, Aikens JE, Hunter CM, Velligan DI, Huntley K, Ogedegbe G, Rand CS, Schron E, Nilsen WJ. Self-report measures of medication adherence behavior: recommendations on optimal use. *Translational Behavioral Medicine*. 2015;5(4):470-482. doi:10.1007/s13142-015-0315-2

37. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology*. 2013;13(1):117. doi:10.1186/1471-2288-13-117

38. Curtis LA, Burns A. *Unit Costs of Health & Social Care 2020*. PSSRU, University of Kent; 2020. Accessed August 20, 2023. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/

39. Mihaylova B, Briggs A, O'Hagan A, Thompson SG. Review of Statistical Methods for Analysing Healthcare Resources and Costs. *Health Econ*. 2011;20(8):897-916. doi:10.1002/hec.1653

40. Husereau D, Drummond M, Augustovski F, Bekker-Grob E de, Briggs AH, Carswell C, Caulley L, Chaiyakunapruk N, Greenberg D, Loder E, Mauskopf J, Mullins CD, Petrou S, Pwu RF, Staniszewska S. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *BMJ*. 2022;376:e067975. doi:10.1136/bmj-2021-067975

14 APPENDIX: Full Protocol for NHS HRA REC reference: 23/NE/0035

SEE NEXT PAGE

[NHS REC protocol added via PDF file merger to retain formatting]

ESTIMATING APPROPRIATE LIPID LOWERING MANAGEMENT IN THE UNITED KINGDOM PAEDIATRIC FAMILIAL HYPERCHOLESTEROLAEMIA REGISTER

Final Version 2.0
18 June 2024

Short title:	Paediatric FH Study
Acronym:	PFHR
IRAS Project ID:	324246
Study Sponsor:	University of Nottingham
Sponsor reference:	23002
Funding Source:	NIHR HTA (National Institute for Health and Care Research Health Technology Assessment)

STUDY PERSONNEL AND CONTACT DETAILS

Sponsor: Contact name	University of Nottingham Ms Angela Shone Research and Innovation University of Nottingham Research and Innovation E-floor, Yang Fujia Building Jubilee Campus Wollaton Road Nottingham NG8 1BB
Study host organisation (Data Controller):	University of Nottingham
Chief investigator and Study Lead	Laila J Tata Associate Professor, Epidemiologist Lifespan and Population Health, School of Medicine, Room B119, Clinical Sciences Building, City Hospital, Hucknall Road, Nottingham, NG5 1PB United Kingdom Phone: +44 (0) 115 823 1353 Email: Laila.tata@nottingham.ac.uk
Co-investigator and Study Co-Lead	Nadeem Qureshi Clinical Professor, General Practitioner Lifespan and Population Health, School of Medicine, Applied Health Research Building, University Park Nottingham, NG7 2RD Phone: +44 (0) 115 846 6900 Email: Nadeem.qureshi@nottingham.ac.uk
Study statistician:	Yana Vinogradova Senior Research Fellow, Medical Statistician Lifespan and Population Health, School of Medicine, Applied Health Research Building, University Park Nottingham, NG7 2RD Phone: +44 (0) 115 846 6900 Email: Yana.Vinogradova @nottingham.ac.uk
Study Coordinating Centre:	School of Medicine Applied Health Research Building, University Park Nottingham, NG7 2RD

SYNOPSIS

Title	ESTIMATING APPROPRIATE LIPID LOWERING MANAGEMENT IN THE UNITED KINGDOM PAEDIATRIC FAMILIAL HYPERCHOLESTEROLAEMIA REGISTER
Acronym	PFHR
Short title	Paediatric FH Register Study
Chief Investigator and Study Lead **Co-Investigator and Study Co-Lead**	Laila J Tata Nadeem Qureshi
Objectives	To collect clinical data on individuals diagnosed with familial hypercholesterolaemia during childhood (data held in a Paediatric Familial Hypercholesterolaemia Register), in combination with questionnaires and qualitative interviews, to answer the following questions: • What are the health benefits and risks in the short-term and longer-term to monitoring health and starting treatment (mainly cholesterol-reducing medications) at different ages and cholesterol concentrations during childhood and adolescence among people diagnosed with familial hypercholesterolaemia (also called clinical effectiveness)? • For children and young people diagnosed with familial hypercholesterolaemia and their families, what is the acceptability of monitoring health and starting treatment (mainly cholesterol-reducing medications) in childhood and adolescence? • How does following health monitoring and taking treatment medications as directed by health services (also called adherence) vary across childhood and adolescence and what are the short-term and longer-term health benefits and risks related to variation? • How do health service costs of clinical familial hypercholesterolaemia monitoring and treatment in childhood and adolescence balance with the savings produced by preventing early heart disease in longer-term and does this provide value for money (also called cost-effectiveness)?
Study Configuration	Multi-centre across England and Wales
Setting	Secondary care sites providing clinical care for paediatric familial hypercholesterolaemia
Number of participants	Over the next 5 years, 1,000-2,000 individuals with familial hypercholesterolaemia diagnosed during childhood will be recruited for clinical data collection. 400-500 of these will

	have questionnaire data collection and 40 will have interview data collection.

Eligibility criteria	**Eligibility criteria**
	
	Individuals who have been diagnosed with FH before the age of 18 years and have been seen and followed-up in an NHS clinical setting for management of their FH during childhood (i.e., under age 18) are eligible for clinical data collection. Individuals with FH who are age 16 years or older and parents/guardians of individuals with FH who are under age 16 are eligible for questionnaire and interview data collection.
	
	Inclusion criteria
	
	• Age 0 years to 25 years (upper age limit can change in future based on data availability)
	  ○ Within the first 4 years of recruitment, case recruitment is prioritised to:
	  ○ a clinical or genetic diagnosis of familial hypercholesterolaemia (excluding confirmed homozygous, compound heterozygous/digenic FH)
	  ○ age 7 years or older with a baseline cholesterol measurement (ideally at diagnosis) and planned clinical follow-up
	  ○ at least 1 available LDL-C measurement before age 16 years
	  ○ for cases on LLT, date treatment started and the pre-treatment LDL-C measurement
	  The above prioritised inclusion criteria are to ensure the primary study objective aligned with the NIHR HTA award (NIHR134993) is answerable, which assesses the clinical effectiveness of cholesterol-reducing mediations which are typically not started until age 8 onwards. Permission to recruit prospective patients who do not meet the prioritised inclusion criteria must be approved by the Study Leads.
	• Ability of participant with FH to provide informed consent at age 16 years or older
	• Ability of participant's parent/guardian to provide informed consent for participants with FH under age 16 years
	• Ability of participant with FH to provide informed assent at age 5-15 years for clinical data collection
	• Attending a clinical site for their FH that has been approved for study recruitment

	Exclusion criteria None beyond limits of eligibility and inclusion criteria other than the following language restrictions: • To facilitate completion by non-English speaking children/young people and/or parents/guardians, study materials can be translated into the 4 commonest non-English languages in the UK and telephone support for patient information sheets and completion of completion of consent forms and questionnaires will be available through LanguageLine UK. However, this may still result in some language restrictions which could exclude some potential participants. • Availability of interpreters will be assessed on an as needed basis for interviews. However, inability to complete interview in English or in a language with an available interpreter will exclude some potential participants.
Description of interventions	Clinical data collection: Commitment requires consent on one occasion by participant individuals with familial hypercholesterolaemia if they are age 16 or over or their parent/guardian if they are under age 16 years. If the parent/guardian consents, a second consent by the participant will be required when they turn age 16 years. Clinicians enter clinical data based on medical notes and clinical consultations with the participant individual with familial hypercholesterolaemia. There is no active intervention with study participants. Questionnaire data collection: Commitment by the participant and/or parent/guardian is up to 3 years, completing questionnaires on 4 different occasions. Semi-structured interview data collection: Commitment by the participant and/or parent/guardian is one interview of up to 1 hour during the 5-year period of the research.
Duration of study	Active enrolment will commence in 2023 for at least 5 years (up to 2028). The study will close as and when ethical approval to continue ceases.
Methods of analysis	Quantitative methods will be used for the clinical data collection and questionnaire research and qualitative methods will be used for the interview research, with triangulation of findings across the research. • To assess clinical effectiveness, the main analysis will be assessing absolute and percentage reductions in low density lipoprotein-cholesterol (LDL-C) concentrations from pre-treatment concentrations associated with age and LDL-C at initiation of

	cholesterol-reducing medications, using linear mixed-effects modelling. The incidence of side-effects will also be described. • Acceptability and adherence will be described quantitatively based on participant characteristics in the questionnaire. High/low adherence will be described using the Medication Adherence Report Scale according to children's age and other characteristics related to their FH and their/their parent/guardian beliefs about FH. • Qualitative data will be analysed using the framework approach to map differences/similarities within and between groups, such as by age at initiation of cholesterol-reducing medications or adherence. • A cost-effectiveness model will be constructed to identify the most cost-effective approach to starting medications at different ages and LDL-C thresholds.

ABBREVIATIONS

BHF	British Heart Foundation
CHD	Coronary Heart Diseases
CRF	Case Report Form
CVD	Cardiovascular Disease
CYP	Children and Young People
CYPAG	Children and Young Peoples' Advisory Group
DMEC	Data Monitoring and Ethics Committee
FH	Familial Hypercholesterolaemia
GCP	Good Clinical Practice
LDL-C	Low Density Lipoprotein Cholesterol
LLT	Lipid Lowering Treatment/Therapy
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NIHR HTA	National Institute for Health and Care Research Health Technology Assessment
NUH	Nottingham University Hospitals
PCAG	Parent and Carer Advisory Group (parents, guardians or adult carers/family members)
PFHR	Paediatric Familial Hypercholesterolaemia Register
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
PPI(E)	Patient and Public Involvement (and Engagement)
R&D	Research and Development department
REC	Research Ethics Committee
SSC	Study Steering Committee
UoN	University of Nottingham

TABLE OF CONTENTS

STUDY BACKGROUND INFORMATION AND RATIONALE

Background

Familial hypercholesterolaemia (FH) is an autosomal dominant monogenic disorder in which high levels of atherogenic low-density lipoprotein cholesterol (LDL-C) accumulates in the blood from birth causing early onset cardiovascular disease (CVD) and a high risk of early death.[1] Once identified, patients with FH can be very effectively treated with lipid lowering treatment (such as a statin) and early identification and treatment have been shown to reduce their future risk of CVD.[2,3]

At an estimated prevalence of 1 in 250,[4] there are roughly 260,000 people with FH in the United Kingdom (UK) with the vast majority being undiagnosed. To tackle this, the National Health Service (NHS) long term plan proposes to identify 25% of predicted FH individuals by 2024.[5]

In 2008, clinical guidelines from the National Institute for Health and Care Excellence (NICE guideline CG71) were published, documenting the care pathway and management of adults and children with FH. One of the strong recommendations was that all children with FH should be identified before the age of 10, in order that lifestyle, and where necessary statin treatment, should be initiated to reduce their subsequent risk. At the time it was recommended that these children were to be primarily found through 'cascade testing' by tracing the relatives of the 15,000 or so known index cases with FH currently being treated in lipid clinics throughout the UK.

Current NICE recommendations (CG71 updated in 2019) recommend initiating lipid-lowering treatment/therapy (LLT) by 10 years of age where LDL-C concentrations are significantly raised[2,6] based on: Reviews of studies on statins (the most common type of LLT) demonstrating they reduce LDL-C and are safe (based on up to around one year of follow-up data);[7] Observational evidence that treating children with FH reduces their long-term CVD risk;[8] Estimates of the impact of raised LDL-C over time on CVD risk;[3] and Clinical consensus.[2]

While statin treatment in adults has a good safety record, there are no long-term studies of safety in children, with the longest studies usually not extending past two years, and restricted to following up lipid concentration levels, growth rates, progression through puberty, and capturing information on any major side effects. The 2019 NICE FH guideline development group recognised the need for more robust evidence for decision making on when to start LLT in children and young people (CYP).[6] Although the results of short trials are reassuring, many clinicians are still reluctant to prescribe statins at an early age because of the lack of long-term data.

It has been suggested that in some children with a modest elevation of LDL-C or where the age of onset of CVD in the family is later, it maybe clinically appropriate to withhold statin treatment until a child reaches adulthood, however, data to address the long-term CVD risk associated with this is lacking. Data on a surrogate measure of atherosclerosis development, namely the thickening of the carotid artery (determined by intima-medial thickness measurements) suggests that CVD developing at a young age. A Dutch study has demonstrated a significantly increased carotid artery thickening in FH children by the age of 10 years compared to their non-FH brothers and sisters, that this thickening increases over time in FH children faster than in their non-FH siblings, and that this increase can be significantly reduced (essentially to that in non-FH children) by treatment with Pravastatin[8].

Rationale

The lack of robust evidence underpinning the current recommendations for the clinical management of CYP with FH, and specifically the age and cholesterol concentrations at which to start LLT, in the 2019 NICE FH guidelines[6] highlights the need for contemporary follow-up information on FH throughout childhood and adolescence. Furthermore, several studies have reported variation in LLT adherence cross-sectionally and real-world data on adherence and side-effects over time are crucial to informing the evidence base on safety monitoring throughout childhood.[9–11]

This study will therefore collect prospective clinical and questionnaire data on children with FH for the purposes of assessing the health benefits and risks of monitoring health and starting treatment (mainly LLT) during childhood and adolescence. Clinical data collection will include clinical monitoring and structured reporting of treatment medication adherence and side effects. Questionnaire data collection will be used for direct patient-reported or patient parent/guardian-reported information on adherence, side-effects, and use of healthcare services. The study will also include semi-structured interview data collection at one time point with CYP with FH and their parents/guardians, exploring their views on adherence, side-effects, and use of healthcare services.

The clinical data collection for this study will based on the structure of the original UK Paediatric Familial Hypercholesterolaemia Register (PFHR) (IRAS Project ID: 238252) which has been suspended since 2019. The previous Register recruited over 600 people diagnosed with FH during childhood or adolescence.[12–14] The revised PFHR will be housed at the University of Nottingham. The setting up of a register to increase the number of children with FH being identified was recommended by NICE and reinforced by the 2019 NHS long term[5] and 2019 NICE guideline update on FH identification and management[6] as a means of monitoring the increasing number of CYP being diagnosed and providing data to inform evidence-based guidance on the clinical management and monitoring of FH during childhood and long-term health into adulthood.

STUDY OBJECTIVES AND PURPOSE

PURPOSE

The purpose of this study is to improve the cholesterol management among CYP with FH. Integral to this purpose is to provide evidence to describe optimal approaches to managing FH during childhood that are acceptable to clinicians, CYP with FH and their families, and to identify a cost-effective approach to managing FH throughout childhood and adolescence. The study was a commissioned call by the National Institute for Health and Care Research Health Technology Assessment (NIHR HTA) with the University of Nottingham awarded 5 years funding (NIHR134993).

PRIMARY OBJECTIVE

The primary objective is to answer the following question:

What are the health benefits and risks in the short-term and longer-term to monitoring health and starting treatment (mainly cholesterol-reducing medications, also known as LLT) at different ages and cholesterol concentrations during childhood and adolescence among people diagnosed with familial hypercholesterolaemia (also called clinical effectiveness)?

SECONDARY OBJECTIVE

Secondary objectives are to answer the following questions:

- For children and young people diagnosed with familial hypercholesterolaemia and their families, what is the acceptability of monitoring health and starting treatment (mainly cholesterol-reducing medications) in childhood and adolescence?
- How does following health monitoring and taking treatment medications as directed by health services (also called adherence) vary across childhood and adolescence and what are the short-term and longer-term health benefits and risks related to variation?
- How do health service costs of clinical familial hypercholesterolaemia monitoring and treatment in childhood and adolescence balance with the savings produced by preventing early heart disease in longer-term and does this provide value for money (also called cost-effectiveness)?

STUDY DESIGN

STUDY CONFIGURATION

The study comprises clinical data collection by healthcare professionals and patient-reported information obtained via questionnaire data collection and semi-structured interview data collection.

The clinical data collection is in the form of an electronic database accessed via the web by clinicians who see individuals diagnosed with FH in childhood and adolescence. Clinicians (or a nominated staff member) are 1) approved for recruiting, consenting and registering patients for clinical data collection, 2) provided with a username and password for entry of clinical data at registration and clinical follow-ups. Trained NHS research volunteers approved by clinical sites will also assist in recruiting and consenting patients following patients' agreement obtained from clinicians or nominated staff members. Currently, 5 English sites and 1 Welsh site will be approved, however, any clinical site in England Wales and Northern Ireland seeing individuals with FH during childhood can be approved; sites that commence clinical data entry will undergo approval in line with this protocol. The clinical data collected for the study will be stored in the PFHR.

Patients who consent to clinical data collection can additionally consent to being contacted for involvement in further research. Patients who consent to being contacted for further research will be invited to participate in questionnaire data collection and/or semi-structured interview data collection. This is in recognition of the need to ensure robust information on the clinical management of FH and the use of LLT including benefits and risks from both clinical practitioner and patient perspectives.

STUDY MANAGEMENT

The study is managed at the University of Nottingham by the Study Management Group. The Study Leads are Co-Chairs of the Study Management Group. The Study Leads have overall responsibility for the study and shall oversee all study management. The Data Custodians will be the Study Leads. A Study Manager oversees communication with and coordination of clinical sites and participant recruitment and follow-up. REDCap, a secure web application will be used for clinical and questionnaire data collection with entered data stored at the University of Nottingham, the Data Controller. Digital recorders and online transcript software will be used for interview data collection with data stored at the University of Nottingham.

The study will be externally monitored by 2 independent committees as directed by the funder, NIHR. NIHR have approved the membership of the following committees for this study, as fulfilling their requirements (https://www.nihr.ac.uk/documents/research-governance-guidelines/12154):

1) The Study Steering Committee (SSC) will oversee the progress of the study. The SSC includes an independent chair (clinical professor), 3 clinicians/service providers, 2 patient and public involvement (PPI) representatives, a health economist, a statistician, a representative from the cholesterol charity HEART UK, a representative from the Genomic Medicine Service Alliance. The SSC will meet twice a year and will interact more frequently if required.

2) The Data Monitoring and Ethics Committee (DMEC) will specifically consider ethical or safety concerns that emerge primarily to monitor the qualitative data from the semi-structured interviews with children, young people and/or parents. The committee includes an independent chair (associate professor in qualitative & mixed-methods applied health research), 2 PPI representatives, and 1 clinician. The DMEC will meet twice a year in the first 3 years and then once a year in the last 2 years of the study; the DMEC will interact more frequently if required.

DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

Participant Duration

a) Clinical data collection: Commitment requires consent on one occasion by participant individual with familial hypercholesterolaemia if they are age 16 or over or by their parent/guardian if they are under age 16 years. If parent/guardian consents, a second consent by the participant will be required when they turn age 16 years. Clinicians enter clinical data based on medical notes and clinical consultations with the participant individual with familial hypercholesterolaemia. There is no active intervention with study participants and they will not be contacted for the purposes of the clinical data collection by the research team. They will only be contacted for b and c below if they have expressed an interest in being contacted for further research.

b) Questionnaire data collection: Commitment by participant and/or parent/guardian is up to 3 years, completing questionnaires on 4 different occasions

c) Interview data collection: Commitment by participant and/or parent/guardian is one interview of up to 1 hour during the 5-year period of the research.

Study Duration: Active enrolment will commence in 2023 for 5 years (up to 2028). The study will close as and when ethical approval to continue ceases. We propose to secure further funding to continue clinical data collection for people on the PFHR after 5 years and hence apply for extension of ethical approval.

End of the Study

The end of the study will be last data collection from the last participant (up to 2028).

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Information about participation in the study is disseminated both actively and passively to clinicians and the public. Clinical teams who see children with FH are identified and

contacted through networks, including the previous FH audit and those organised by the cholesterol charity HEART UK. Study information packs will be provided to clinical teams with materials to publicise the study to their patients. Information is also published in HEART UK newsletters and on their website with information tailored for health professionals and members of the public who may have lived experience of familial hypercholesterolaemia. Details about participant information sheets and consent forms will be available from the HEART UK website.

Recruitment has 3 phases:

a) Patients are recruited for clinical data collection by clinicians (or a nominated staff member who will usually be a clinical member of staff with experience of working with the patient group) at NHS clinical sites seeing individuals diagnosed with FH during childhood across the England and Wales. The clinician or nominee will inform the participant and/or their parent/guardian, of all aspects pertaining to participation in the study. The clinical setting is chosen for base recruitment as data collection is from clinical records and consultations with health professionals. Patients or their parents/guardians are initially approached for recruitment during or between clinic visits, via email, telephone, text message or post, based on accepted recruitment practices and patient-contact methods within the clinical site.

   Clinical teams also have the option of using trained NHS research volunteers who will be approved by the site PI to assist in recruiting participants. Patients will only be put in contact with research volunteers following their direct agreement which will be obtained by the clinician or nominated staff member asking the patient if they agree to talk with the research volunteer about potential participation. Contact with the research volunteer may be in person on remote by phone/online depending on processes agreed at the clinical site. Trained NHS Research volunteers will have undergone Nottingham University Hospitals (NUH) training and registration as a research volunteer in accordance with the NUH PPI and NUH Research & Innovation PPI policies. Under these policies, research volunteers are required to registered as an NUH volunteer under NUH voluntary services as they meet criteria of having a patient facing contact when representing NUH. This registration ensures the research volunteer is affiliated to NUH and is covered by NUH indemnity (with no personal risk nor liability), receives appropriate support, must complete all relevant training and ensure patient safety. Mandatory training includes Good Clinical Practice and the following modules completed via the NHS England Volunteer Passport:
   Roles and responsibilities
   Communications
   Conflict resolution
   Child sexual exploitation
   Preventing radicalisation
   Mental health awareness
   Fluids and nutrition
   Resuscitation
   Moving and assisting
   Data security
   Health, safety and infection control
   Safeguarding adults
   Safeguarding children
   Equality diversity and human rights
   Fire safety

As our research volunteers will be talking with families and children they will also have a full Disclosure and Barring Service (DBS) check completed. Following training and registration, research volunteers sign a values and behaviours contract which is a formal affiliation with NUH Trust to ensure the volunteer is a member of NUH. Their NUH training and registration as a research volunteer allows them to work nationally across NHS sites in England and this will be enabled by site-specific agreements within our study.
The research volunteers will have lived experience of FH in their family or undergo training paediatric FH from the study team which includes clinical professionals working in paediatric FH.

It is possible for patients or parents/guardians to approach their clinicians with interest in participating in the study; their clinical team will need to have been approved for data collection prior to recruitment.

b) Patients aged 16 years and over or parents/guardians of younger patients are recruited for questionnaire data collection if they express an interest in being contacted for participation in further research when they enrol for clinical data collection, i.e., they must have completed consent for a). They are initially approached using the preferred contact method they provide which can be via email, telephone, text message or post. Based on patient preference, questionnaires are provided electronically via the REDCap web application, which is usable on a computer or mobile device, sent as paper copies for return post, or administered over the telephone. Patient recruitment for questionnaire data collection will target all individuals who express an interest to being contacted for participation in further research.

c) Patients aged 16 years and over or parents/guardians of younger patients are recruited for semi-structured interviews if they express an interest in being contacted for participation in further research when they enrol for clinical data collection, i.e., they must have completed consent for a). They are initially approached using the contact information they provide which can be via email, telephone, text message or post. Based on patient preference, interviews are conducted via telephone or online using Microsoft Teams. In-person interviews will only be conducted if patients are not willing to use telephone or online methods. Patient recruitment for interview data collection will be initially focussed on obtaining a sample that will provide diversity based on sociodemographic, geographical, and FH-related characteristics. Specifically, a main purpose is to obtain information on adherence, side-effects, and use of healthcare services in line with the aim of continuing to monitor the safety of current and new treatments. Therefore, questionnaire data on patient-reports of low-high adherence and clinical data on medication use will be combined with sociodemographic and geographical data to form an interview sampling framework, ensuring recruitment represents diverse characteristics and there is oversampling of underrepresented populations (e.g., based on ethnicity or adherence). A data extraction protocol for the sampling framework will be designed by the Study Leads and the Study Statistician that will include the patient's identity code and date of birth but no other personal information. If interview recruitment is low from questionnaire participants, the remaining patients consented for clinical data collection who expressed an interest to participate in further research will be approached for recruitment.

It will be explained to the potential patient participant and/or their parent/guardian 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 from any research where it has been used and we will seek consent to use the data in the final analyses where appropriate.

Strategies for recruitment and retention

Whilst recruitment to the study for clinical data collection will be open to any interested eligible clinical site, recruitment efforts will initially focus on 6 clinical sites representing a breadth of geographic and sociodemographic diversity. For initial estimates of case recruitment, clinical sites provide estimates at baseline of their existing paediatric case load and the number of newly presenting patients they see each 1-2 months. Sites are then contracted and funded for recruitment.

Recruitment for clinical data collection will use multiple contact methods as described in a) above and will not be restricted to clinic visits because visit frequency for young people with FH typically varies between every 6 months to every 2 years. Clinical sites will keep in contact with patients on their lists wherever possible to obtain a definitive answer as to whether they wish to participate. They will be able to send reminders/re-invitations to patients to facilitate this if patients are still under their care and have not declined participation. Up to 5 reminders/re-invitations will be sent via different contact methods, as appropriate for the clinic/patient, over a period of up to 2 years. This is to account for use of the 3 different remote contact methods (email, text, post) and the potential for unreceived invitations due to technical problems with not receiving these (e.g., incorrect email, text or address; email not noticed as gone to junk mail). It is also to account for reminders/re-invitations where the patient/family have expressed interest in joining the register with the clinical team, but then not fully completed the remote consent process; As the process requires consent of a parent or patient age 16 as well as assent for patients age 5-15 the process, this recognises organisation and time pressures for these can be a barrier to full completion of consent. The 2-year period is in recognition that clinic appointments for patients may be only annual or less frequent if appointments are missed; this thus allows for re-discussion of the paediatric register in person or remotely with patients at a subsequent appointment or between appointments to see if they are still interested in joining and being re-invited if they have lost an initial invitation. Reminders/re-invitations will be sent only as appropriate to the situation of each patient and their initial contact method and will be the decision of the clinical team. The REDCap data capture system will also be used to generate automatic reminders to clinicians for annual clinical data entry. Where there is no response from the clinician, this is followed up manually by the Study Manager or Study Administrator to determine whether the clinician or the patient has left the clinic, in which case the necessary actions will be taken to assess requirements for consent and continued follow-up.

The Study Manager and Study Administrator will coordinate communication for recruitment, consent, and completion of a baseline questionnaire and 3 follow-up questionnaires. For the questionnaire data collection, if the participant prefers only to be contacted via email or text message, the REDCap system will generate an automatic invitation via a unique link that will include the participant information sheet and access to the electronic baseline questionnaire with consent to complete the questionnaire. The REDCap data capture system will also be used to generate automatic reminders to participants, as necessary, to complete initial consent and each questionnaire. In the situation of low recruitment (e.g., low patient response), strategies for advertising participation in questionnaire data collection will be agreed with teams at clinical sites, such as advertising opportunities questionnaire participation, the reasons for this data collection and what participation involves.

Recruitment materials will be available in the 5 commonest languages in the UK. LanguageLine UK will be accessible to facilitate recruitment. For semi-structured interview consent and data collection, availability of an interpreter will be assessed on an as needed basis. In clinical settings hospital interpreters and translator services can be used if available.

To maintain engagement with participants and parent/guardians of participants, newsletters about the study will be published every 6 months on the HEART UK website and disseminated to clinical sites with encouragement to share with their FH patients and display in clinics as appropriate. For participants who have expressed interest in being contacted for participation in further research, the Study Manager will disseminate newsletters directly to them with information and updates about the data collection and research progress.

Eligibility criteria

Individuals who have been diagnosed with FH before the age of 18 years and have been seen and followed-up in an NHS clinical setting for management of their FH during childhood (i.e., under age 18) are eligible for clinical data collection. Individuals with FH who are age 16 years or older and parents/guardians of individuals with FH who are under age 16 are eligible for questionnaire and interview data collection.

Inclusion criteria

- Age 0 years to 25 years (upper age limit can change in future based on data availability)
    - Within the first 4 years of recruitment, case recruitment is prioritised to:
        - a clinical or genetic diagnosis of familial hypercholesterolaemia (excluding confirmed homozygous, compound heterozygous/digenic FH)
        - age 7 years or older with a baseline cholesterol measurement (ideally at diagnosis) and planned clinical follow-up
        - at least 1 available LDL-C measurement before age 16 years
        - for cases on LLT, date treatment started and the pre-treatment LDL-C measurement

      The above prioritised inclusion criteria are to ensure the primary study objective aligned with the NIHR HTA award (NIHR134993) is answerable, which assesses the clinical effectiveness of cholesterol-reducing mediations which are typically not started until age 8 onwards. Permission to recruit prospective patients who do not meet the prioritised inclusion criteria must be approved by the Study Leads.
- Ability of participant with FH to provide informed consent at age 16 years or older
- Ability of participant's parent/guardian to provide informed consent for participants with FH under age 16 years
- Ability of participant with FH to provide informed assent at age 5-15 years for clinical data collection
- Attending a clinical site for their FH that has been approved for study recruitment

Exclusion criteria

None beyond limits of eligibility and inclusion criteria other than the following language restrictions:

- To facilitate completion by non-English speaking children/young people and/or parents/guardians, study materials can be translated into the 4 commonest non-English

languages in the UK and telephone support for patient information sheets and completion of completion of consent forms and questionnaires will be available through LanguageLine UK. However, this may still result in some language restrictions which could exclude some potential participants.

- Availability of interpreters will be assessed on an as needed basis for interviews. However, inability to complete interview in English or in a language with an available interpreter will exclude some potential participants.

Expected duration of participant participation

a) Clinical data collection: Commitment requires consent on one occasion by participant individual with familial hypercholesterolaemia if they are age 16 years or over. Commitment requires consent on one occasion by a parent/guardian of a participant if they are under age 16 years and assent by the participant. Commitment requires consent by study participants who turn age 16 years who had previously provided assent. The data collection period (described below) does not require any time commitment from the participant as data collection is done by clinical sites.
b) Questionnaire data collection: Commitment by participant and/or parent/guardian is up to 3 years, completing questionnaires on 4 different occasions of 15-20 minutes each.
c) Semi-structured interviews: Commitment by participant and/or parent/guardian is one interview of up to an hour.

Participant Withdrawal

Participants with FH aged 16 years and older or parents/guardians of a participant who is under age 16 may withdraw from further data collection. The participants will be made aware that this will not affect their current or future healthcare. Participants will be made aware (via the information sheets and consent forms) that should they withdraw, the data collected to date cannot be erased from any research where it has already been used. As consent for clinical, questionnaire and interview data collection are separate (see **Informed consent** section) it will be possible for participants to withdraw from one aspect of the study whilst maintaining participation in another (e.g., withdrawal from interview but still participate in clinical data collection).

Clinical site staff participating in clinical data collection may not withdraw a participant without the consent of the participant or their parent/guardian.

Informed consent

Informed consent is sought separately for each aspect of study participation as follows:

a) Clinical data collection: The clinician or nominated staff member at clinical sites will explain the details of the electronic clinical data collection and its purpose and provide access to written information in paper or electronic format, ensuring the prospective participant has sufficient time to consider participating or not. The clinician or nominated staff member will answer any questions that the prospective participant has concerning participation. With the agreement of the prospective participant, a clinician or nominated staff member will also be able to direct the prospective participant to a trained NHS research volunteer to explain these details. The research volunteer will also answer any questions or re-direct the prospective participant to the clinician or nominated staff member if they are not able to answer some questions. Prospective participants will be provided with the contact details of the Study Management Group/Manager/Administrator if they would like further information.

Informed consent will be obtained as follows:

- Informed consent by the individual with FH if they are age 16 years or older
- Informed consent by a parent/guardian if the individual with FH is under age 16 years
- Informed assent by the individual with FH if they are under age 16 years (in conjunction with parent/guardian consent)
- Informed consent by the individual with FH who has previously provided informed assent when they reach 16 years of age

If an individual with FH who is under age 16 years has capacity to assent but does not want to participate, they will not be recruited to the study, regardless of whether the parent/guardian wishes to provide consent. In the absence of capacity to assent by an individual with FH who is under age 16 years, parent/guardian consent will be deemed sufficient.

b) Questionnaire data collection: The Study Manager/Administrator or a nominated staff member at the University of Nottingham will provide written information about the questionnaire data collection and its purpose in paper or electronic format (where the participant has previously provided preference to be contacted via email, post, or text message) or will telephone the participant to provide the same information (where the participant has previously provided preference to be contacted by phone). Prospective participants will be given sufficient time to consider participating or not. The Study Manager/Administrator or a nominated staff member at the University of Nottingham will answer any questions that the prospective participant has concerning participation.

Individuals with FH who are 16 years of age or older and parents/guardians of individuals with FH who are under age 16 will be approached for participation in questionnaire data collection.

Informed consent will be obtained as follows:

- Informed consent by the individual with FH if they are age 16 years or older
- Informed consent by a parent/guardian if the individual with FH is under age 16 years

c) Semi-structured Interviews: The Study Manager/Administrator or a nominated staff member at the University of Nottingham will provide written information about the interview data collection and its purpose in paper or electronic format (where the participant has previously provided preference to be contacted via email, post, or text message) or will telephone the participant to provide the same information (where the participant has previously provided preference to be contacted by phone). Prospective participants will be given sufficient time to consider participating or not. The Study Manager/Administrator or a nominated staff member at the University of Nottingham will answer any questions that the prospective participant has concerning participation.

Individuals with FH who are 16 years of age or older and parents/guardians of individuals with FH who are under age 16 will be approached for participation in interview data collection. Individuals with FH who are age 16 years of age or older will be interviewed by themselves but will be given the option to have a parent/guardian with them. Parents/guardians of individuals with FH who are under age 16 will be interviewed by themselves but will be given the option to have their child participate with them if the child is at least age 11 years. Appropriate consent and assent forms will be used based on participation.

Informed consent will be obtained as follows:

- Informed consent by the individual with FH if they are age 16 years or older
- Informed consent by a parent/guardian if they participate in an interview with their child with FH who is age 16 years or older (in conjunction with their child's consent)
- Informed consent by a parent/guardian if the individual with FH is under age 16 years
- Informed assent by the individual with FH if they are age 11-15 years and participate in an interview with their parent/guardian (in conjunction with parent/guardian consent)

Written information about the Study is in the form of participant information sheets, consent forms or assent forms in paper or electronic format. Electronic format will be via REDCap, a secure web application. Participants requesting initial contact by telephone will require online access to complete the consent form or completion via posted paper form. Telephone guidance will be provided for completion of the paper/online consent form at the request of the participant. This will be facilitated by the clinical team or research team, as appropriate. Consent/assent forms for the relevant participation (clinical data collection, questionnaire data collection, interview data collection) will be signed and dated by the individual with FH and/or their parent/guardian before any relevant data are collected. Electronic versions of the forms on REDCap include tick boxes for confirming consent options and electronic signatures are recorded by tracing using a mouse, trackpad, or touchscreen.

Where individuals require participant information sheets and consent/assent forms in a language other than English, paper copies will be available in the next 4 commonest languages in the UK.

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 amended consent/assent forms which will be signed by the participant.

STUDY/ REGIMEN

Clinical data collection: Following provision of consent, no active involvement/follow-up is required by the participant individual with FH or their parent/guardian. Clinicians enter clinical data based on medical notes and clinical consultations from the course of their routine clinical care for the individual with FH. The period of data collection will depend on the paediatric clinical follow-up of the patient with FH and will typically be up to age 18 years but will vary based on the clinical service provision from approximately age 16 to age 25 years.

At the point of providing consent for clinical data collection, participants can additionally express an interest in being contacted for involvement in further research and will provide their contact details and preferred method of contact. They will be given the choice to provide one or more of the following: email address, telephone number, postal address, and a preference for one or more of the following: contact via email, text message, telephone call or by post.

Questionnaire data collection: Following provision of consent, participant individuals with FH who are age 16 years or older or parents/guardians of individuals with FH who are younger will complete a baseline questionnaire (Q1) using the REDCap web application or a paper questionnaire. At 8, 16, and 24 months, follow-up questionnaires (Q2, Q3, Q4) will be sent to the participant for completion with automatic reminders at 2 weeks and 4 weeks automatically generated by the REDCap system or via contact by the Study Manager/Administrator or nominee.

Information at the start of the questionnaire will explain to parents/guardians that they can fill out the questionnaire independently or with input from their child with FH. Information at the

start of the questionnaire will explain to individuals with FH who are age 16 years or older that they can fill out the questionnaire independently or with input from their parent/guardian. Participants will be asked to record whether it was filled out independently or with a family member.

Semi-structured Interviews: Following provision of consent, participant individuals with FH who are age 16 years or older or parents/guardians of individuals with FH who are younger will undergo an interview of up to 1 hour conducted via telephone or online using Microsoft Teams (or in-person if patients are not willing to use telephone or online methods). The University of Nottingham has a contract for Microsoft Teams as a secure web facility for interviews. Individuals who are age 16 and over have the option of being interviewed with a parent/guardian and parent/guardian participants have the option of including their child with FH who is under age 16 years in their interview if they are age 11-15 years. All interviews will be recorded using a handheld digital audio recorder. For interviews conducted online using Microsoft Teams, the transcription utility will be used to transcribe the interview without the use of audio-visual recording; the audio recording will be retained as a backup for listening to any sections of interview where the text transcription file is unclear. For interviews where there is only a digital audio recording, audio files will be transcribed using TranscribeIt software, a University of Nottingham approved supplier (https://www.transcribeit.co.uk), where audio and transcription files are securely uploaded and downloaded to/from the online transcription platform.

Compliance

There is no intervention, study regime or change to a participant's routine care or daily lives and as such, so basis for which to define compliance. Participants will be able to withdraw from research participation at any time which includes from the clinical data collection, questionnaires, or interview participation. No participant will be expected or obliged to complete a questionnaire or interview if they wish to withdraw during their participation, i.e., this will not be used to define compliance.

Criteria for terminating the study

If a security breach or data breach is identified where the clinical data entry database is stored (the University of Nottingham), access to the REDCap data entry interface will be stopped and data collection paused until systems are deemed secure.

If insecure access to the REDCap clinical data entry web interface was discovered at a clinical site, login and passwords would be suspended until deemed secure. If unresolved, clinical site access would be permanently suspended.

If insecure access to the REDCap consent, clinical or questionnaire data entry web interfaces was discovered from an external unauthorised source, the REDCap data entry interface would be suspended until methods of access were deemed secure.

Due to the nature and use of the data that is due to be collected as part of this study, there is no criterion for terminating the study.

ANALYSES

Methods

Statistical support for appropriate monitoring of study participant numbers, data completeness, data quality and the interview sampling frame will be provided by the Study Statistician at the

University of Nottingham with oversight of the Study Leads. Monitoring and analysis protocols will also be shared with the SSC and DMEC for their review.

Quantitative analyses will be conducted using Stata and R software by researchers with epidemiological, statistical and health economics expertise. Qualitative analyses will be conducted using NVivo software by researchers with qualitative methodology and analysis expertise.

Clinical effectiveness analysis

For the primary assessment of clinical effectiveness, absolute (mmol/L) and percentage reductions in LDL-C from pre-treatment (LLT) concentration levels will be estimated using a linear mixed-effects model. A multi-level structure will be used to account for patients being grouped at clinical sites, with site as a random effect. LDL-C changes in those exposed to LLT will be compared with changes in those never exposed or unexposed up to a certain age, measured as the difference between the earliest and later follow-up measurements. We will use the inverse probability of treatment weighting techniques[15] to balance exposed and unexposed groups according to both baseline, and time-varying measured confounders: family history of CVD and/or FH in the family, gender, genetic testing, body mass index (BMI), ethnicity, other health conditions, smoking status, socioeconomic deprivation (using post-code mapped to index of multiple deprivation), reasons for not being on LLT or non-adherence, process factors such as attendance frequency.

We will primarily estimate intention-to-treat effects, i.e., the effect of prescribing LLT to people with FH on LDL-C concentrations.[16] We will then estimate per-protocol effects corresponding to the effect of continuously taking LLT during the following period. Potential treatment non-adherence and loss to follow-up will be accounted for via censoring weights.[16]

We will conduct sensitivity analyses to assess the extent to which the effects of age and LDL-C at initiation are robust to potential unmeasured confounding. We will adopt the E-value approach,[17] which essentially explores how strong (the association with both LLT initiation and LDL-C outcomes) the unmeasured confounders need to be to change the study conclusions.

Secondarily to LDL-C, we will also assess total cholesterol, HDL-C, triglycerides, and non-HDL changes using a similar analysis approach.

This will be a descriptive analysis and estimates will be provided with confidence intervals and p-values as appropriate. Estimates will also be used to derive effectiveness estimates that will feed into the cost-effectiveness model, where uncertainty will be fully propagated.[18]

Cumulative LDL-C (cholesterol burden) will be calculated as the area under the age trajectory of LDL-C up to 18 using a linear mixed-effects model, following methods described by Zhang et al.[19,20] To estimate the LDL-C slope for each participant, we will fit a linear mixed-effects model of the imputed LDL-C values against age, with age modelled as restricted cubic splines with random intercepts and slopes. The final LDL-C slope for each participant will be calculated as the population mean slope plus the individual random slope. LDL-C trajectories of CYP with current exposure to LLT will be compared with those never exposed or unexposed up to a certain age. We will also calculate Time-Weighted Average LDL-C (cumulative LDL-C divided by time) to measure the average LDL-C burden. We will use the same approach in the analysis above (of absolute and percentage LDL-C changes) to model associations with age and LDL-C at LLT initiation and address potential confounding. We expect to have at least 4 LDL-C measures available on most CYP. Since we will have representation across all ages,

we will also create models where we impute un-observed LDL-C using previously described methods.[21]

Achievement of treatment LDL-C targets before and after puberty, and at age 18 will be estimated using logistic regression, assessing confounding. We will evaluate by age and LDL-C threshold at LLT initiation, the achievement of (i) recommended targets of 30-50% reduction or <3.5mmol/l[2,22] and (ii) general (non-FH) population expected LDL-C concentrations from children in the Avon Longitudinal Study of Parents and Children (ALSPAC) who have repeated health and lifestyle measures into adulthood.[23]

Incidence of side-effects and adverse events associated with LLT

We expect that the side effects related to LLT will be very rare in CYP with FH, so this will be a descriptive analysis presenting the side effects/adverse events.

Among children on LLT, liver enzyme (transaminases) measures >2.5 times the upper limit of normal before and after puberty will be described according to LLT type (of statin and more rarely used medications such as ezetimibe) and dose. Logistic regression models will be used to adjust for clinical and sociodemographic factors.

Age at first menstruation, weight-for-age and weight-for-height z-scores (BMI in adolescents) according to LLT exposure (type, dose, age at initiation) will be modelled using generalized estimating equations (GEE)/growth models adjusting for clinical and sociodemographic factors.

We will estimate the incidence of side effects/adverse events during follow-up calculated from the number of side effects/adverse events over the exposure period in person-years. Incidence rates of side-effects and adverse events will be described according to LLT exposure (type, dose, age at initiation) where numbers are sufficient. Poisson regression will be used to adjust for clinical and sociodemographic factors. We will test the model for overdispersion and use a negative binomial model as an alternative.

Treatment adherence and acceptability quantitative analysis

Adherence will be described quantitatively based on information captured in clinical data from routine follow-up visits. Acceptability and adherence will be described quantitatively based on participant characteristics in the questionnaire. High/low adherence will be described using the Medication Adherence Report Scale[24] according to children's age and other characteristics related to their FH and their/their parent/guardian beliefs about FH.

Following descriptive analysis, GEE for repeated measures analysis will be used to examine associations of high adherence (versus low/moderate) with age, gender, ethnicity, deprivation, frequency of LDL-C testing and clinic visits, age and LDL-C concentration at LLT initiation, reasons for sub-optimal adherence, reported side-effects and family history of CVD.

Views of treatment acceptability, monitoring and adherence qualitative analysis

Interview transcripts will be analysed using the framework approach, which is a hierarchical, matrix-based method developed for applied research. The framework will enable us to map thematic differences/similarities within and between groups, such as by age at LLT initiation or adherence. Transcripts will be coded both according to a priori themes and inductively. Initial readings will facilitate familiarisation and will lead to the generation of codes. Further analysis will result in more substantive themes and sub-themes (the analytical framework). Data will

then be indexed according to the analytical framework. A sub-sample of data will be double coded to ensure validity of interpretations. We will also incorporate respondent validation whereby young people and parents will be invited to check initial accuracy of transcripts, add to them after a period of reflection, and review whether mapped themes are a reasonable reflection of their data. Finally, themes will be discussed and agreed between the research team, allowing clarification of the final framework that will then be applied across all transcripts.

Cost-effectiveness of starting treatment at different ages and LDL-C thresholds

A cost-effectiveness model will be constructed to identify the most cost-effective approach to starting medications at different ages and LDL-C thresholds. To identify the cost-effective approach to initiating LLT at a range of ages and LDL-C thresholds we will develop a new cost-effectiveness model. A decision model is required to estimate long-term reductions in CVD risk (which cannot be observed without decades of follow-up), given observed shorter-term LDL-C reductions. We will take the NHS perspective and express health outcomes primarily in quality-adjusted life years (QALYs) and capture outcomes that matter to patients, families, clinicians, and healthcare commissioners. The cost-effectiveness analysis will be conducted and reported in accordance with current methodological guidance for cost-effectiveness analysis.[25]

The model structure will start with linking LDL-C to CVD risk based on the well-established concept that LDL-C increases CVD risk and this effect increases over time.[26] Hence, the same LDL-C reductions over longer periods (from earlier LLT initiation) result in greater CVD risk reductions and more CVD events avoided. We will account for the impact of adherence in terms of its impact on LDL-C reductions from LLT (which are inherent to the estimates from the clinical effectiveness data analyses described above) and via the proportion of CYP who continue LLT use into adulthood.

We will evaluate a range of decision options for age and LDL-C at LLT initiation, highlighting combinations with major policy and clinical evidence, e.g., starting LLT at age 10 if LDL-C >3.5 mmol/L (as recommended by the European Atherosclerosis Society and the HEART UK Consensus Statement)[2,22] compared with starting later or at lower or higher LDL-C thresholds. We anticipate our model will comprise two modules:

Module (a) will quantify LDL-C, safety (i.e., adverse events, impact on health-related quality of life), costs during childhood/adolescence, and the likelihood of remaining on LLT into adulthood.

Module (b) will estimate long-term CVD consequences of raised LDL-C, potential long-term LLT side-effects, and the impact of CVD and LLT side-effects on health-related quality of life, life expectancy, QALYs and NHS costs, over individuals' expected lifetime. We will use published data on CVD risk in adulthood.

Sample size and justification

This is descriptive research using the available paediatric patient population diagnosed with FH across the United Kingdom (except Scotland). Based on estimates of paediatric patients with FH currently being seen and newly presenting patients at clinical sites contacted by the Study Leads, we estimate at least 1,300 patients with clinical data entry on the PFHR over the next 5 years. Clinical sites will be contracted and funded for recruitment.

We estimate 400-500 participants with questionnaire data and 40 participants with interview data.

It is acknowledged that FH is currently underdiagnosed in the general population, however, cascade testing aims to increase earlier diagnosis. Based on currently available estimates from mid-2020[27], the general population age 0-19 years is 13,330,355 in England, 701,777 in Wales, and 484,495 in Northern Ireland. At an estimated paediatric FH prevalence of 0.28% in the UK,[4] there are potentially 37,325 children living with FH in England, 1,964 in Wales, and 1,356 in Northern Ireland.

ADVERSE EVENTS

The occurrence of an adverse event as a result of participation in this study is not expected. There is no participation in any interventions as a result of participation in this study. Participation will have no consequences to an individual's clinical care.

ETHICAL AND REGULATORY ASPECTS

There are no interventions, separate clinical visits nor measurements required for participation in the study, beyond the patient's usual NHS clinical follow-up. Participation in the study involves consent for the patient's NHS clinical care information to be collected by the patient's clinical team for the study with the option for the patient or their parent/guardian to fill out questionnaires of self-reported information about their experience of FH, and the option of participating in an interview about their experience of FH.

Patients will be provided with contact details for the Study Management Team to discuss any concerns relating to participation and will be directed to discuss any personal clinical concerns with their FH clinical care team or general practitioner.

Filling out questionnaires and participating in interviews will involve questions about FH symptoms, FH treatment and treatment medications, and potential adverse events or side-effects related to LLT. Participation therefore has the potential to raise queries, uncertainty or anxiety about FH as well as increasing understanding about the condition. All participant-facing materials will be designed with and approved by stakeholders in FH including healthcare professionals and people with lived experience of FH to ensure they are appropriate for use with minimal ethical risks. This process will involve patient and health professional representatives on the Study Management Group, the Study Parent and Carer Advisory Group (PCAG) and the Study Children & Young People's Advisory Group (CYPAG).

Where data collection involves direct communication with participants, this will be conducted via telephone or using online communication platforms. In the situation where participants wish only to do an in-person interview, lone working risk will be considered. Where researchers work outside of University premises (e.g., in conducting face-to-face interviews at participants' homes), the University of Nottingham Lone Working Policy will be adhered to, ensuring that a colleague is aware the researcher is off-site and has made contact or been contacted at the anticipated end time of the interview, for example.

ETHICS COMMITTEE AND REGULATORY APPROVALS

The study will not be initiated before the protocol, consent/assent forms and participant information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective NHS Research & Development (R&D) department(s). 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/assent 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 UK Department of Health Policy Framework for Health and Social Care, 2017.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant (individual with FH and/or their parent/guardian as relevant to the clinical, questionnaire or interview data collection) informed consent and assent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The participant (individual with FH and/or their parent/guardian) shall sign and date the consent form before the individual with FH can participate in data collection for the study. Details are outlined in the **Informed consent** section of this protocol.

One copy of a consent/assent form is kept by the participant and one copy is kept in secure storage at the University of Nottingham. Where paper consent/assent forms have been used for clinical data collection in the clinical site, they will be scanned electronically or posted by the clinical site and sent to the Study Management Team at the University of Nottingham. Where paper consent/assent forms have been used for the questionnaire or interview data collection, the participant will be provided with pre-paid postage to return the form(s) to the Study Management Team at the University of Nottingham. Participating clinical sites can chose to retain or request a copy of the consent/assent form for the patient's hospital records at their discretion.

The decision regarding participation in the study is entirely voluntary. Participants in the clinical data collection can decide whether to participate in the questionnaire data collection, the interview, or both, as consent forms for each component of the study are separate. The clinician (or nominee), for clinical data collection, and the Study Manager (or nominee), for questionnaire and interview research, shall emphasise to participants that consent regarding participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No specific interventions will be done before informed consent has been obtained.

The participant's clinical team or the Study Manager (or nominee) 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 data collection period, 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).

RECORDS

Study forms

Forms are as follows:

- REDCap consent components (for consent forms and logging of consent/assent)
- REDCap clinical data entry (for clinical data collection and NHS sites)
- REDCap questionnaire data entry (for questionnaire data collection from participants)
- Interview data (for interview transcript text files)

Each participant (i.e., individual with FH) will be assigned a unique study identity code for use across the clinical, questionnaire and interview data entry platforms and on logged consent forms. This identity code will be automatically generated by the REDCap system when informed consent for clinical data entry is logged and meets validity checks by the REDCap system, signed off by the Study Manager (or nominee). This identity code will be used on the electronic database within REDCap and on paper documentation as required.

All study forms will be treated as confidential documents and held securely in accordance with regulations. Study forms shall be restricted to those personnel approved by the Study Leads and recorded as such in the study records. Study forms for clinical data entry will additionally be accessible by approved clinical site staff members, restricted to study participants at their clinical site.

All paper forms shall be filled in using blue or black pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled, and dated.

REDCap consent components

The consent components will be filled in electronically using REDCap accessed online by the participant individual with FH (or their parent/guardian for individuals with FH who are under age 16 years). This will include assent forms filled out by children age 5-15 years as relevant to the type of study participation (as described in **Informed consent** section). Where consent is obtained using paper forms, the Study Manager (or nominee) will fill out the REDCap consent/assent form details and attach a scanned copy of the completed form on the REDCap system.

Alongside the identity code and clinical site, the consent components will have the date of birth and first and last name of the participant individual with FH (and first and last name of the parent/guardian where consent is obtained for individuals with FH who are under age 16 years) and clinical site code.

If the participant (or their parent/guardian if they are under age 16) additionally agrees to be contacted for participation in further research, the consent components will also contain contact details of the participant or parent/guardian.

If the participant (or their parent/guardian if they are under age 16) consent to take part in questionnaires and/or interviews, the REDCap system will separately log these when they meet validity checks by the REDCap system, signed off by the Study Manager (or nominee).

All identifiable data and contact details will be kept separate from the research data within the REDCap system and access to this will be restricted to the Study Manager (or nominee).

REDCap clinical data entry

Clinical data entry will be electronically using REDCap accessed online by clinicians (or their nominee) from approved clinical sites using a login and password. Data entry for a participant will be available to clinicians automatically following generation of the identity code by the REDCap system. A clinician login will enable data entry for records of all consented patients at their clinical site.

Alongside the identity code, clinical data entry will include the postcode, NHS number, date of birth and first and last name of the participant individual with FH.

REDCap questionnaire data entry

Questionnaires will be filled in electronically using REDCap accessed online by participant individuals with FH (or a parent/guardian for individuals with FH who are under age 16 years). Participants will not require identity codes to fill out questionnaires; they will be sent a unique link for each questionnaire using an electronic URL (Uniform Resource Locator) that is linked to their identity code. Where participants complete paper questionnaires, their unique identity codes will be used and the Study Manager (or nominee) will fill out the REDCap questionnaire form and attach a scanned copy of the completed questionnaire on the REDCap system.

Questionnaire data entry will contain the date of birth and first and last name of the participant individual with FH as confirmation that the questionnaire information is referring to the correct study participant who was originally consented for clinical data collection.

Interview data

Interview data will be populated by the Study Manager (or nominee) once consent for interview has been signed off and the interview completed. A secure password protected file held on Microsoft OneDrive on an encrypted device will contain the participant identity code along with the date of birth and first and last name of the participant individual with FH as confirmation that the interview information is referring to the correct study participant who was originally consented for clinical data collection.

Original digital audio recordings of interviews will be saved in a separate secure password protected folder on Microsoft OneDrive. Files will be named as the participant identity code.

Original interview transcript text files from online transcription in Microsoft Teams and downloaded from TranscribeIt will be saved in a separate secure password protected folder on Microsoft OneDrive. These files will be securely erased once de-identification of the transcript is completed, as described below.

Copies of the original interview transcript text files will be saved in a separate secure password protected folder on Microsoft OneDrive. These files will be edited to remove any identifiable information from the transcript text, including information identifying hospitals or health care professionals. Only the participant identity code, the initials of the participant individual with FH (representing first and last names separated by a hyphen or a middle name initial when available) and their age at the time of interview will be retained in the transcript text file. Resulting de-identified interview transcript text files will be named as the participant identity code.

Source documents

Source documents shall be filed at the Study Leads' site and may include but are not limited to, consent forms, study records, field notes, interview transcriptions and audio records. The clinical data collection form contains information inputted by clinicians (or nominee at their clinical site), from their patient notes or consultations with patients, and will serve as its own source data. Clinicians (or their nominee) will have access to forms for the patients they have entered into REDCap.

Study staff at the University of Nottingham (assigned by the Study Management Group) will have selective access to participant records on the REDCap clinical data entry, the REDCap

questionnaire data entry, or data related to patient interviews based on the needs of their specified role. Only study staff shall have access to database documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The clinical, questionnaire and interview data collection items, data collection tools used for their administration to clinicians and patients, and all source documents shall be always made available for review by the Study Leads, University of Nottingham's designee and inspection by relevant regulatory authorities.

DATA PROTECTION

All study staff and investigators will endeavour to protect the rights of the participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The study forms will only collect the minimum required information for the purposes of the study. Paper 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 data will be held securely and password protected. All data will be held on University of Nottingham secure storage. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method). Access to participant personal data will be restricted to the Study Leads and Study Manager (or their nominees). Electronic study forms (consent, clinical and questionnaire data entry) will be held securely on University of Nottingham REDCap servers situated on campus. The REDCap clinical data entry will be within its own REDCap Project database separate from the REDCap questionnaire database. Interview data will be held on University of Nottingham secure licenced Microsoft OneDrive storage. This will allow for secure and controlled storage and sharing of data. Microsoft OneDrive encrypts data both in transit and at rest and is approved against the University's Handling Restricted Data Policy. The service provides several layers of automatic back up and, in a disaster scenario, files can be recovered. Access to data stored in OneDrive is via secure log-in with multi-factor authentication.

Access to data file locations on University servers is granted only by written request from the Study Leads or the Study Manager/Administrator. Access to secure data file locations is managed by University Digital and Technology Services and accessed by University username and password. Access to the REDCap database for administration and data extraction is only possible on the University network whilst physically on campus or via Virtual Private Network (VPN) access that must be provided by Digital and Technology Services with prior approval.

Each participant will be assigned a unique identity code that has no meaning external to the study. Participant personal details on the clinical data entry forms will be verified annually by clinicians (or their nominee) at the participant's clinical site via use of a verification date flag. Patients will typically see their clinical teams every 6 months to 1 year so this verification will take place through completion of follow-up data from routine clinical visits; however, after 11 months have elapsed with no verification, the REDCap system will send an automatic email notification to the clinician as a reminder for verification even if a longer time may elapse between clinic visits. It will also be possible to flag if the patient has left and is no longer receiving FH care at the clinical site. When participant personal details on the clinical data entry form has been changed, their record will be flagged by the REDCap system and an automatic email notification will be sent to the Study Manager to ensure details (i.e., name and date of birth) on the consent components coincide.

Personal/contact details of individuals with FH and their parent/guardian on the consent components will be maintained by the Study Manager who will contact patients every year to ensure such details are accurate and up to date. For participants who have consented to participate in questionnaires or interviews, completing a questionnaire or interview will be taken as verification that contact details are up to date.

The Study Manager will be aware of their professional duty to always maintain participant confidentiality.

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 with both public liability insurance and clinical trials insurance in respect of claims made by research subjects.

STUDY CONDUCT

Procedures for the collection and storage of data 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 questionnaire completion); accountability of study materials.

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 Manager, or nominee, shall carry out monitoring of study data as an ongoing activity.

Consent/assent forms and logging of consent for clinical, questionnaire and interview data collection will be continuously monitored with automatic notifications from REDCap software to the Study Manager/Administrator.

Clinical data will be downloaded on a weekly basis containing individual patient data entered via the REDCap clinical data entry, the patient's clinical site code, and the patient's identity code (patient names and hospital number will NOT be included). The patient's postcode will be mapped to the Index of Multiple Deprivation using openly available data from the UK Government Ministry of Housing, Communities & Local Government[28,29] and the postcode will then be deleted from the monitoring data. The patient's date of birth will be used to calculate the child's current age in years and months and the date of birth will then be deleted from the monitoring data.

An analysis protocol designed by the Study Leads and the Study Statistician will be run on the pseudonymised monitoring data to provide the Weekly Clinical Data Monitoring Report (Weekly Report) containing aggregate patient data of the:

- Overall and clinical site summaries of registered patient numbers
- Overall and clinical site summaries of data completeness and quality control (appropriate ranges for data items)
- Overall geographic and sociodemographic distribution and representativeness

Weekly Reports will be checked and approved by the Study Leads and/or the Study Statistician. The same protocol will be used to provide Monthly Reports for clinical sites to check for consistency with their source clinical data and the clinical data entry forms. Where deemed necessary by the Study Leads, clinical sites will be provided with summary information from the Weekly Reports.

To ensure appropriate cases are being recruited within the first 4 years of the study, clinical sites will have quarterly monitoring reports for evaluation of cases. This is to ensure the primary study objective aligned with the NIHR HTA award (NIHR134993) is answerable, which assesses the clinical effectiveness of cholesterol-reducing mediations.
Quarterly clinical site monitoring reports for evaluation of cases will be an automated data summary of:

- Diversity of case socio-demographics
- Completeness of REDCap data collection items
- Proportion of cases achieving a minimum of 2 time points of data entered over a 15-month period, that include cholesterol measurements and whether or not the patient is on LLT
- Whether site is meeting target of at least 60% of cases having at least 3 years of follow up data (from either retrospective and/or prospective clinical case notes)
- Whether site is meeting target of at least 30% of cases having prospective data collection

Quarterly report evaluation by the Study Team will be in accordance with each clinical site's timeline of recruitment, i.e., recognising that targets may not be met in very early stages of recruitment. If clinical sites are not achieving appropriate case recruitment targets and data completeness in accordance with their stage of recruitment, the Study Management Team will work with sites to revisit the recruitment strategy. If repeated evaluations are not achieving appropriate case recruitment, case recruitment at the site will be ceased.

Database 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 International Conference on Harmonisation GCP Guideline (ICH GCP) guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Study Leads 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 Study Leads and Study Manager shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all pseudonymised audio recordings, database 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

At 4-5 years of recruitment, a national summary report of the clinical data will be disseminated to clinical sites.

At 5 years, a project report will be submitted to the NIHR HTA containing research using clinical, questionnaire and interview data. Versions of the report will be developed for and disseminated to health professionals and public stakeholders with input from the PCAG and the CYPAG. The research will also be published as separate peer-reviewed journal publications and presented at conferences between 3-6 years.

No participants will be identifiable in any publications or disseminations of data. For all publications and dissemination, numerical clinical and questionnaire data will be suppressed where values are less that 5 (i.e., where there are fewer than 5 people in a table cell, numbers will be replaced by <5 and estimates that may enable calculation of numbers, e.g., a percentage, will be suppressed). Where text data are published (written free-text or quotes from interviews), participants will be described using a number (e.g., participant 3) that has no relationship to the study identity code.

USER AND PUBLIC INVOLVEMENT

In developing the design of this study, two Children and Young People's Advisory Group (CYPAG) meetings of 2 hours each were coordinated by the Nottingham University Hospitals Head of PPIE (patient and public involvement and engagement). They included young people with a breadth of lived experience of different health conditions and specifically advised on the conceptual design of questionnaire and interview data collection methods and content. A patient representative with FH and his son who also has FH have advised extensively on

various aspects of the study design. The patient representative has provided extensive feedback and editing of items for the clinical, questionnaire, and interview data collection, and associated participant information sheets and consent/assent forms. The patient representative will also be PPIE representative on the Study Management Group.

During the study a study-specific Children and Young People's Advisory Group (CYPAG) and Parent and Carer Advisory Group (PCAG) will provide regular PPIE input across all study aspects. CYPAG meetings are planned 2 times per year and PCAG meetings are planned annually. Members of the CYPAG and PCAG will also provide input on design and feedback for written materials between meetings. A PPIE Strategic Adviser with expertise of working directly with children and young people and a PPIE Administrator are on the Study Management Group to ensure the responsibilities and contributions of the CYPAG and PCAG are appropriately integrated into the development and outputs of the study. PPIE over 5 years has been appropriately funded in accordance with NIHR good practice for involving patients and will follow the Nottingham University Hospitals PPIE Standard Operating Procedure under guidance of the PPIE Strategic Adviser.

STUDY FINANCES

Funding source

The study is funded by a 5-year project grant from the NIHR HTA (NIHR134993).

Participant stipends and payments

Participants (and/or individuals with parental responsibility) will not be paid for their enrolment in the study for clinical data collection, i.e., when they provide consent or assent for clinical data entry from clinical notes and consultations.

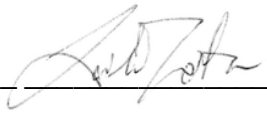
Participants (and/or individuals with parental responsibility) will not be paid for their time in filling out questionnaires.

Participants (and/or individuals with parental responsibility) will not be paid for their time to participate in interviews. Participants will be offered a £20 gift voucher. Participants will not incur travel expenses as interviews will be conducted via telephone or online using Microsoft Teams (or at patient's choice of location if in-person).

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator / Study Lead: Laila J Tata

Signature: 

Date: __12 January 2023_____

Co-Investigator / Study Co-Lead: Nadeem Qureshi

Signature: 

Date: __12 January 2023_____

REFERENCES

1. Humphries SE, Cooper JA, Seed M, Capps N, Durrington PN, Jones B, McDowell IFW, Soran H, Neil HAW. Coronary heart disease mortality in treated familial hypercholesterolaemia: Update of the UK Simon Broome FH register. *Atherosclerosis*. 2018;274:41-46. doi:10.1016/j.atherosclerosis.2018.04.040

2. Ramaswami U, Humphries SE, Priestley-Barnham L, Green P, Wald DS, Capps N, Anderson M, Dale P, Morris AA. Current management of children and young people with heterozygous familial hypercholesterolaemia - HEART UK statement of care. *Atherosclerosis*. 2019;290:1-8. doi:10.1016/j.atherosclerosis.2019.09.005

3. Vuorio A, Docherty KF, Humphries SE, Kuoppala J, Kovanen PT. Statin treatment of children with familial hypercholesterolemia – Trying to balance incomplete evidence of long-term safety and clinical accountability: Are we approaching a consensus? *Atherosclerosis*. 2013;226(2):315-320. doi:10.1016/j.atherosclerosis.2012.10.032

4. Akioyamen LE, Genest J, Shan SD, Reel RL, Albaum JM, Chu A, Tu JV. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. *BMJ Open*. 2017;7(9):e016461. doi:10.1136/bmjopen-2017-016461

5. NHS. The NHS Long Term Plan. Published online September 2019. Accessed October 23, 2022. https://www.longtermplan.nhs.uk/publication/nhs-long-term-plan/

6. NICE. CG71 Familial hypercholesterolaemia: full guideline. NICE. Accessed December 7, 2012. http://www.nice.org.uk/

7. Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Tonstad S, Wiegman A, Drogari E, Ramaswami U. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst Rev*. 2019;2019(11). doi:10.1002/14651858.CD006401.pub5

8. Luirink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, de Groot E, Kastelein JJP, Hutten BA. 20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia. *New England Journal of Medicine*. 2019;381(16):1547-1556. doi:10.1056/NEJMoa1816454

9. Langslet G, Johansen AK, Bogsrud MP, Narverud I, Risstad H, Retterstøl K, Holven KB. Thirty percent of children and young adults with familial hypercholesterolemia treated with statins have adherence issues. *American Journal of Preventive Cardiology*. 2021;6:100180. doi:10.1016/j.ajpc.2021.100180

10. Braamskamp MJAM, Kusters DM, Avis HJ, Smets EMA, Wijburg FA, Kastelein JJP, Wiegman A, Hutten BA. Long-Term Statin Treatment in Children with Familial Hypercholesterolemia: More Insight into Tolerability and Adherence. *Paediatr Drugs*. 2015;17(2):159-166. doi:10.1007/s40272-014-0116-y

11. Joyce NR, Wellenius GA, Eaton CB, Trivedi AN, Zachariah JP. Patterns and predictors of medication adherence to lipid-lowering therapy in children aged 8 to 20 years. *J Clin Lipidol*. 2016;10(4):824-832.e2. doi:10.1016/j.jacl.2016.03.002

12. Ramaswami U, Cooper J, Humphries SE. The UK Paediatric Familial Hypercholesterolaemia Register: preliminary data. *Archives of Disease in Childhood*. 2017;102(3):255-260. doi:10.1136/archdischild-2015-308570

13. Humphries SE, Cooper J, Dale P, Ramaswami U. The UK Paediatric Familial Hypercholesterolaemia Register: Statin-related safety and 1-year growth data. *Journal of Clinical Lipidology*. 2018;12(1):25-32. doi:10.1016/j.jacl.2017.11.005

14. Ramaswami U, Futema M, Bogsrud MP, Holven KB, Roeters van Lennep J, Wiegman A, Descamps OS, Vrablik M, Freiberger T, Dieplinger H, Greber-Platzer S, Hanauer-Mader G, Bourbon M, Drogari E, Humphries SE. Comparison of the characteristics at diagnosis and treatment of children with heterozygous familial hypercholesterolaemia (FH) from eight European countries. *Atherosclerosis*. 2020;292:178-187. doi:10.1016/j.atherosclerosis.2019.11.012

15. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34(28):3661-3679. doi:10.1002/sim.6607

16. Hernán MA, Alonso A, Logan R, Grodstein F, Michels KB, Stampfer MJ, Willett WC, Manson JE, Robins JM. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology*. 2008;19(6):766-779. doi:10.1097/EDE.0b013e3181875e61

17. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med*. 2017;167(4):268-274. doi:10.7326/M16-2607

18. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *Journal of Health Economics*. 1999;18(3):341-364. doi:10.1016/S0167-6296(98)00039-3

19. Zhang Y, Pletcher MJ, Vittinghoff E, Clemons AM, Jacobs DR Jr, Allen NB, Alonso A, Bellows BK, Oelsner EC, Zeki Al Hazzouri A, Kazi DS, de Ferranti SD, Moran AE. Association Between Cumulative Low-Density Lipoprotein Cholesterol Exposure During Young Adulthood and Middle Age and Risk of Cardiovascular Events. *JAMA Cardiology*. Published online September 22, 2021. doi:10.1001/jamacardio.2021.3508

20. Zhang Y, Woo JG, Urbina EM, Jacobs DR Jr, Moran AE, de Ferranti SD. Low-Density Lipoprotein Cholesterol Trajectories and Prevalence of High Low-Density Lipoprotein Cholesterol Consistent With Heterozygous Familial Hypercholesterolemia in US Children. *JAMA Pediatrics*. 2021;175(10):1071-1074. doi:10.1001/jamapediatrics.2021.2046

21. Zeki Al Hazzouri A, Vittinghoff E, Zhang Y, Pletcher MJ, Moran AE, Bibbins-Domingo K, Golden SH, Yaffe K. Use of a pooled cohort to impute cardiovascular disease risk factors across the adult life course. *International Journal of Epidemiology*. 2019;48(3):1004-1013. doi:10.1093/ije/dyy264

22. Reiner Ž, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D, Bax J, Vahanian A, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Filippatos G, Funck-Brentano C, Hasdai D, Hobbs R, Hoes A, Kearney P, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu BA, Reiner Ž, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vardas P, Widimsky P, Windecker S, Reviewers: D, Funck-Brentano C, Poldermans D, Berkenboom G, De Graaf J, Descamps O, Gotcheva N, Griffith K, Guida GF, Gulec S, Henkin Y, Huber K, Kesaniemi YA, Lekakis J, Manolis AJ, Marques-Vidal P, Masana L, McMurray J,

Mendes M, Pagava Z, Pedersen T, Prescott E, Rato Q, Rosano G, Sans S, Stalenhoef A, Tokgozoglu L, Viigimaa M, Wittekoek ME, Zamorano JL, Developed with the special contribution of: European Association for Cardiovascular Prevention & Rehabilitation † EC for PG (CPG) 2008–2010 and 2010–2012 C. ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *European Heart Journal*. 2011;32(14):1769-1818. doi:10.1093/eurheartj/ehr158

23. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Molloy L, Ness A, Ring S, Davey Smith G. Cohort Profile: The 'Children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol*. 2013;42(1):111-127. doi:10.1093/ije/dys064

24. Chan AHY, Horne R, Hankins M, Chisari C. The Medication Adherence Report Scale: A measurement tool for eliciting patients' reports of nonadherence. *Br J Clin Pharmacol*. 2020;86(7):1281-1288. doi:10.1111/bcp.14193

25. Husereau D, Drummond M, Augustovski F, Bekker-Grob E de, Briggs AH, Carswell C, Caulley L, Chaiyakunapruk N, Greenberg D, Loder E, Mauskopf J, Mullins CD, Petrou S, Pwu RF, Staniszewska S. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *BMJ*. 2022;376:e067975. doi:10.1136/bmj-2021-067975

26. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Borén J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen MR, Tokgözoğlu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38(32):2459-2472. doi:10.1093/eurheartj/ehx144

27. Population estimates for the UK, England and Wales, Scotland and Northern Ireland - Office for National Statistics. Accessed October 29, 2022. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2020

28. English indices of deprivation 2019: Postcode Lookup. Accessed November 17, 2022. https://imd-by-postcode.opendatacommunities.org/imd/2019

29. The English Indices of Deprivation 2019 FAQs. Accessed November 17, 2022. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/853811/IoD2019_FAQ_v4.pdf