Identification and management of familial hypercholesterolaemia (FH)

Full guideline – draft version

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National Collaborating Centre for Primary Care

Citation

DeMott K, Nherera L, Humphries SE, Minhas R, Shaw EJ, Kathoria M, Ritchie G, Davies D, Lee P, McDowell I, Neil A, Qureshi N, Rowlands P, Seed M, Stracey H, Thorogood M, Watson M. *Clinical Guidelines and Evidence Review for Familial hypercholesterolaemia: the identification and management of adults and children with familial hypercholesterolaemia.* 2008. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners.

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Appendices (these are available in a separate file)

Preface

**TO add for final version

Key priorities for implementation

A number of key priority recommendations have been identified for implementation listed below. These recommendations are considered by the GDG to have the most significant impact on patients' care and patients' outcomes.

The criteria the GDG used to select these key priorities for implementation included whether a recommendation is likely to:

- have a high **impact** on patients' outcomes in particular mortality and morbidity
- have a **high impact** on reducing variation in the treatment offered to patients
- lead to a **more efficient** use of NHS resources
- enable patients to **reach important points in the care pathway more rapidly**

Please note, the numbering (in square brackets) is as in the NICE guideline.

Diagnosis

- A family history should always be obtained from an individual being investigated for FH to determine if a dominant pattern of inheritance is present. [1.1.6]
- In children at risk of FH because of an affected parent, LDL-C concentrations should usually be measured by the age of ten years. This measurement should be repeated after puberty before a diagnosis of FH can be excluded. [1.1.8]
- Individuals with FH are at a very high risk of coronary heart disease. Risk estimation tools such as those based on the Framingham algorithm should not be used to assess their risk. [1.1.10]

Identifying individuals with FH using cascade testing

- All individuals with FH should be referred to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing. [1.2.2]
- Cascade testing using a combination of lipid concentration measurement and DNA testing should be used to identify relatives of index cases with a clinical diagnosis of FH. [1.2.4]

- The establishment and use of a nationwide family based follow-up system is recommended to enable comprehensive identification of affected individuals.* [1.2.8]

Management

Adults

- Prescription of a potent statin should usually be considered when trying to achieve a reduction of LDL-C concentrations of greater than 50% (from baseline). [1.3.1.2]

Children

- Children and young people diagnosed with, or being investigated for a diagnosis of, FH should be referred to a specialist with expertise in FH in an appropriate child focused setting. [1.3.1.14]

Women and girls

- When lipid modifying medication is first considered for girls and women, risks to the pregnancy and the fetus while taking lipid modifying medication should be discussed. This discussion should be regularly revisited. [1.4.2.1]

Ongoing assessment and monitoring

Review

- All treated individuals with FH should have a regular structured review carried out at least annually. [1.5.1.1]

* See also the Department of Health FH Cascade Testing Audit Project, available at www.fhcascade.org.uk

Guideline recommendations

The following guidance is based on the best available evidence.

Unless otherwise indicated, recommendations are relevant for individuals with possible or definite FH. Recommendations are also applicable for individuals with both heterozygous and homozygous FH, unless otherwise indicated.

Please note, the numbering is as in the NICE guideline.

1.1 Diagnosis

(see also 1.4 on Information needs and support)

1.1.1 The diagnosis of FH should be made using the Simon Broome criteria which includes a combination of family history, clinical examination (specifically arcus and tendon xanthomata), lipid profile (see Appendix E of the NICE guideline, or Appendix F of the full guideline) or by using molecular techniques.

1.1.2 A clinical diagnosis of homozygous FH should be considered in individuals with LDL-C concentrations greater than 13mmol/l and they should be referred to a specialist centre.

1.1.3 Secondary causes of hypercholesterolaemia should be considered and excluded before a diagnosis of FH is made.

1.1.4 To confirm the diagnosis of FH, at least two measurements of elevated LDL-C concentrations are necessary because biological and analytical variability occurs.

1.1.5 Absence of clinical signs (arcus and tendon xanthomata) in adults and children does not exclude a diagnosis of FH.

1.1.6 A family history should always be obtained from an individual being investigated for FH to determine if a dominant pattern of inheritance is present.

1.1.7 Standardised pedigree terminology should be used to document a three- to four-generation pedigree including relatives' age of onset of coronary heart disease and lipid concentrations. For deceased relatives the age and cause of death, and

smoking history should be documented. If possible the proband should verify this information with other family members.

1.1.8 In children at risk of FH because of an affected parent, LDL-C concentrations should usually be measured by the age of ten years. This measurement should be repeated after puberty before a diagnosis of FH can be excluded.

1.1.9 Ultrasonography of the Achilles tendon is not recommended in the diagnosis of FH.

1.1.10 Individuals with FH are at a very high risk of coronary heart disease. Risk estimation tools such as those based on the Framingham algorithm should not be used to assess their risk.

1.1.11 Individuals with a clinical diagnosis of FH should be offered a DNA test to increase the certainty of their diagnosis and to aid diagnosis amongst their relatives.

1.1.12 Individuals with a clinical diagnosis of FH and their relatives who have a detected mutation should be informed they have an unequivocal diagnosis of FH.

1.1.13 Where DNA testing has excluded FH in a member of a family in which a mutation has been identified, CHD risk should be managed as in the general population (see the NICE Lipid Modification guideline).

1.2 Identifying individuals with FH using cascade testing

1.2.1 Systematic methods should be used for case identification of FH.

1.2.2 All individuals with FH should be referred to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing.

1.2.3 Healthcare professionals should discuss the implications of cascade testing with individuals.

1.2.4 Cascade testing using a combination of lipid concentration measurement and DNA testing should be used to identify relatives of index cases with a clinical diagnosis of FH.

1.2.5 In families in which a mutation has been identified, the mutation should be used to identify affected relatives.

1.2.6 In the absence of a DNA diagnosis, cascade testing using lipid measurements should be undertaken.

1.2.7 To diagnose FH in relatives, the gender and age-specific probabilities based on LDL cholesterol concentrations in Appendix E (of the NICE guideline and Appendix F of the full guideline) should be used. Simon Broome LDL-C criteria should not be used.

1.2.8 The establishment and use of a nationwide family based follow-up system is recommended to enable comprehensive identification of affected individuals.[*]

1.3 Management

1.3.1 Drug treatment

Adults

1.3.1.1 Statins should be the initial treatment for all adults with FH.

1.3.1.2 Prescription of a potent statin should usually be considered when trying to achieve a reduction of LDL-C concentrations of greater than 50% (from baseline).

1.3.1.3 Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who would otherwise be initiated on statin therapy but who are unable to do so because of contraindications to initial statin therapy[†].

[*] See also the Department of Health FH Cascade Testing Audit Project, available at www.fhcascade.org.uk

[†] Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. London, National Institute for Health and Clinical Excellence (NICE). Technology Appraisal 132, 2007. www.nice.org.uk/page.aspx?o=289446.

1.3.1.4 Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who are intolerant to statin therapy (as defined in section 1.3.1.8)*.

1.3.1.5 Ezetimibe, coadministered with initial statin therapy, is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who have been initiated on statin therapy when*:

- serum LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy and
- consideration is being given to changing from initial statin therapy to an alternative statin.

1.3.1.6 When the decision has been made to treat with ezetimibe coadministered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost*.

1.3.1.7 For the purposes of this guidance, appropriate control of cholesterol concentrations should be based on individualised risk assessment in accordance with national guidance on the management of cardiovascular disease for the relevant populations (see 1.1.10)*.

1.3.1.8 For the purposes of this guidance, intolerance to initial statin therapy should be defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised. Adverse effects include evidence of new-onset muscle pain (often associated with levels of muscle enzymes

* Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. London, National Institute for Health and Clinical Excellence (NICE). Technology Appraisal 132, 2007. www.nice.org.uk/page.aspx?o=289446.

in the blood indicative of muscle damage), significant gastrointestinal disturbance or alterations of liver function tests*.

1.3.1.9 Prescribing of drugs for adults with homozygous FH should be undertaken within a specialist centre (see 1.1.2).

1.3.1.10 Individuals not achieving a reduction in LDL-C concentrations of greater than 50% from baseline should be referred to a specialist with expertise in FH.

1.3.1.11 Individuals with FH should be referred to a specialist with expertise in FH if they are assessed to be at high risk, that is, they have

- established coronary heart disease; or
- a family history of premature coronary heart disease; or
- two or more other cardiovascular risk factors (for example, smoking, hypertension, diabetes, male sex).

1.3.1.12 Individuals with intolerance or contraindications to statins or ezetimibe should be referred to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant (resin), nicotinic acid, or a fibrate to reduce LDL-C concentrations.

1.3.1.13 Caution must be exercised when adding a fibrate or nicotinic acid to a statin due to the risk of muscle-related side effects including rhabdomyolysis. Gemfibrozil and statins should not be used together.

* Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. London, National Institute for Health and Clinical Excellence (NICE). Technology Appraisal 132, 2007. www.nice.org.uk/page.aspx?o=289446.

Children and young people

1.3.1.14 Children and young people diagnosed with, or being investigated for a diagnosis of, FH should be referred to a specialist with expertise in FH in an appropriate child focused setting.

1.3.1.15 The decision to defer or offer drug therapy for a child or young person should take into account their age, the age of onset of cardiovascular disease within the family, and presence of other cardiovascular risk factors including LDL-C concentrations greater than 6mmol/l in the child or young person.

1.3.1.16 Where the decision to initiate statins has been made in children and young people (aged 10 years upwards), those licensed for use in the appropriate age group should be chosen.

1.3.1.17 Statin therapy for children and young people with FH should usually be prescribed at the doses specified in the BNF for children.

1.3.1.18 In children with homozygous FH, LDL concentration may be lowered by lipid modifying medication and should be considered.

1.3.1.19 In exceptional instances (for example, where there is a family history of cardiovascular disease in early adulthood) a higher dose of statin, or more than one lipid modifying treatment, may be considered for the child/young person at a younger age.

1.3.1.20 In children and young people with FH who are intolerant of statins, other drug therapies capable of reducing LDL-C (bile acid sequestrants [resins], fibrates, or ezetimibe) should be considered.

1.3.1.21 Routine monitoring of growth and pubertal development in children and young people with FH is recommended.

Adults and children

1.3.1.22 Decisions about the choice of treatment should be made following discussion with the individual, and be informed by consideration of concomitant medication, co-morbidities, safety, and tolerability.

1.3.1.23 The decision to add a bile acid sequestrant (resin), nicotinic acid or a fibrate should be taken in a specialist centre following consideration of the need for a further reduction in LDL-C concentrations.

1.3.1.24 Vitamin supplementation should be considered for individuals on long-term treatment with bile acid sequestrants (resins).

1.3.1.25 Individuals experiencing unusual side effects should be referred to a specialist with expertise in FH.

1.3.1.26 Individuals prescribed nicotinic acid should receive advice on strategies that reduce flushing. This includes taking low initial doses with meals and/or non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin 30 minutes prior to the first daily dose.

1.3.1.27 Baseline liver and muscle enzymes, including transaminases and creatine kinase respectively, should be measured before initiation of a statin. However individuals with raised liver or muscle enzymes should not routinely be excluded from statin therapy.

1.3.1.28 Monitoring of creatine kinase is not routinely recommended in asymptomatic individuals treated with a statin.

1.3.2 Lifestyle interventions

1.3.2.1 Lifestyle advice should be regarded as a component of medical management, and not as a substitute for lipid-modifying medication.

Diet

1.3.2.2 All individuals and families with FH should be offered individualised nutritional advice from a healthcare professional with specific expertise in nutrition.

1.3.2.3 Individuals and families with FH should be given the same advice as that given to individuals with a high cardiac risk.

1.3.2.4 Individuals and families with FH should be advised to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 10% or less of total energy intake, intake of dietary cholesterol is less than 300 mg/day and

saturated fats are replaced by increasing the intake of monounsaturated fats and polyunsaturated fats. It may be helpful to suggest they look at www.eatwell.gov.uk/healthydiet for further practical advice

1.3.2.5 Individuals and families with FH should be advised to eat at least five portions of fruit and vegetables per day, in line with national guidance for the general population. Examples of what constitutes a portion can be found at www.eatwell.gov.uk/healthydiet and www.5aday.nhs.uk

1.3.2.6 Individuals and families with FH should be advised to consume at least two portions of fish (one of which should be oily) per week. Pregnant women with FH should be advised to limit their oily fish to no more than two portions per week. Further information and advice on healthy cooking methods can be found at www.eatwell.gov.uk/healthydiet

1.3.2.7 The range and costs of food products containing stanols and sterols may be discussed. Individuals should be advised that if they wish to take stanols and sterols these need to be taken consistently to be effective.

1.3.2.8 Individuals with FH should not routinely be recommended to take omega-3 fatty acid supplements. For individuals post MI cross refer to NICE guidance on MI: secondary prevention' (NICE clinical guideline 48).

Physical activity

1.3.2.9 Individuals with FH should be advised to take 30 minutes of physical activity a day, of at least moderate intensity, at least 5 days a week, in line with national guidance for the general population.[*]

1.3.2.10 Individuals with FH who are unable to perform moderate intensity physical activity at least 5 days a week because of comorbidity, disability, medical

[*] See: Department of Health (2004) At least five a week: evidence on the impact of physical activity and its relationship to health. A report from the Chief Medical Officer. London, Department of Health. Available from www.dh.gov.uk

conditions or personal circumstances should be encouraged to exercise at their maximum safe capacity.

1.3.2.11 Recommended types of physical activity include those that can be incorporated into everyday life, such as brisk walking, using stairs and cycling. (See 'At least five a week'.)

1.3.2.12 Individuals with FH should be advised that bouts of physical activity of 10 minutes or more accumulated throughout the day are as effective as longer sessions. (See 'At least five a week'.)

Weight management

1.3.2.13 Individuals with FH who are overweight or obese should be offered appropriate advice and support to achieve and maintain a healthy weight in line with the NICE obesity guideline.

Alcohol consumption

1.3.2.14 As for the general population, alcohol consumption for adult men with FH should be limited to up 3 to 4 units a day, and for adult women with FH up to 2 to 3 units of alcohol a day. Binge drinking should be avoided. Further information can be found on the Foods Standards Agency website www.eatwell.gov.uk/healthydiet.

Smoking advice

1.3.2.15 Individuals, especially children, with FH who do not smoke should be strongly discouraged from starting because of their already greatly increased CHD risk.

1.3.2.16 Individuals with FH who smoke should be advised that because of their already greatly increased CHD risk, they should stop.

1.3.2.17 Individuals who want to stop smoking should be offered support and advice, and referral to an intensive support service in line with the NICE guidance on smoking cessation.*

1.3.2.18 Individuals with FH who do not wish to accept a referral to an intensive support service should be offered pharmacotherapy in line with NICE guidance on nicotine replacement therapy, bupropion and varenicline.†

1.3.3 Specialist treatment

LDL-lowering apheresis

1.3.3.1 Adults and children with clinical homozygous FH should be considered for apheresis. The timing of initiation of apheresis will depend on other factors, such as response to lipid modifying medication and presence of coronary heart disease.

1.3.3.2 In exceptional cases, individuals with heterozygous FH with progressive, symptomatic CHD, despite maximal tolerated lipid modifying medication and optimal medical therapy, should be considered for apheresis. This should be undertaken in a specialist centre on a case by case basis and data collected into an appropriate registry.

1.3.3.3 Fistulae are the preferred access in individuals treated with apheresis and individuals should be counselled about possible benefits and complications.

1.3.3.4 Routine monitoring of iron status should be carried out and iron supplementation initiated as required in individuals being treated with apheresis.

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* 'Brief interventions and referral for smoking cessation in primary care and other settings', NICE Public Health Guidance 1 (2006)

† 'Guidance on the use of Nicotine replacement therapy (NRT) and bupropion for smoking cessation', NICE technology appraisal guidance 39 (2002) and 'Varenicline for smoking cessation' NICE technology appraisal guidance 123 (2007)

1.3.3.5 ACE inhibitors should not be used in individuals being treated with LDL apheresis, and instead substituted with angiotensin receptor blocking agents.

1.3.3.6 All hypotensive agents should be reviewed and considered for discontinuation on the morning of the day of apheresis.

1.3.3.7 Warfarin should be discontinued approximately 4 days before apheresis and substituted with low molecular weight heparin.

1.3.3.8 Anti-platelet therapy should be continued for individuals treated with apheresis.

Liver transplantation

1.3.3.9 Individuals with homozygous FH should be offered liver transplantation as an option following failure of medication and apheresis.

1.3.3.10 The decision to refer for organ transplantation should be undertaken in conjunction with the patient and/or relatives in an appropriate specialist setting, following a discussion of the benefits and potential harms of intervention.

1.4 Information needs and support

1.4.1 General information and support

1.4.1.1 During the assessment and communication of familial risk, individuals should receive clear and appropriate educational information about FH and about the process of family testing.

1.4.1.2 A specialist with expertise in FH should provide information to individuals with FH on their specific level of risk of coronary heart disease, its implications for them and their families, lifestyle advice and treatment options.

1.4.1.3 Individuals with FH should be encouraged to contact their relatives to inform them of their potential risk and to facilitate cascade testing.

1.4.1.4 When considering cascade testing, a specialist with expertise in FH should facilitate the sharing of information about FH with family members.

1.4.1.5 Individuals and families with FH should be offered written advice and information about patient support groups.

1.4.2 Information and counselling on contraception for women and girls with FH

1.4.2.1 When lipid modifying medication is first considered for girls and women, risks to the pregnancy and the fetus while taking lipid modifying medication should be discussed. This discussion should be regularly revisited.

1.4.2.2 Women with FH should be given specific information tailored to their needs and offered a choice of all effective contraceptive methods. Because of the small increased risk of cardiovascular events with the use of combined oral contraceptives, other forms of contraception may be considered initially.

1.4.3 Information for pregnant women with FH

1.4.3.1 Women with FH should be advised that in general, pregnancy is not contraindicated.

1.4.3.2 Lipid-modifying medication should not be taken by women planning to conceive or during pregnancy because of the potential risk of fetal abnormality.

1.4.3.3 Lipid-modifying medication should be stopped 3 months prior to attempting to conceive.

1.4.3.4 Women with FH who conceive whilst taking statins or other systemically absorbed lipid-modifying medication should be advised to stop treatment immediately and be referred urgently to an obstetrician for fetal assessment. This assessment will then inform shared decision making about continuation of the pregnancy.

1.4.3.5 Shared care arrangements, to include expertise in cardiology and obstetrics, should be made for women with FH who are considering pregnancy or are pregnant. Such care should include an assessment of coronary heart disease risk, particularly to exclude aortic stenosis. This is essential for women with homozygous FH.

1.4.3.6 Serum lipids should not be measured routinely during pregnancy.

1.4.3.7 Breast feeding is not contraindicated in women with FH. Potential risks and benefits of re-starting lipid modifying medication for the breast feeding

mother and infant should be discussed. Resins are the only lipid modifying medication that should be considered during lactation.

1.5 Ongoing assessment and monitoring

1.5.1 Review

1.5.1.1 All treated individuals with FH should have a regular structured review carried out at least annually.

1.5.1.2 The progress of cascade testing amongst relatives should be recorded. If there are still relatives who have not been tested, further action should be discussed.

1.5.1.3 Family history should be updated and any changes in the coronary heart disease status of relatives should be noted.

1.5.1.4 Review should include assessment of smoking status, a fasting lipid profile, discussion about concordance with medication, side effects of treatment, and any changes that may be required to achieve recommended cholesterol concentrations.

1.5.2 Referral

1.5.2.1 Individuals with FH should be referred urgently* to a specialist with expertise in cardiology for evaluation if they have signs or symptoms of possible coronary heart disease.

1.5.2.2 Individuals with FH should be considered for referral for evaluation of coronary heart disease if they have a family history of coronary heart disease in early adulthood, or two or more other cardiovascular risk factors (e.g. smoking, hypertension, diabetes, male sex).

1.5.2.3 Adults and children with homozygous FH should be referred for an evaluation of coronary heart disease upon diagnosis.

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* The GDG considered 'urgently' to be within a week, depending on the severity of symptoms

1.5.2.4 In asymptomatic children and young people with heterozygous FH, evaluation of coronary heart disease is unlikely to detect clinically significant disease and referral is not routinely recommended.

1 Introduction

1.1 Epidemiology

In some individuals, a high cholesterol concentration in the blood is caused by an inherited genetic defect known as familial hypercholesterolaemia (FH). Raised cholesterol concentrations in the blood are present from birth and lead to early development of atherosclerosis and coronary heart disease. The disease is transmitted from generation to generation in such a way that siblings and children of a person with FH have a 50 per cent risk of having FH.

Most individuals with FH have inherited a defective gene for FH from only one parent and are therefore heterozygous. Rarely, an individual will inherit a genetic defect from both parents and will have homozygous FH.

The prevalence of heterozygous FH in the UK population is estimated to be 1 in 500, which means that approximately 110,000 people are affected. The elevated serum cholesterol concentrations that characterise heterozygous FH lead to a greater than 50% risk of coronary heart disease by the age of 50 years in men and at least 30% in women by the age of 60 years.

Homozygous FH is rare with symptoms appearing in childhood, and is associated with early death from coronary heart disease. Homozygous FH has an incidence of approximately one case per million.

1.2 Management

Early detection and treatment with hydroxy-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors (statins) has been shown to reduce morbidity and mortality in those with heterozygous FH. LDL apheresis and liver transplantation are treatment options for individuals with homozygous FH, with LDL apheresis being occasionally used for heterozygous FH individuals who are refractory to conventional lipid-lowering therapy.

There is evidence that screening can be effective in identifying people in the early stages of FH. Methods proposed include opportunistic screening and cascade screening of the relatives of people identified as having FH ("index cases").

Currently, diagnosis involves clinical assessment and biochemical tests (lipid profile).

1.3 Aim of the guideline

Clinical guidelines are defined as 'systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances'[1].

This guideline gives recommendations to clinicians and others about diagnosis; identification strategies; drug, specific and general treatments; and assessment and monitoring of FH.

1.4 How the guideline is set out

The recommendations for all the topics in each clinical chapter are listed at the start of the chapter. Both the evidence statements and narratives of the research studies on which our recommendations are based are found within each topic section. The evidence statements precede the narrative for each topic. Also included in each chapter is a brief explanation of why the GDG made the specific recommendations. The evidence tables with details of the research studies that describe the studies reviewed are found in Appendices C and D.

Unless otherwise indicated, recommendations are relevant for individuals with possible or definite FH. Recommendations are also applicable for individuals with both heterozygous and homozygous FH, unless otherwise indicated.

1.5 Scope

The guideline was developed in accordance with a scope given by the National Institute for Health and Clinical Excellence (NICE, 'the Institute'). The scope set the remit of the guideline and specified those aspects of the identification and

management of FH to be included and excluded. The scope was published in January 2007 and is reproduced here in Appendix A.

Whom the guideline is intended for

This guideline is of relevance to those who work in or use the National Health Service (NHS) in England and Wales:

- primary, secondary or tertiary care settings dealing with case identification, diagnostic testing and the management of heterozygous FH in adults and children
- tertiary care for the rare condition of homozygous FH in all age groups.

Areas outside the remit of the guideline

- Techniques for liver transplantation.
- Measurement and reporting of blood lipids (this is covered by the NICE clinical guideline on cardiovascular risk assessment).
- Population-based screening programmes for FH.

1.6 Responsibility and support for guideline development

1.6.1 The National Collaborating Centre for Primary Care (NCC-PC)

The NCC-PC is a partnership of primary care professional associations and was formed as a collaborating centre to develop guidelines under contract to NICE. It is entirely funded by NICE. The NCC-PC is contracted to develop five guidelines at any one time, although there is some overlap at start and finish. Unlike many of the other centres which focus on a particular clinical area, the NCC-PC has a broad range of topics relevant to primary care. However, it does not develop guidelines exclusively for primary care. Each guideline may, depending on the scope, provide guidance to other health sectors in addition to primary care.

The Royal College of General Practitioners (RCGP) acts as the host organisation. The Royal Pharmaceutical Society and the Community Practitioners and Health Visitors' Association are partner members with representation from other professional and lay bodies on the Board. The RCGP holds the contract with the Institute for the NCC-PC.

1.6.2 The development team

The development team had the responsibility for this guideline throughout its development. They were responsible for preparing information for the Guideline Development Group (GDG), for drafting the guideline and for responding to consultation comments. The development team working on this guideline consisted of the:

- **Guideline lead**
  who is a senior member of the NCC-PC team who has overall responsibility for the guideline
- **Information scientist**
  who searched the bibliographic databases for evidence to answer the questions posed by the GDG
- **Reviewer (Health Services Research Fellow**)
  with knowledge of the field, who appraised the literature and abstracted and distilled the relevant evidence for the GDG
- **Health economist**
  who reviewed the economic evidence, constructed economic models in selected areas and assisted the GDG in considering cost effectiveness
- **Project manager**
  who was responsible for organising and planning the development, for meetings and minutes and for liaising with the Institute and external bodies
- **Clinical advisor**
  with an academic understanding of the research in the area and its practical implications to the service, who advised the development team on searches and the interpretation of the literature
- **Chair**
  who was responsible for chairing and facilitating the working of the GDG meetings

Applications were invited for the post of Clinical Advisor, who was recruited to work on average, a half a day a week on the guideline. The members of the development team attended the GDG meetings and participated in them. The development team

also met regularly with the Chair of the GDG during the development of the guideline to review progress and plan work.

1.6.3 The Guideline Development Group (GDG)

A Chair was chosen for the group and his primary role was to facilitate and chair the GDG meetings.

Guideline Development Groups (GDGs) are working groups consisting of a range of members with the experience and expertise needed to address the scope of the guideline. Nominations for GDG members were invited from the relevant stakeholder organisations which were sent the draft scope of the guideline with some guidance on the expertise needed. Two patient representatives and 8 healthcare professionals were invited to join the GDG as full members, with a further 6 healthcare professionals invited as co-opted experts.

Nominees who were not selected for the GDG were invited to act as Expert Peer Reviewers and were sent drafts of the guideline by the Institute during the consultation periods and invited to submit comments using the same process as stakeholders.

Each member of the GDG served as an individual expert in their own right and not as a representative of their nominating organisation, although they were encouraged to keep the nominating organisation informed of progress.

In accordance with guidance from NICE, all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships, and support from the healthcare industry. Details of these can be seen in Appendix G.

The names of GDG members appear listed below.

Full GDG members

- Dr Rubin Minhas (Chair)
  General Practitioner, Primary Care CHD Lead, Medway Primary Care Trust, Gillingham, Kent

- Professor Steve E Humphries, PhD MRCP, FRCPath (Clinical Advisor)
  Professor of Cardiovascular Genetics, British Heart Foundation Laboratories, Royal Free and University College Medical School, London
- Ms Dawn Davies
  Patient, Weston-Super-Mare, Director and Trustee of HEART UK
- Dr Philip Lee, DM FRCPCH FRCP
  Consultant and Honorary Reader in Metabolic Medicine, National Hospital for Neurology and Neurosurgery and Great Ormond Street Hospital for Children, London
- Dr Ian McDowell, MD FRCP FRCPath
  Senior Lecturer and Consultant, University Hospital of Wales, Cardiff
- Professor Andrew Neil, MA MB DSc FRCP
  Professor of Clinical Epidemiology/Honorary Consulting Physician, Division of Public Health & Primary Health Care, University of Oxford, Oxford
- Dr Rossi Naoumova
  Honorary Consultant Physician in Lipidology and Lead Clinician (Lipid Clinic); MRC Senior Clinical Scientist (resigned, October 2006)
- Dr Nadeem Qureshi
  GP and Clinical Senior Lecturer in Primary Care, University of Nottingham, Derby
- Mr Philip Rowlands
  Patient, Penarth
- Dr Mary Seed, DM FRCPath FRCP
  Honorary Consulting Physician and retired Clinical Senior Lecturer, Imperial College, Faculty of Medicine, London
- Ms Helen Stracey
  Dietetic Services Manager/Registered Dietitian. Chelsea and Westminster NHS Foundation Trust, London
- Ms Melanie Watson
  FH Specialist Nurse and DH Trainee Genetic Counsellor, All Wales Genetic Service, Cardiff

- Professor Margaret Thorogood PhD
  Professor of Epidemiology, University of Warwick, Coventry

Members of the GDG from the NCC-PC were:

- Ms Elizabeth Shaw
  Guideline Lead and Deputy Chief Executive, NCC-PC (until February 2008)
- Dr Kathleen DeMott
  Health Services Research Fellow, NCC-PC
- Dr Meeta Kathoria
  Project Manager, NCC-PC (until December 2007)
- Ms Vanessa Nunes
  Project Manager, NCC-PC (from January 2008)
- Mr Leo Nherera
  Health Economist, NCC-PC
- Ms Gill Ritchie
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- Ms Mei-yin Tok
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- Dr Neill Calvert
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Co-opted GDG Members

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Observers

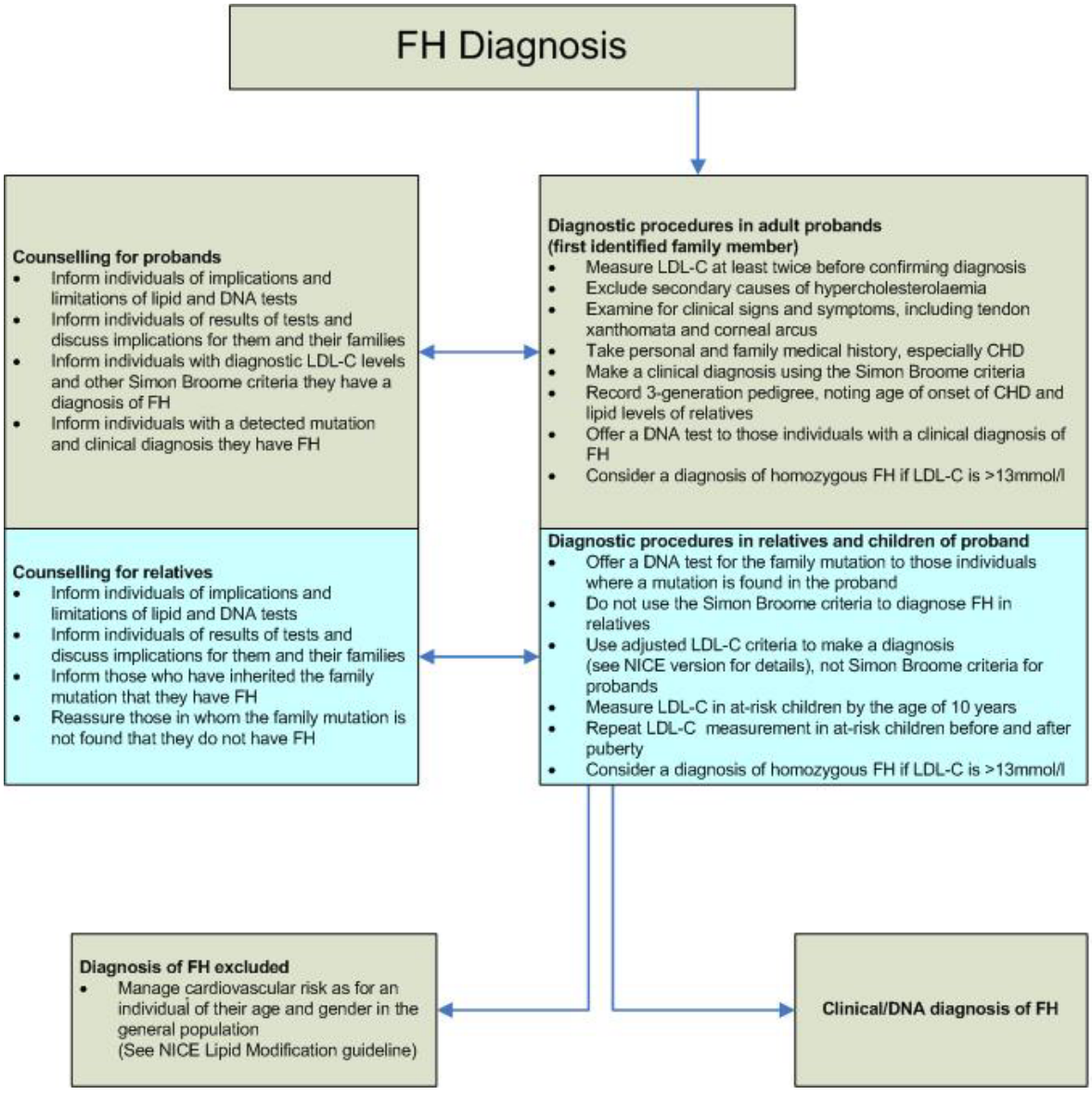
- Ms Colette Marshall
  Commissioning Manager, National Institute for Health and Clinical Excellence (until August 2007)
- Ms Sarah Willett
  Commissioning Manager, National Institute for Health and Clinical Excellence (from December 2007)

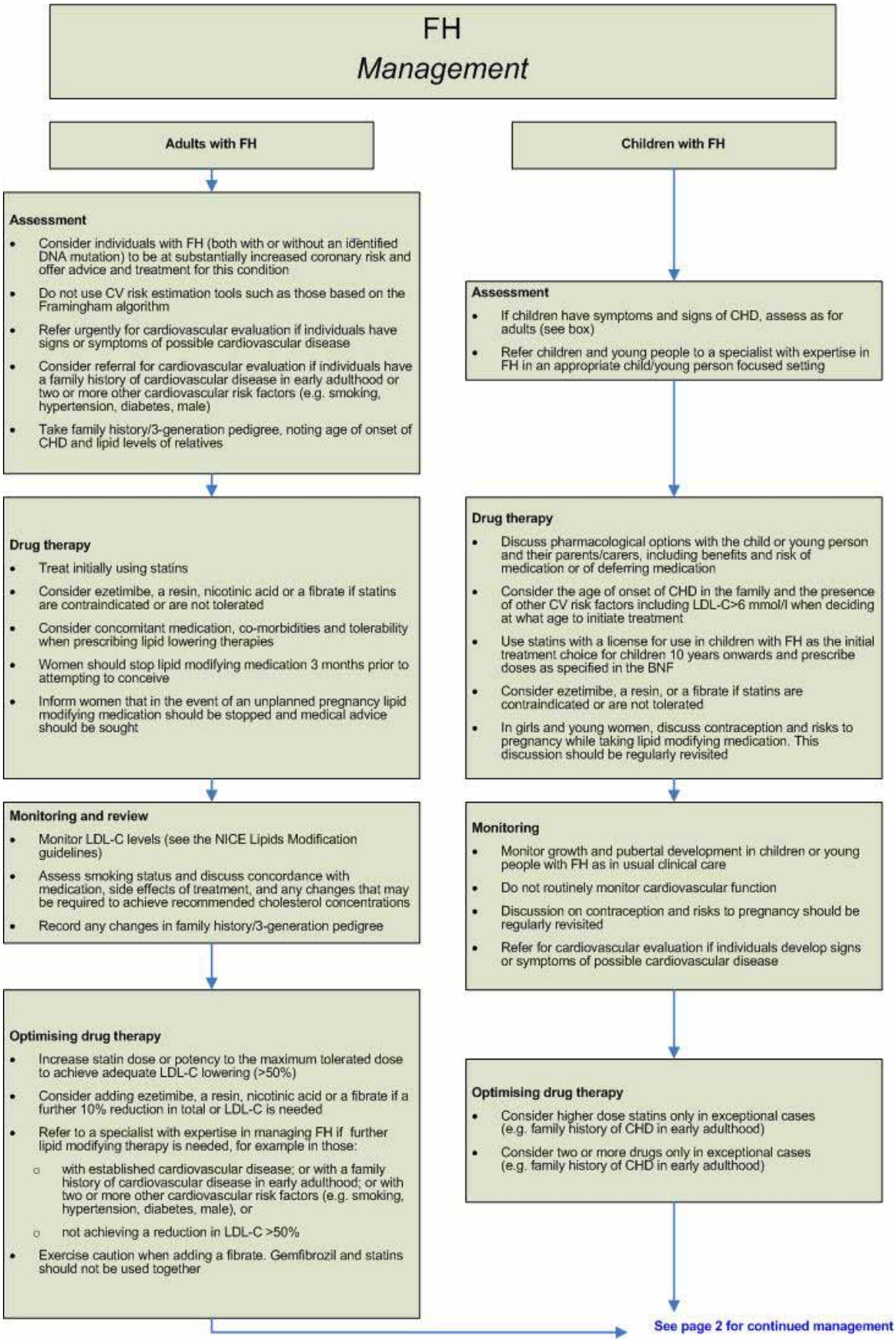
1.6.4 Guideline Development Group meetings

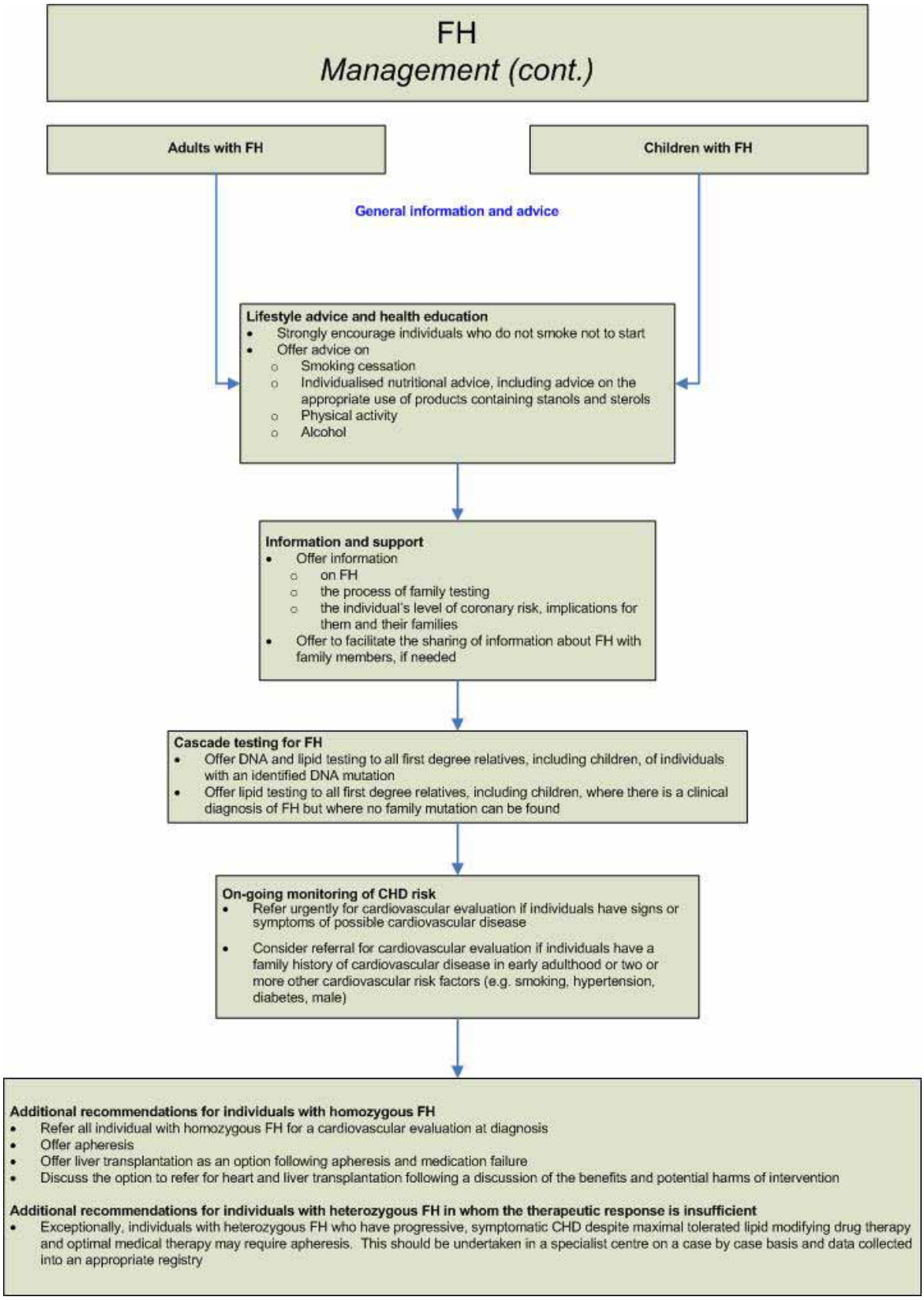
The GDG met at 5 to 6 weekly intervals for 16 months to review the evidence identified by the development team, to comment on its quality and relevance, and to develop recommendations for clinical practice based on the available evidence. The recommendations were agreed by the full GDG.

1.7 Care pathways

Two clinical care pathways have been developed to indicate the key components in identification/diagnosis and management of FH in adults and children.




FH
Management
Adults with FH
Children with FH
Assessment
Consider individuals with FH (both with or without an identified DNA mutation) to be at substantially increased coronary risk and offer advice and treatment for this condition
Do not use CV risk estimation tools such as those based on the Framingham algorithm
Refer urgently for cardiovascular evaluation if individuals have signs or symptoms of possible cardiovascular disease
Consider referral for cardiovascular evaluation if individuals have a family history of cardiovascular disease in early adulthood or two or more other cardiovascular risk factors (e.g. smoking, hypertension, diabetes, male)
Take family history/3-generation pedigree, noting age of onset of CHD and lipid levels of relatives
Assessment
If children have symptoms and signs of CHD, assess as for adults (see box)
Refer children and young people to a specialist with expertise in FH in an appropriate child/young person focused setting
Drug therapy
Treat initially using statins
Consider ezetimibe, a resin, nicotinic acid or a fibrate if statins are contraindicated or are not tolerated
Consider concomitant medication, co-morbidities and tolerability when prescribing lipid lowering therapies
Women should stop lipid modifying medication 3 months prior to attempting to conceive
Inform women that in the event of an unplanned pregnancy lipid modifying medication should be stopped and medical advice should be sought
Drug therapy
Discuss pharmacological options with the child or young person and their parents/carers, including benefits and risk of medication or of deferring medication
Consider the age of onset of CHD in the family and the presence of other CV risk factors including LDL-C>6 mmol/l when deciding at what age to initiate treatment
Use statins with a license for use in children with FH as the initial treatment choice for children 10 years onwards and prescribe doses as specified in the BNF
Consider ezetimibe, a resin, or a fibrate if statins are contraindicated or are not tolerated
In girls and young women, discuss contraception and risks to pregnancy while taking lipid modifying medication. This discussion should be regularly revisited
Monitoring and review
Monitor LDL-C levels (see the NICE Lipids Modification guidelines)
Assess smoking status and discuss concordance with medication, side effects of treatment, and any changes that may be required to achieve recommended cholesterol concentrations
Record any changes in family history/3-generation pedigree
Monitoring
Monitor growth and pubertal development in children or young people with FH as in usual clinical care
Do not routinely monitor cardiovascular function
Discussion on contraception and risks to pregnancy should be regularly revisited
Refer for cardiovascular evaluation if individuals develop signs or symptoms of possible cardiovascular disease
Optimising drug therapy
Increase statin dose or potency to the maximum tolerated dose to achieve adequate LDL-C lowering (>50%)
Consider adding ezetimibe, a resin, nicotinic acid or a fibrate if a further 10% reduction in total or LDL-C is needed
Refer to a specialist with expertise in managing FH if further lipid modifying therapy is needed, for example in those:
with established cardiovascular disease; or with a family history of cardiovascular disease in early adulthood; or with two or more other cardiovascular risk factors (e.g. smoking, hypertension, diabetes, male), or
not achieving a reduction in LDL-C >50%
Exercise caution when adding a fibrate. Gemfibrozil and statins should not be used together
Optimising drug therapy
Consider higher dose statins only in exceptional cases (e.g. family history of CHD in early adulthood)
Consider two or more drugs only in exceptional cases (e.g. family history of CHD in early adulthood)
See page 2 for continued management


FH
Management (cont.)
Adults with FH
Children with FH
General information and advice
Lifestyle advice and health education
Strongly encourage individuals who do not smoke not to start
Offer advice on
Smoking cessation
Individualised nutritional advice, including advice on the appropriate use of products containing stanols and sterols
Physical activity
Alcohol
Information and support
Offer information
on FH
the process of family testing
the individual's level of coronary risk, implications for them and their families
Offer to facilitate the sharing of information about FH with family members, if needed
Cascade testing for FH
Offer DNA and lipid testing to all first degree relatives, including children, of individuals with an identified DNA mutation
Offer lipid testing to all first degree relatives, including children, where there is a clinical diagnosis of FH but where no family mutation can be found
On-going monitoring of CHD risk
Refer urgently for cardiovascular evaluation if individuals have signs or symptoms of possible cardiovascular disease
Consider referral for cardiovascular evaluation if individuals have a family history of cardiovascular disease in early adulthood or two or more other cardiovascular risk factors (e.g. smoking, hypertension, diabetes, male)
Additional recommendations for individuals with homozygous FH
Refer all individual with homozygous FH for a cardiovascular evaluation at diagnosis
Offer apheresis
Offer liver transplantation as an option following apheresis and medication failure
Discuss the option to refer for heart and liver transplantation following a discussion of the benefits and potential harms of intervention
Additional recommendations for individuals with heterozygous FH in whom the therapeutic response is insufficient
Exceptionally, individuals with heterozygous FH who have progressive, symptomatic CHD despite maximal tolerated lipid modifying drug therapy and optimal medical therapy may require apheresis. This should be undertaken in a specialist centre on a case by case basis and data collected into an appropriate registry

1

1.8 Research recommendations

Please see also the more concise versions of these in the NICE guideline.

1.8.1 What is the clinical and cost-effectiveness of identifying an FH patient (defined by DNA testing) from GP registers and from secondary care registers?

Research is needed to compare the utility of strategies other than cascade screening to identify new index cases, because currently recommended strategies are likely to lead to the identification of less than 50% of the predicted people with this condition in the UK. These additional strategies should evaluate note searching in general practice and from secondary care CHD registers (e.g. MINAP), using a 'reference standard' of known FH-causing mutations. This will require the development of different algorithms for patient identification in primary and secondary care, based on the UK FH diagnostic criteria and a combination of different cut points for untreated total or LDL cholesterol, age of onset of heart disease in the index case, age of onset of heart disease in first degree relatives, etc. This research would examine the possibility that, for example, though it might be more costly to identify an FH patient in general practice, it may be more efficient in terms of subsequently identifying relatives, since they would often be known to the practice and could be more easily tested. By contrast, the relatives of FH patients identified through secondary care may be harder to contact or less willing to respond, so that, overall, the cost per FH relative tested would be higher.

1.8.2 What is the clinical effectiveness and safety of differing doses of lipid modifying therapy in children with FH?

There have been no published studies attempting to establish target lipid concentrations in children treated with FH. Treatment is recommended from 10 years onwards, however this lack of data prevents a recommendation regarding the aim of pharmacological treatment on lipid concentrations during childhood

Establishing the aim of therapy of lipid-lowering therapy will help clinicians, the children, and their parents choose the most appropriate agent and titrate doses of pharmacological agents, to ensure the best efficacy with the minimum dose, and

allow centres caring for children with FH to tailor the pharmacological intervention to the individual.

Research (both cross-sectionally and longitudinally) should assess evidence of end-organ involvement (eg carotid intimal thickness, IMT) to determine at which age abnormalities can first be seen. Included children should be diagnosed either biochemically or molecularly with FH, between 10 and 18 years of age. The intervention is the introduction of statin therapy. The comparison group will be those children with FH before and after the introduction of statin therapy. Children can be randomly allocated different doses of statin to achieve different cholesterol lowering effects. The outcome for children with FH will be the fasting serum total and LDL-cholesterol concentrations measured before and after the introduction of statin therapy. At the same time carotid artery IMT, and measures of growth and pubertal development will be assessed. The aim would be to identify a threshold effect with a cholesterol concentration below which carotid IMT is normal and where thickening is absent and above which it is abnormal and where thickening is observed.

1.8.3 What are the appropriate indications, effectiveness, and safety of apheresis in heterozygous FH patients?

There is limited evidence available from clinical trials to inform specific indications for apheresis in patients with heterozygous FH. Also there is limited published evidence on the cardiovascular outcome of such patients who are treated with LDL apheresis.

Investigations that need to be considered are various measures of vascular status, which are considered to reflect the extent or activity of atherosclerotic vascular disease of the coronary arteries.

Evidence on the value of investigations in predicting the outcome from LDL-apheresis should ideally be based on evidence from randomised controlled trials with clinical outcomes. However it is difficult to identify a suitable alternative treatment as apheresis is generally only considered in patients for whom no other treatment option is available. One possible comparator may be novel therapies with antisense oligonucleotides (Apolipoprotein B).

In addition it is also recommended that a national register be established for all FH patients who have been referred for and/or are undergoing LDL apheresis in the UK. Data should be collected independently in a standardised manner and collated contemporaneously. This would enable conclusions to be drawn about the natural history of the condition and to document the temporal relationship of clinical and vascular features in relation to treatments and other parameters.

1.8.4 What are the implications of FH for the safety of a mother during pregnancy and what are the risks of fetal malformations attributable to pharmacological therapies?

There is a paucity of information on the outcomes of pregnancy in women with FH. A small number of conflicting studies have suggested a small increase in fetal abnormalities if the mother has taken statins during the first trimester, but there are not sufficient data to provide an accurate estimate of the level of risk.

There is also very little information on the risk of pregnancy in a woman with FH. Excluding suicide, cardiac deaths are the most common cause of death in pregnancy, but there is no information on the level of this risk in women with FH.

New data on the incidence of cardiac problems in pregnancy and the incidence of fetal malformation would allow future NICE guidelines to give clearer and more precise advice on the management of pregnancy in women with FH. The impact of such advice would, at a minimum, reduce uncertainty for women, and may help to identify, for example, particular risks during the pregnancy that could be better managed. The only feasible research method to address these questions is an observational longitudinal study following women with FH and other women (not diagnosed with FH) using statins through their pregnancies using a national register.

1.8.5 What is the utility of routine cardiovascular evaluation for asymptomatic people with familial hypercholesterolaemia?

Because of their inherent high risk of developing CHD, a low threshold of suspicion for coronary disease is recommended for individuals with FH. A number of studies have assessed the prevalence of coronary artery calcification and positive exercise

tests in individuals with FH, and it is plausible that the positive predictive value of an abnormal test in this group of patients may be higher than in the general population. The research aims are to identify a group of individuals with FH who have subclinical atherosclerosis that will increase the individual's risk of a CHD event and will thus warrant invasive intervention.

Routine monitoring to detect sub-clinical atherosclerosis should be non-invasive, sensitive, specific and cost-effective therefore research to assess the prevalence of both asymptomatic coronary and non-coronary atherosclerosis in patients with definite heterozygous familial hypercholesterolaemia is required. The patients for such a study should ideally all be mutation positive individuals, and information will be required on age, sex, duration of statin treatment and pre and on-treatment lipid levels and cigarette smoking. As well as exercise ECG testing followed by stress echocardiography prior to possible angiography in individuals with an abnormal exercise test and ankle brachial pressure measures it should include magnetic resonance imaging in addition to other modalities such as carotid IMT and coronary calcification. Outcomes would be changes in exercise ECG/ ankle brachial pressure testing /IMT/calcification over time. Comparison groups could include 25-35 year olds vs 36-45 vs 46-50 year olds. Comparison with non-FH subjects with elevated LDFL-C levels would also be of value.

The major limitation would be that no information on differences in morbidity or mortality outcome attributable to early diagnosis would be provided. To obtain this information consideration would need to be given to the feasibility of conducting a long-term randomised trial to compare the outcome of routine monitoring with symptom-based investigation.

1.9 Acknowledgements

We gratefully acknowledge the contributions of Joanne Lord (NICE) for her advice on the health economics, and also Dalya Marks and Gayle Hadfield for their detailed input to the health economic modelling. Our thanks also go to Dr Angela Cooper of the NCC-PC and Dr Tim Stokes for their advice. Finally we are also very grateful all those who advised the development team and GDG and so contributed to the guideline process.

We would also like to acknowledge the contributions of the expert peer reviewers, namely

**TO BE ADDED for final version

1.10 Glossary

Cascade testing	Cascade testing is a mechanism for identifying people at risk of a genetic condition by a process of family tracing. For FH the test employed is measurement of (LDL) cholesterol in the blood, and/or a DNA test if a disease-causing mutation has been identified in the proband (see below).
Case finding	A strategy of surveying a population to find those who have the specified disease or condition which is under investigation.
Dominant pattern of inheritance (autosomal dominant pattern of inheritance)	An affected individual has one copy of a mutant gene and one normal gene on a pair of autosomal (i.e. non-sex) chromosomes. Individuals with autosomal dominant diseases have a 50-50 chance of passing the mutant gene, and therefore the disorder, onto each of their children.
Family history	The structure and relationships within the family that relates information about diseases in family members.
First degree relatives	Parents, siblings, and children of an individual.
Heterozygous FH	High LDL cholesterol concentration in the blood caused by an inherited mutation from one parent only. Individuals with FH are at increased risk of cardiovascular disease.

Homozygous FH	Very high LDL cholesterol level in the blood caused by an inherited mutation from both parents. Where a person inherits exactly the same affected gene from both parents this is called truly “homozygous” FH. When the mutations in the LDL receptor gene (or equivalent) are different, this state is called “compound heterozygous”. In general the overall effect in both states is similar, in that LDL cholesterol concentrations are very high. Both groups of patients have the same clinical pattern and high risk of cardiovascular disease. For clinical purposes both homozygous FH and compound heterozygous FH can be regarded as behaving in a similar manner. Therefore, for the purposes of this guideline the term “homozygous FH” is used to also encompass compound heterozygous FH.
Genetic counsellor	A health professional with specialised training and experience in both areas of medical genetics and counselling.
Index case	The original patient (proband) who is the starting point for follow up of other members of a family when investigating for possible causative genetic factors of the presenting condition.
Lipid measurements/ concentrations/levels	These terms refer to the measurement of total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol. LDL cholesterol is not usually measured directly but calculated from the total cholesterol, triglycerides and HDL cholesterol, ideally using a fasting sample. Such tests are usually done in a clinical biochemistry laboratory.

Molecular Genetics Diagnostic Service	The laboratory where blood samples are received, and tested for mutations causing disease. Laboratories are run under accredited schemes to ensure confidentiality and quality control of the results.
Mutation	An identified change in the DNA sequence of a gene which is predicted to damage the normal function of the gene and so cause disease.
Pedigree	A method of characterizing the relatives of an index case and their family relationship as well as problems or illnesses within the family. This information, often represented graphically as a family tree, facilitates analysis of inheritance patterns. Study of a trait or disease begins with the affected person (the index case). The pedigree is drawn as the relatives are described. One begins with the siblings of the proband and proceeds to the parents; relatives of the parents, including brothers, sisters, nephews, and nieces; grandparents; and so on. At least 3 generations are usually included. Illnesses, hospitalizations, causes of death, miscarriages, abortions, congenital anomalies, and any other unusual features are recorded.
Proband	The affected individual through whom a family with a genetic disorder is ascertained.
Simon Broome register	A computerized research register of individuals with FH, based in Oxford. Research from this voluntary register has lead to several publications describing the natural history of FH in the UK. The “Simon Broome Criteria” for diagnosis were based on study of this group of individuals with FH.

Specialist	One who has expertise in a particular field of medicine by virtue of additional training and experience. For this guideline, we use specialist to refer to a healthcare professional with an expertise in FH.
Specialist centre	The definition of a specialist centre is not rigid and is based on a combination of patient treatment services, numbers and ages of individuals attending there, the presence of a multi-disciplinary team (which may include for example, physicians, lipidologists, specialist nurses, dieticians), the ability to manage the more unusual manifestations of the condition and the additional functions such as research, education and standard setting. Care is supervised by expert healthcare professionals but shared with local hospitals and primary care teams. Whilst details of the model may vary between patients and areas, the key is that specialist supervision oversees local provision with the patient seen at diagnosis for initial assessment and then at minimum, annually for review.
Targeted testing	A mechanism for identifying individuals at increased risk of developing a particular condition. In the case of FH, targeted cascade screening of relatives of positively diagnosed individual aims to provide a greater rate of case identification than general population screening.
Tendon xanthoma	A clinically detectable nodularity and/or thickening of the tendons caused by infiltration with lipid-laden histiocytes (macrophages in connective tissue). A distinctive feature of FH which most frequently affects the Achilles tendons but can also involve tendons on the back of the hands, elbows, and knees..

2 Methods

2.1 Introduction

This chapter sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the subsequent chapters of this guideline. The methods are in accordance with those set out by the Institute in 'The guidelines manual'. April 2006. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidelinesmanual. *The Guideline Development Process – an overview for stakeholders, the public and the NHS* describes how organisations can become involved in the development of a guideline.

2.2 Developing key clinical questions (KCQs)

The first step in the development of the guideline was to refine the guideline scope into a series of key clinical questions (KCQs). These KCQs formed the starting point for the subsequent review and as a guide to facilitate the development of recommendations by the Guideline Development Group (GDG).

The KCQs were developed by the GDG and with assistance from the methodology team. The KCQs were refined into specific evidence-based questions (EBQs) specifying interventions to search and outcomes to be searched for by the methodology team and these EBQs formed the basis of the literature searching, appraisal and synthesis.

The total list of KCQs identified is listed in Appendix B. The development team, in liaison with the GDG, identified those KCQs where a full literature search and critical appraisal were essential. Also, where appropriate, high quality evidence in populations other than that of individual with FH was used to corroborate the limited direct evidence. Literature searches were not undertaken where there was already national guidance on the topic to which the guideline could cross refer. This is detailed in Appendix B.

2.3 Literature search strategy

Systematic literature searches are undertaken to identify published evidence to answer the clinical questions identified by the methodology team and the GDG. The information scientist developed search strategies for each question, with guidance from the GDG, using relevant MeSH (medical subject headings) or indexing terms, and free text terms. Searches were conducted between October 2006 and September 2007. Update searches for all questions were carried out in December 2007 to identify any recently published evidence.. Full details of the sources and databases searched and the strategies are available in Appendix B. In addition to the update searches, we also considered any important evidence published before the final guideline was submitted.

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: National Library for Health (NLH) Guidelines Finder, National Guidelines Clearinghouse, Scottish Intercollegiate Guidelines Network (SIGN), Guidelines International Network (GIN), Canadian Medical Association (CMA) Infobase (Canadian guidelines), National Health and Medical Research Council (NHMRC) Clinical Practice Guidelines (Australian Guidelines), New Zealand Guidelines Group, BMJ Clinical Evidence, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Heath Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED) National Research Register and Current Controlled Trials

For each clinical question the following bibliographic databases were searched from their inception to the latest date available: Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effects (DARE) Health Technology Database (HTA), MEDLINE, MEDLINE in Process, EMBASE, CINAHL, CENTRAL (Cochrane Controlled Trials Register), Science Citation Index. When appropriate to the question PsycINFO was also searched.

The search strategies were developed in MEDLINE and then adapted for searching in other bibliographic databases. For the pharmacological questions, methodological search filters designed to limit searches to systematic reviews or randomised controlled trials were used. These were developed by the Centre of Reviews and

Dissemination and The Cochrane Collaboration. For all other questions, no restriction was placed on study design.

The economic literature was identified by conducting searches in NHS Economic Evaluations Database (NHSEED) and in MEDLINE, MEDLINE in process, EMBASE Science Citation Index, and Social Science Citation Index using an economics search strategy developed by ScHARR at the University of Sheffield.

Databases of the results of the searches for each question or topic area were created using the bibliographic management software Reference Manager.

2.4 Identifying the evidence

After the search of titles and abstracts was undertaken, full papers were obtained if they appeared to address the KCQ. The highest level of evidence was sought. However observational studies, surveys and expert formal consensus results were used when randomised control trials were not available. In general, only English language papers were reviewed however, for the questions on apheresis we also searched for foreign language papers (specifically in Japanese and German) on the advice of the GDG. Following a critical review of the full text paper, articles not relevant to the subject in question were excluded. Studies that did not report on relevant outcomes were also excluded.

We also contacted the relevant manufacturers of key drugs for data on the safety of lipid-modifying drugs in children due to the lack of published evidence. This request was conducted according to the process outlined in the 'The guidelines manual'. April 2006. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidelinesmanual.

The reasons for rejecting any paper ordered were recorded and details can be seen in Appendix C.

2.5 Critical appraisal of the evidence

From the papers retrieved, the Health Service Research Fellow (HSRF) synthesised the evidence for each question or questions into a narrative summary. These form

the basis of this guideline. Each study was critically appraised using the Institute's criteria for quality assessment and the information extracted for included studies is given in Appendix C. Background papers, for example those used to set the clinical scene in the narrative summaries, were referenced but not extracted.

2.5.1 Choice of outcomes

FH is a condition characterised by abnormally high concentrations of LDL-C. Therefore the GDG decided that only those papers reporting LDL-C as a primary outcome would therefore be included. This is also reflected in the wording of the recommendations, for example, referral specifically to measurement of LDL-C concentrations, rather than total cholesterol.

2.6 Economic analysis

The essence of economic evaluation is that it provides a balance sheet of the benefits and harms as well as the costs of each option. A well conducted economic evaluation will help to identify, measure, value and compare costs and consequences of alternative policy options. Thus the starting point of an economic appraisal is to ensure that healthcare interventions are clinically effective and then also cost effective. Although NICE does not have a threshold for cost effectiveness, interventions with a cost per quality adjusted life year of up to £20,000 are deemed cost effective, those between £20-30,000 may be cost effective and those above £30,000 are unlikely to be judged cost effective. If a particular treatment strategy were found to yield little health gain relative to the resources used, then it could be advantageous to re-deploy resources to other activities that yield greater health gain.

To assess the cost effectiveness of different management strategies in FH a comprehensive systematic review of the economic literature relating to FH patients was conducted. For selected components of the guideline original cost effectiveness analyses were performed. The primary criteria applied for an intervention to be considered cost effective were either:

- the intervention dominated other relevant strategies (that is it is both less costly in terms of resource use and more clinically effective compared with the other relevant alternative strategies); or

- the intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy (or usual care).

2.6.1 Health economic evidence review

Identified titles and abstracts from the economic searches were reviewed by a single health economist and full papers obtained as appropriate. No criteria for study design were imposed a priori. In this way the searches were not constrained to randomised controlled trials (RCTs) containing formal economic evaluations.

Papers were included if they were full/partial economic evaluations, considered patients with FH, were written in English, and reported health economic information that could be generalised to UK.

The full papers were critically appraised by the health economist using a standard validated checklist[2]. A general descriptive overview of the studies, their quality, and conclusions was presented and summarised in the form of a narrative review (see also Appendix D for the full extractions and reasons for exclusion).

Each study was categorized as one of the following: cost effectiveness analysis or cost utility analysis (i.e. cost effectiveness analysis with effectiveness measured in terms of QALYs or life year gained). Some studies were categorized as 'cost consequences analyses' or 'cost minimisation analyses'. These studies did not provide an overall measure of health gain or attempt to sythesise costs and benefits together. Such studies were considered as partial economic evaluations.

2.6.2 Cost effectiveness modelling

Some areas were selected for further economic analysis if there was likelihood that the recommendation made would substantially change clinical practice in the NHS and have important consequences for resource use.

The following areas were chosen for further analysis

- the use of high intensity statins compared with low intensity stains in the treatment of FH

- a cost effectiveness analysis of cascade testing for FH using DNA testing and LDL-C

Full reports for each analysis are in the Appendix E of the guideline. The GDG was consulted during the construction and interpretation of each model to ensure that appropriate assumptions, model structure and data sources were used. All models were done in accordance to the NICE reference case outlined in the 'The guidelines manual'. April 2006. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidelinesmanual.

2.7 Assigning levels to the evidence

The evidence levels and recommendation are based on the Institute's technical manual 'The guidelines manual'. April 2006. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidelinesmanual. Evidence levels for included studies were assigned based upon Table 1.

Table 1 Levels of evidence

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

2.8 Forming recommendations

In preparation for each meeting, the narrative and extractions for the questions being discussed were made available to the GDG one week before the scheduled GDG meeting. These documents were available on a closed intranet site and sent by post to those members who requested it.

GDG members were expected to have read the narratives and extractions before attending each meeting. The GDG discussed the evidence at the meeting and agreed evidence statements and recommendations. Any changes were made to the electronic version of the text on a laptop and projected onto a screen until the GDG were satisfied with these.

All work from the meetings was posted on the closed intranet site following the meeting as a matter of record and for referral by the GDG members.

2.9 Areas without evidence and consensus methodology

The table of clinical questions in Appendix B indicates which questions were searched.

In cases where evidence was sparse, the GDG derived the recommendations via informal consensus methods, using extrapolated evidence where appropriate. All details of how the recommendations were derived can be seen in the 'Evidence to recommendations' section of each of the chapters.

2.10 Consultation

The guideline has been developed in accordance with the Institute's guideline development process. This has included allowing registered stakeholders the opportunity to comment on the scope of the guideline and the draft of the full and short form guideline. In addition, the draft was reviewed by an independent Guideline Review Panel (GRP) established by the Institute.

The comments made by the stakeholders, peer reviewers and the GRP were collated and presented for consideration by the GDG. All comments were considered systematically by the GDG and the development team recorded the agreed responses.

2.11 Relationships between the guideline and other national guidance

2.11.1 National Service Frameworks

In formulating recommendations consideration was given to the National Service Framework for Coronary Heart Disease (2000).

2.11.2 Related NICE Guidance

It was identified that this guideline intersected with the followed NICE guidelines published or in development. Cross reference was made to the following guidance as appropriate.

Published

Statins for the prevention of cardiovascular events in people at increased risk of developing cardiovascular disease or those with established cardiovascular disease. NICE technology appraisal 94 (2006). Available from www.nice.org.uk/TA094

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. NICE technology appraisal 132 (2007). Available from www.nice.org.uk/TA132

Long acting reversible contraception: the effective and appropriate use of long-acting reversible contraception. NICE clinical guideline 30 (2005) Available from www.nice.org.uk/CG030

Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline. NICE clinical guideline 48 (2007) Available from www.nice.org.uk/CG048

Brief interventions and referral for smoking cessation in primary care and other settings. NICE public health intervention guidance 1 (2006). Available from www.nice.org.uk/PHI001

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline. Publication expected 2008.

Through review of published guidance, personal contact and commenting on guideline scope, endeavours were made to ensure that boundaries between guidance were clear and advice was consistent.

3 Diagnosis

3.1 Introduction

3.1.1 Diagnosis of FH

3.1.1.1 Diagnosis using clinical criteria

The clinical diagnosis of FH is based on personal and family history, physical examination, and lipid concentrations. Three groups have developed clinical diagnostic tools for FH: the US MedPed Program, the Simon Broome Register Group in the United Kingdom, and the Dutch Lipid Clinic Network.

The MedPed criteria specify cut points for total cholesterol concentrations specific to an individual's age and family history. The cut points are different for individuals who are the first-, second- or third-degree relatives of a patient with FH, and for the general population, because individuals with a relative with FH have a higher prior probability of having FH.

The Simon Broome Register criteria include cholesterol concentrations, clinical characteristics, molecular diagnosis, and family history.

- A "definite" diagnosis of FH is made if an individual has elevated cholesterol concentrations (concentrations differ for children under the age of 16 years) and tendinous xanthomata, or if the individual has an identified mutation in a gene known to cause FH (currently the genes coding for the LDL receptor (*LDLR*) or the for apolipoprotein B-100 (*APOB*) or for an enzyme called *PCSK9*).
- A "probable" diagnosis is made if the individual has elevated cholesterol concentrations and a family history of hypercholesterolemia or premature heart disease.[3]

The Dutch Lipid Clinic Network criteria[4] are similar to the Simon Broom Register criteria. Points are assigned for family history of hyperlipidaemia or heart disease, clinical characteristics such as tendinous xanthomata, elevated LDL cholesterol, and/or an identified mutation. A total point score of greater than eight is considered

"definite" FH, 6-8 is "probable" FH, and 3-5 is "possible" FH. Although the Simon Broome Register criteria consider a molecular diagnosis as evidence for definite FH, the Dutch Lipid clinic Network requires that at least one other criterion be met in addition to molecular diagnosis.[5]

3.1.1.2 ***DNA testing***

DNA tests are carried out to find the specific cause of the disorder in an individual with a clinical diagnosis of FH. The diagnostic procedures and protocols used for FH are essentially identical to those used routinely for genetic testing for other diseases such as cystic fibrosis or familial breast cancer.

To-date, mutations in three genes have been found to cause FH, (*LDLR, APOB, PCSK9*)[6]. A number of different methods are used to test for some common mutations and to look for large deletions or re-arrangements in the *LDLR* gene. Further testing is carried out by screening the entire coding and control regions of the *LDLR* gene, using direct sequencing or by methods called fluorescent single-strand conformation polymorphism test (SSCP) and denaturing high-performance liquid chromatography test (dHPLC)[7]. These tests identify the cause of FH in a significant number of individuals (70-80% of those with a clinical diagnosis of definite FH and 20-30% of those where the clinical diagnosis is less certain)[6-8]. Samples from individuals where no mutation is found can be kept for further testing with the individuals' consent if, for example, other genes causing FH are subsequently identified.

Not finding a mutation does not mean that the individual does not have FH, since the molecular techniques are not 100% sensitive. In either case, the individual's LDL-C and other CHD risk factors should be actively treated.

Knowing the specific family mutation means that the individual's relatives can be offered a simple single DNA test, where the laboratory tests just for the family mutation.

3.1.2 Diagnosis in relatives

There are specific issues associated with the diagnosis of FH in individuals of the proband using LDL-C concentrations or DNA testing.

In the absence of information about the family mutation, the diagnosis of FH in a relative is made based on the elevation of fasting LDL-C concentrations. Because of the prior probability of FH in relatives (1 in 2), the cut-offs used for diagnosis in the general population are too high (where prevalence is 1 in 500). In addition, LDL-C concentrations differ in men and women and generally increase with age, and different cut-offs should be used when diagnosing FH in relatives (see appendix G for recommended cut-offs). However, because of the overlap in LDL-C levels between FH and non-FH relatives[9] the use of such cut-offs still results in diagnostic ambiguity in an estimated 15% of children (aged 5-15 years) and in nearly 50% in adults aged (45-55 years)[10].

Where the family mutation has been identified, this can be quickly and accurately tested for in blood samples from relatives, and further cascade testing undertaken as recommended in the guideline (see Identification strategies for a detailed review of the evidence and the health economic modelling).

3.1.3 Diagnosis in children

The Simon Broome criteria cannot be used to diagnose FH in children aged under 16 years of age. Also, clinical signs – xanthelasma, tendinous xanthomata and corneal arcus – are rarely present in affected children. Total and LDL cholesterol concentrations increase with age and affected children can have concentrations below those expected in adults with FH.

As for diagnosis in relatives, there are issues with using LDL-C concentrations and DNA testing for diagnosis in children. For example, although it is expected that cholesterol will be greater than the 95th centile (taken from age- and sex-specific charts) in an affected child, in reality, concentrations are often much higher than this. DNA diagnosis therefore is extremely helpful in children aged under 16 years.

Children with homozygous FH often have total cholesterol concentrations greater than 20mmol/l. They generally present with cutaneous xanthomata that can be

misdiagnosed as warts and may also have tendinous xanthomata and corneal arcus. Molecular evaluation is helpful to confirm the diagnosis and it is important to screen both the maternal and paternal sides of the family.

3.2 Diagnosing FH

3.2.1 Recommendations

Unless otherwise indicated, recommendations are relevant for individuals with possible or definite FH. Recommendations are also applicable for individuals with both heterozygous and homozygous FH, unless otherwise indicated.

Please note, numbering is as in the NICE guideline.

1.1 Diagnosis

(see also Information needs and support in Chapter 6.2)

1.1.1 The diagnosis of FH should be made using the Simon Broome criteria which includes a combination of family history, clinical examination (specifically arcus and tendon xanthomata), lipid profile (see Appendix E of the NICE guideline, or Appendix F of the full guideline) or by using molecular techniques.

1.1.2 A clinical diagnosis of homozygous FH should be considered in individuals with LDL-C concentrations greater than 13mmol/l and they should be referred to a specialist centre.

1.1.3 Secondary causes of hypercholesterolaemia should be considered and excluded before a diagnosis of FH is made.

1.1.4 To confirm the diagnosis of FH, at least two measurements of elevated LDL-C concentrations are necessary because biological and analytical variability occurs.

1.1.5 Absence of clinical signs (arcus and tendon xanthomata) in adults and children does not exclude a diagnosis of FH.

1.1.6 A family history should always be obtained from an individual being investigated for FH to determine if a dominant pattern of inheritance is present.

1.1.7 Standardised pedigree terminology should be used to document a three- to four-generation pedigree including relatives' age of onset of coronary heart disease and lipid concentrations. For deceased relatives the age and cause of death, and

smoking history should be documented. If possible the proband should verify this information with other family members.

1.1.8 In children at risk of FH because of an affected parent, LDL-C concentrations should usually be measured by the age of ten years. This measurement should be repeated after puberty before a diagnosis of FH can be excluded.

1.1.9 Ultrasonography of the Achilles tendon is not recommended in the diagnosis of FH.

1.1.10 Individuals with FH are at a very high risk of coronary heart disease. Risk estimation tools such as those based on the Framingham algorithm should not be used to assess their risk.

1.1.11 Individuals with a clinical diagnosis of FH should be offered a DNA test to increase the certainty of their diagnosis and to aid diagnosis amongst their relatives.

1.1.12 Individuals with a clinical diagnosis of FH and their relatives who have a detected mutation should be informed they have an unequivocal diagnosis of FH.

1.1.13 Where DNA testing has excluded FH in a member of a family in which a mutation has been identified, CHD risk should be managed as in the general population (see the NICE Lipid Modification guideline).

3.2.2 Evidence statements on the effectiveness of different diagnostic strategies

Key clinical question:

In adults and children, what is the effectiveness of the following tests to diagnose heterozygous FH in individuals with a history of family history of early heart disease and/or hypercholesterolemia;

- biochemical assays?
- clinical signs and symptoms?
- DNA testing?
- combinations and/or sequences of above?

Question 1 of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
No single method of diagnostic testing provides sufficient accuracy to be used exclusively. [2+] In one study[11] that compared the sensitivity and specificity of different clinical criteria for diagnosing FH, the Simon Broome criteria performed at least as well as the Dutch criteria for individuals with definite FH and both Simon Broome and the Dutch criteria demonstrated better performance than MEDPED. [2+] In 25 babies at risk of FH because of an affected parent, there was significant overlap in LDL-C concentrations within mutation positive (14 babies) and mutation negative (11 babies) groups at birth[12]. The individual ranges of LDL-C and TC were non overlapping at one year of age. [2+] In a study of 18 children at risk of FH because of an affected parent[13], serial total cholesterol measurements increased to above the 95th percentile in seven children over 1-7 years. [2+] LDL-C concentrations within the normal range for childhood do not necessarily exclude FH in children. [2+] In a single study[14] of 88 children (mean age range 8.31-8.79 years, ±3.31-4.00) with molecularly defined FH only two children displayed arcus and none had xanthomata on clinical examination. [2+] In 21 children with molecularly defined FH[15], an ultrasonographic study demonstrated an average of 1.3mm thickening in Achilles tendon; this was abnormal in 8/21 of individuals. [2+] In a study[16] of 290 adults, of whom 127 had FH (81 genetically ascertained), the detection rate of tendon xanthomata by clinical examination and	Where appropriate, the GDG considered results of diagnostic studies conducted in the UK or comparable European populations as being of greater applicability to the UK population than those from other parts of the world, due to differences in prevalence and genetic distributions. <u>Clinical diagnosis</u> Although there was little difference in the accuracy of the different methods, the Simon Broome criteria were recommended for making a clinical diagnosis because they were considered to be simpler than other criteria and were developed based on a UK population. The Simon Broome criteria allow for a diagnosis of 'probable' or 'definite' FH. However in the recommendations it was not considered helpful to distinguish between 'probable' or 'definite' FH, but that where appropriate, evidence statements should reflect any difference between the groups. In relatives of people with FH, there is a higher pre-test probability if using LDL-C alone for diagnosis (thus lowering the sensitivity) so this is not a useful method of diagnosis and clinicians should use both DNA and LDL-C. Simon Broome criteria should therefore not be used when cascade testing as this would lead to considerable numbers of false negatives. The criteria should also be different for adults and children. Recommendations on the appropriate use of the diagnostic methods were made (see Appendix F). <u>DNA testing</u> Mutations can be found in 80% of people with definite FH, with lower rates of mutation identification in the 'probable' group.

ultrasonography were comparable [2+] In people with FH, LDL-C concentrations may be significantly elevated from infancy and remain elevated throughout adult life, such that the cholesterol years burden accumulated by an FH individual is significantly higher than for an individual in the general population of their age and gender with similar LDL-C concentrations. [2+] LDL-C cholesterol concentrations in the general population and individuals with FH overlap [2+] In UK studies, with individuals from different parts of the country, DNA tests demonstrated a mutation in approx. 20% of those with a clinical diagnosis of possible FH; and up to 80% of those with a clinical diagnosis of definite FH [2+] In individuals with a clinical diagnosis of FH, the absence of an identified DNA mutation does not exclude the possibility that they have FH [2+] The concentrations of LDL-C recommended by the Simon Broome Register for identifying individuals in the general population who have a high probability of having FH were chosen to have an acceptable specificity and sensitivity where the expected frequency is 1 in 500. Because of the higher probability (1 in 2) of a relative of an individual with FH having the disease these concentrations have a lower discrimination and are too high.[10] [2+] (see also Chapter 4)	<u>Differentiation of risk</u> Although DNA testing has a role in increasing the certainty of diagnosis, FH can be managed without the knowledge of DNA mutation. Also, the lack of an identified mutation does not mean that the individual is not at high risk, and treatment should be based according to the clinical assessment. Assessment tools based on the Framingham risk assessment equation should not be used. The evidence showed that people with possible FH are still at a considerable higher risk and should therefore be treated accordingly. At this time, the evidence was not conclusive on whether different mutation patterns were associated with different risks.

3.2.3 Evidence summary on the effectiveness of different diagnostic strategies

3.2.3.1 Methods of the clinical evidence review

The searches for Question 1 were not restricted by study type or age of study participants.

- Identified: 2422
- Ordered: 63
- Included: 21
- Excluded: 42

3.2.3.2 Clinical evidence

A large retrospective, multi-centre cohort study[17] was conducted using data on 4000 randomly selected individuals from the DNA bank at the University of Amsterdam. Each record was reviewed and 2400 individuals were defined as having FH by criteria based upon MedPed (USA), Simon Broome Register (UK) and the Dutch Lipid Clinic Network (the Netherlands). The FH diagnostic criteria for this study included the presence of a documented LDL receptor mutation (*LDLR* mutation) or an LDL cholesterol concentration above the 95th percentile for sex and age in combination with at least one of the following:

- the presence of typical tendon xanthomas in the individual or in a first degree relative
- an LDL cholesterol concentration above the 95th percentile for age and sex in a first degree relative
- proven CAD in the individual or in a first degree relative under the age of 60 years.

Patients were tested for the 14 most prevalent Dutch *LDLR* gene mutations. An *LDLR* mutation was identified in 52.3% of these individuals (*LDLR* plus), with 47.8% where no *LDLR* mutation was found (*LDLR* minus). In a random sample of 199 individuals from the *LDLR* minus group, an *LDLR* mutation was found by sequencing in 40 (20%) of these individuals. Further sequencing is currently being performed.

There were significant differences in clinical and laboratory profiles between *LDLR* plus and *LDLR* minus individuals who had been clinically diagnosed with FH. The *LDLR* minus groups

had significantly higher BMI measurements as well as other risk factors including smoking and hypertension and elevated glucose concentrations. The *LDLR* plus group showed significantly higher concentrations of LDL-C, TC, and TG.

Table 2 Significant differences between *LDLR* positive and negative individuals with a clinical diagnosis of FH

	***LDLR* +ve n=1255**	***LDLR* -ve n=1145**	**Statistical significance**
Male gender	45.8 % (575/680)	52.8% (605/540)	p<0.001
Age at first visit (years)	42.1 (±12.6)	47.6 (±12.2)	p<0.001
Smoking, ever	68.7% (787/359)	79.5% (811/209)	p<0.001
Hypertension	7.8% (97/1146)	11.7% (133/1000)	p<0.001
First degree relative family history	56.4% (596/460)	65.5% (664/350)	p<0.001
BMI	24.7 (±3.4)	25.6 (±3.6)	p<0.001
Systolic BP (mmHg)	133 (±19)	137 (±20)	p<0.001
Diastolic BP (mmHg)	81 (±10)	83 (±10)	p<0.001
TC (mmol/l)	10.25 (±2.13)	8.80 (±1.54)	p<0.001
LDL-C (mmol/l)	8.18 (±2.05)	6.61 (±1.47)	p<0.001
HDL-C (mmol/l)	1.19 (±0.35)	1.23 (±0.36)	p=0.003
TG (mmol/l)	1.39 (0.98-2.03)	1.71 (1.24-2.35)	p<0.001
Glucose (mmol/l)	4.9 (4.5-5.3)	5.0 (4.6-5.5)	p<0.001

Adapted from published paper[17]

The authors discussed the value of genetic testing particularly in children who may begin to develop cardiovascular disease at a very young age and in whom clinical manifestations such as a high LDL cholesterol and tendon xanthomas often do not appear until a later age.

A study of 1053 individuals was undertaken to determine the mutational spectra of FH among the Danish population[18]. A secondary outcome of this study, which was of interest for this

review, showed differences in lipid concentrations (TC significant p=0.0001) between individuals with a mutation and those with no mutation All results are in mmol/l:

Table 3 Differences in probands and relatives with and without an identified mutation

Lipid s (mmol/l)	Proband (mutation)	Proband (no mutation)	Relatives (mutation)	Relatives (no mutation)
TC	9.82±2.15	8.97±1.55	8.02±2.18	6.23±1.87
HDL-C	1.53±1.57	1.56±0.53	1.53±0.66	1.51±0.39
TG	2.05±3.25	2.01±1.13	1.43±0.70	1.48±0.96
LCL-C	7.12±1.96	6.22±1.5	5.73±1.98	4.00±1.64

Adapted from published paper[18]

Another Danish study[11] aimed at testing the ability of three different sets of clinical criteria, MEDPED, Simon Broome Register and the Dutch Lipid Clinic Network, to predict the results of molecular genetic analysis and to test whether population based age and sex specific percentiles of LDL-C offer useful supplemental information in the selection of individuals for molecular genetic analysis. Four hundred and eight index individuals and 385 relatives were included. There was a 61.3% (49.4-72.4) mutation detection rate among index individuals categorized as definite FH by Simon Broome criteria. If only individuals who met Simon Broome criteria were offered molecular genetic analysis the sensitivity would be 34.1% (26.1-42.7) and specificity would be 89.4% (85.1-92.8). The false positive rate would be 10.6% (7.2-14.9).

Using the Dutch Lipid Clinic Network criteria for definite FH, a 62.9 % (52.0-72.9) mutation detection rate was noted. If the Dutch criteria positive individuals only were offered molecular genetic analysis, the sensitivity would be 41.5% (33.1-50.3) and specificity would be 87.9% (83.4-91.5). The false positive rate would be 12.1% (8.5-16.6).

MEDPED, which used LDL-C and TC concentrations had a mutation detection rate of 53.5% (45.4-61.6) by TC and 51.6% (43.6_59.5) by LDL-C and sensitivities of 63.4% (54.5-71.6) and 70.3% (61.2-78.4) respectively. The respective specificities were 73.4% (67.8-78.6) and 69.8% (63.8-75.3).

If individuals with a diagnosis of probable FH by Simon Broome and the Dutch criteria were included in molecular genetic analysis, both sets of criteria result in high sensitivities (90.4%

and 99.3% respectively) with correspondingly lower mutation detection rates (38.%3 and 34.3% respectively).

Detection by LDL-C at the 95th percentile level and the 90th percentile level were as follows:

	Mutation carriers	**Non- carriers**
Index individuals with LDL-C >95th percentile	94.7%	70.5%
FH relatives with LDL-C >95th percentile	67.0%	6.5%
Index individuals with LDL-C >90th percentile	99.2%	91.2%
FH relatives with LDL-C >90th percentile	76.5%	14.7%

Adapted from published paper[11]

The authors concluded that either inadequacy of the molecular genetic analysis or a more complex, polygenic background for the FH phenotype, must be invoked to explain that almost 40% of individuals with definite FH by clinical criteria did not have an identifiable mutation in the *LDLR* gene.

The use of corneal arcus for case finding was studied in a UK population by Winder et al[19]. A graded prevalence of corneal arcus with age was determined for 81 males and 73 females with newly diagnosed heterozygous FH and for 280 males and 353 females with no known disease. Arcus was recorded by one or both of two experienced observers. The proportion of individuals with any grade of arcus within age intervals of 5 years was analysed. Some degree of arcus affected 50% of individuals with FH by age 31-35 years and 50% of healthy individuals by age 41-45 years. Complete full ring arcus affected 50% of the FH group by age 50 years, with only 5% similarly affected in the healthy group. Arcus grade was not related to the presence of coronary disease.

Sonographic Achilles tendon characteristics were evaluated in 290 hypercholesterolaemic individuals[16]. One hundred and twenty seven individuals had FH (81 genetically ascertained); there were 88 controls and 163 further individuals with FCH and polygenic hypercholesterolemia. Tendon xanthoma were detected by clinical examination in 43% of the mutation positive group and 22% in the mutation negative group, and by ultrasound, the detection rate was not significantly different in the two groups (40% and 24% respectively).

Using data from the Netherlands FH screening programme cholesterol concentrations among 1005 *LDLR* gene mutation carriers were analysed[20]. Results of total cholesterol concentrations in untreated screenees (n=853) using conventional cut off values (6.5 and 8.0 mmol/l) compared with FH status by DNA testing were as follows:

	Mutation +ve (men)	**Mutation –ve (men)**	**Mutation +ve (women)**	**Mutation –ve (women)**
	99(22.4%)	306(75.6%)	101(22.5%)	347(77.5%)
Mean TC mmol/l	7.3(1.3)	5.7(1.1)	7.4(1.4)	5.5(1.1)
TC<6.5 mmol/l	27(27.3%)	245(80.1%)	28(27.7%)	281(81.0%)
6.5<TC<8.0 mmol/l	42(42.4%)	52(17.0%)	44(43.6%)	60(17.3%)
TC>8.0 mmol/l	30(30.3%)	9(2.9%)	29(28.7%)	6(1.7%)
%age>95th percentile	67.7%	15.0%	71.3%	13.3%

Adapted from published paper[20]

Another study of the Dutch screening program compared diagnosis of family members in which a functional mutation of the *LDLR* gene had been detected by DNA analysis with that by cholesterol measurement, and also assessed whether or not active identification of individuals with FH would lead to more cholesterol lowering treatment[21]. The results were as follows:

	Carriers (n=2039) Mean (sd)	**Non carriers (n=3403) Mean (sd)**
TC (mmol/l)	7.43 (1.65)	5.49 (1.34)
LDL-C (mmol/l)	5.62 (1.59)	3.56 (1.11)
HDL-C (mmol/l)	1.09 (0.35)	1.20 (0.37)
TG (mmol/l)	1.47 (1.08)	1.66 (1.10)
Treatment with statins	667 (39%)	160 (5%)

Adapted from published paper[21]

The figure used to diagnose FH in relatives by total cholesterol concentration was the age-specific and sex-specific 90th percentile. A total cholesterol concentration below these

percentiles was reported in 18% (95% CI 13-22%) of mutation positive individuals (false negatives). These individuals would have been missed if only cholesterol concentrations had been measured. The proportion of false positives was also 18% when the sample cut off was used. Given a cholesterol concentration above the 90th percentile, the post test likelihood of having a mutation detected was 1.52(1.22-1.78) corresponding to a probability of 0.60 (0.55-0.64). For cholesterol concentrations below the 90th percentile, the odds of having the disorder was 0.08 (0.05-0.10).

At the time of examination 39% of the individuals with FH were on statins. One year later after DNA diagnosis, this percentage had increased to 93%.

Genotype/phenotype correlations were studied by Graham et al[22]. Probands of 158 families with clinical definitions of probable (120) or definite (38) FH were studied. Mutations were identified in 52 (33%) of the families. However, eight clinically definite FH families remained who had no identified mutations. Comparisons between various mutations, lipid concentrations and tendon xanthoma were presented for 57 of the 60 families studied.

Mutation	n	TC (mmol/l) ±sd*	LDL-C (mmol/l) ±sd	Tendon xanthoma	Diagnosis
Frameshift	12	38.5±12.9	11.4±1.8	9.3±1.7	83%
Nonsense	8	39.4±14.2	10.3±1.7	8.5±2.0	50%
Mis-sense	21	41.0±17.3	10.1±1.7	7.8±1.9	62%
FDB-R3500Q	8	44.3±12.2	8.8±1.3	6.4±4.1	25%
No mutation	8	47.8±9.2	10.2±1.5	8.3±1.8	100%

.* LDL C values were not presented. Adapted from published paper[22]

DNA screening of 790 family members of molecularly characterised South African FH index individuals was undertaken to determine what percentage of adults with FH, who were heterozygous for three common mutations, could be diagnosed accurately on the basis of

* Assumed to be sd (for both TC and LDL-C) as not documented in the paper

raised total cholesterol concentrations[23]. The sensitivity and specificity of FH diagnosis according to TC values (80th percentile) were reported to be 89.3% and 81.9% respectively.

Evaluation of biochemical versus DNA diagnosis revealed that 15.6% of cases may be misdiagnosed when the 80th percentile is used as a biochemical cut-off point for a diagnosis of FH compared with 12.4% using the 95th percentile for age and gender. In total, 16/150 relatives (10.7%) with an FH mutation were falsely classified as normal (negative predictive value of 89.3%), while 53/293 (18.1%) without the mutation were falsely classified as FH heterozygotes (positive predictive value of 81.9%).*

A study was conducted to investigate the usefulness of Achilles tendon sonography in detecting individuals with FH[24]. One hundred and thirty individuals with hypercholesterolaemia were examined by ultrasound. Individuals with obvious secondary hypercholesterolaemias were excluded. Forty individuals had clinically evident FH. Fifty-one individuals had clinically evident hypercholesterolaemia without evidence of FH. In 19 of the 51 individuals FH had to be ruled out by DNA testing. The following results were obtained:

	FH (n=40)	**No FH (n=51)**	**Controls (n=41)**
Achilles tendon thickness (mm, mean±sem)	11.0±0.5	7.3±0.2	7.1±0.2
Thickened tendons (%)	25 (63%)	2 (4%)	0
Low or mixed echogenicity of tendons (%)	36 (90%)	3 (6%)	0

Adapted from published paper[24]

FH could not be confirmed by DNA testing in the three individuals with high cholesterol and tendon xanthoma.

The concordance of clinical and molecular genetic diagnoses of heterozygous FH was studied in 65 participants from 10 Finnish families[25]. Using DNA testing as the 'gold standard,' a correct

* The GDG questioned the statistics reported in this study. The sensitivity and specificity were re-calculated and found to be 92% and 89% respectively. The positive predictive value was 72% and negative predictive value was 94% when re-calculated.

clinical diagnosis was made in 55 (85%) of 65 individuals. In the age group aged under 18 years only two of the five FH children were correctly diagnosed clinically, because the serum LDL-C concentrations in the other three individuals were lower than diagnostic limits. However, when age- and sex-specific LDL cholesterol concentration curves were used, this permitted correct diagnosis in 95% of those with a family history. Two of the four undiagnosed individuals were children. The other two individuals had co-morbidities.

Xanthomatosis was demonstrated in 17 of the 25 adult DNA verified individuals with FH (68%) but in none of the mutation negative individuals. Xanthomatosis was also suspected in one young and six adults with FH . Thus, only two (8%) of the 25 adults with FH were totally free of signs of xanthomatosis.

Diagnosis by statistical methods

Four studies[9;26-28] used statistical methods and genetic validation to develop criteria for making the diagnosis of FH.

The statistical concept of a priori probabilities was applied by Williams et al[26] to derive two sets of practical screening criteria: one for people participating in general population screening studies and another for close relatives of confirmed FH cases. The results showed dramatic differences. At a total cholesterol (TC) concentration of 310 mg/dl (7.95 mmol/l) only 4% of people in the general population would receive a diagnosis of FH but 95% of those who were first degree relatives of known cases would have been diagnosed with FH. In population screening, the calculated FH criteria required a TC >360 mg/dl (9.23 mmol/l) for adults aged 40 years or older, or 270 mg/dl (6.92 mmol/l) in young people and children aged under 18 years. Among first degree relatives of confirmed cases in families with FH the new TC is much lower: 290 mg/dl (7.44 mmol/l) for adults aged 40 years or older, and >220 mg/dl (5.64 mmol/l) in young people and children aged under 18 years. These criteria were validated among 207 people in 5 large FH pedigrees in whom genetic testing established (n=75) or ruled out (n=132) the diagnosis of FH, revealing a specificity of 98% and sensitivity of 87%. Using the proposed LDL-C criteria, the sensitivity was 91% while specificity was again 98%.

In a Japanese study of 181 individuals with FH genetically diagnosed and 100 unaffected relatives[27], distributions of serum total cholesterol and LDL-C showed distinct bimodality when graphed, while HDL-C and log TG concentrations did not. A TC of 225 mg/dl (5.77 mmol/l) and an LDL-C of 160 mg/dl (4.10 mmol/l) were seen to be the cutoff points between normal

individuals and those with FH. Sensitivity and specificity of these criteria were tested by ROC analysis of a sample of 281 sequentially sampled first- and second-degree relatives in whom the diagnosis of FH had been established using genetic testing. The proposed total cholesterol criteria of 224 mg/dl (5.74 mmol/l) and 225 mg/dl (5.77 mmol/dl) were in agreement with the DNA marker, resulting in an observed specificity of 98.5% and sensitivity of 99.4%. LDL-C cutoffs of 161 mg/dl (4.13 mmol/l) to 163 mg/dl (4.18 mmol/dl) produced an observed specificity of 98.5% and a sensitivity of 98.3%. Three of the 181 individuals with FH showed LDL-C concentrations less than 160 mg/dl (4.10 mmol/l) and none of the non-FH individuals showed LDL-C concentrations higher than 160 mg/dl. (These data may not be relevant to the UK due to very low concentrations of LDL-C in the Japanese population).

One hundred thirty four children, aged between 1 and 16 years, from 57 kinships were seen at the Hospital for Sick Children, Great Ormond Street, London because at least one first-degree relative was considered to have FH[9]. Total cholesterol concentrations were taken (although not in a consistent manner) and the resulting distribution was bimodal. The two peaks represented the FH children and healthy children. The estimated mean in the unaffected group was 4.9 (3.2-7.3) mmol/l and in the FH children was 8.9 (6.6-12) mmol/l. Two curves, logarithm transformed and the fitted curves, of FH and healthy children intersected at 6.77 mmol/l. At the point of intersection, a minimum (4.25%) of the total population would be misclassified.

In an early study of children aged 1-19 years who each had one parent with FH[28] the natural logarithm of LDL-C from 217 children was plotted and the observed distribution was bimodal and two populations were derived by the maximum likelihood method. The 'antimode' was 4.2 mmol/l and 55% of the observations were in the left distribution. In the normal (left) population 7.2% were above the cut point (false positives) and 9.7% of those in the affected (right) population were below the cut point (false negatives). When TC was plotted in 236 children the degree of overlap was sufficiently great so that the sum of the two populations was not bimodal but bitangential. The antimode for TC was 6.03 mmol/l. Among children in the normal (left) population, 8.5% were above the cut point (false positives) and 18.9% of the children in the affected (right) population were below the cut point (false negatives).

The analysis of the data collected for this study also supported the hypothesis (at the time of this study) that FH is inherited as a monogenic trait with early expression in children.

Diagnosis in children

Three founder related *LDLR* mutations cause FH in approximately 90% South African Afrikaners[29]. Two hundred and twenty one children from 85 families were screened for mutations. Total and LDL-C concentrations were similar among the different mutation positive children and mean values were significantly higher compared to those without a detected mutation ($p<0.0001$). The results were as follows:

Mean (sd)	FH	Non-FH
Male/female	60/56	50/54
age (years)	11 (4)	12 (4)
TC (mmol/l)	7.7(1.3)	4.7(0.7)
LDL-C (mmol/l)	6.0(1.3)	2.8(0.6)
HDL-C (mmol/l)	1.2(0.3)	1.3(0.3)
TG (mmol/l)	1.0(0.6)	1.1(0.7)

Adapted from published paper[29]

Among these children a TC concentration of 6 mmol/l was the best at discriminating between FH children and those without a mutation. Using this value 4.5% of the total group of 220 children would have been misdiagnosed compared with 11.4% using the 80th percentile, and 7.7% using the 95th percentile for age and sex. In total, 8/116 (6.9%) of the children with an FH mutation were falsely classified as normal (negative predictive value of 93%) whilst 2/104 (1.9%) without the mutation were falsely classified as FH (positive predictive value of 98%). The sensitivity and specificity of FH diagnosis according to TC values were 93 and 98% when testing children from FH families where the prevalence is expected to be 50%. The sensitivity, specificity and predictive values would be considerably lower in the general population.

A study of 25 babies born to 21 parents in Finland[12] was designed to compare blood lipid concentrations in newborns with molecularly defined heterozygous FH to those in non-affected babies and to clarify the value of lipid determinations in assessment of diagnosis of FH at birth and 1 year of age. Of 25 babies born to an FH parent, 14 were DNA positive and 11 were DNA negative. Mean TC and LDL cholesterol concentrations in cord serum were significantly elevated ($p<0.001$) in the DNA positive newborns compared to DNA negative or controls.

	Mean TC mmol/l±sd*	Mean LDL-C mmol/l±sd	Mean HDL-C mmol/l±sd	Mean TG mmol/l±sd
Controls (n=30)	1.84±0.46	1.03±0.30	0.75±0.24	0.13±0.08
DNA –ve at birth (n=10)	1.54±0.23	0.78±0.15	0.63±0.14	0.28±0.23
DNA +ve at birth (n=14)	2.60±0.70	1.77±0.56	0.69±0.23	0.29±0.24
DNA –ve, aged I2 months (n=16)	4.40±0.66	2.89±0.68	1.16±0.15	0.78±0.39
DNA +ve, aged 12 months (n=18)	8.38±1.18	7.02±1.07	0.95±0.14	0.93±0.40

Adapted from published paper[12]

Mean TC and LDL-C concentrations in cord serum were significantly elevated in the affected newborns compared to the non-affected or controls. There was however, a considerable overlap between the ranges of individual lipid concentrations in these three groups. The mean serum TC and LDL-C in the combined two non-affected groups would yield 95th percentile values of 2.60 and 1.44 mmol/l. If these concentrations were used as diagnostic criteria then only 5 or 6 of the 14 DNA positive newborns would have been correctly identified

* Assumed to be mean±sd for all variables

Plasma lipoprotein-lipid concentrations were compared in a cohort of 266 heterozygous FH children and adolescents (1-19 years) and a control group of 120 healthy siblings and unrelated children from Canada[30]. All FH children were defined by one of three mutations in the *LDLR* gene. The results were as follows:

Mean±sd	**Controls**	**FH>15-kb**	**FH C646Y**	**FH W66G**
n	120	188	21	57
Mean age (years)	9.05±4.63	8.21±4.14	7.06±4.09	8.00±4.12
TC (mmol/l)	4.32±0.60	8.17±1.45	8.18±1.53	7.19±1.23
LDL-C (mmol/l)	2.60±0.56	6.58±1.42	6.65±1.50	5.62±1.16
HDL-C (mmol/l)	1.26±0.29	1.11±0.23	1.08±0.28	1.14±0.20
TG (mmol/l)	1.04±0.40	1.09±0.49	1.24±0.76	1.01±0.43

Plasma TC and LDL-C concentrations were significantly lower in mutation W66G which is a defective mutation compared to >15 kb and C646Y ($p<0.05$). In the latter groups, TC and LDL-C were essentially similar. The significant differences between mutation groups remained when results were analyzed by gender.

In a study of 88 unrelated French Canadian children with a persistent increase in LDL-C and a parental history of hyperlipidaemia[14] 71% of the participants were found positive for one of the five molecular defects common in this population. The first objective was to define the molecular basis for hypercholesterolaemia in the 88 children (mean age 8 years). Heterozygosity for the common French-Canadian LDL receptor gene mutation (>10-kb deletion) was found in 50 children (57%, group 1). The presence of one of the other four *LDLR* mutations previously identified in this population was found n 12 individuals (14%, group 2). In 26 children (29%, group 3) none of these five mutations were detected.

Clinically, only one individual in group 1 displayed arcus corneae and none had xanthomas.

Table 4 Lipid concentrations in three groups of children

Mean±sd	>10-kb Group 1	Other Group 2	None Group 3	Control	p-value compared to control
TC mmol/l	7.6 (0.1)	6.8 (0.9)	7.3 (1.5)	3.6 (0.6)	p=0.0001
LDL-C mmol/l	6.2 (1.3)	5.3 (1.1)	5.6 (1.5)	2.3 (0.03)	p=0.0001
HDL-C mmol/l	1.03 (0.03)	1.05 (0.2)	1.2 (0.3)	1.2 (0.4)	p=0.0030

Adapted from published paper[14]

Sonography of Achilles tendon xanthomata was studied in children with FH[15]. Both Achilles tendons of 21 FH children aged 3-18 years were examined. Seven children were studied twice. There were 68 healthy controls. All FH children had one parent with FH or had a diagnosis of FH verified by a positive DNA test. If there was controversy over the diagnosis or if the child had a serum cholesterol value less than 8 mmol/l, an *LDLR* test was done. The tendons of the FH children were significantly thicker (mean±sd 7.1±1.5, range 5-10mm) than controls (5.8±1.0, 3-7mm, p=0.0001). Achilles tendon ultrasound in FH children were abnormal in 33% (3/9) of children aged <10 years and in 42% (5/12) of children aged 10-18 years. Interestingly, only four of the eleven *LDLR* positive children had evidence of xanthomata. One was aged 3 years, one 8 years and one 15 years. One boy aged 9 years who was mutation positive developed hypoechoic areas on US when he was re-studied after two years. Five of seven children with a family history had xanthomata and the three children with a first degree relative with positive *LDLR* had no evidence of xanthomata.

Another diagnostic study of children with high cholesterol[13] followed 85 children ages 4-19 years each with a first degree relative with FH. Initially, 39 had high cholesterol concentrations suggestive of FH. Mean cholesterol for all boys was higher than for all girls but not significantly different. Eighteen of the remaining 46 children with cholesterol concentrations below the childhood 95th percentile were followed with serial cholesterol measurements. Eleven of these children showed a small elevation with a mean year to year increase of 0.096 mmol/l (sem 0.080, ns difference to control). Seven of the children showed marked increases in serum cholesterol concentrations over an interval of 1-7 years, reaching above 95th percentile (approximately 5.6 mmol/l, as read from the graph presented in the paper), which was significantly different to control with mean year to year change of 0.34 mmol/l (sem 0.062, p<0.01). Thus children who would not have been diagnosed as having FH on initial cholesterol

concentration, developed hypercholesterolaemia consistent with a diagnosis of FH. The diagnosis of FH was confirmed retrospectively by DNA analysis in three of these children. It is important to note that 6 of the 7 children were under the age of thirteen years when first tested.

Neonatal diagnosis of FH was studied in 29 infants who had one parent with FH[31]. Cord blood was obtained from these infants and from 36 babies not related to the study sample who served as controls. Controls were compared with at risk infants considered 'positive' due to LDL-C greater than 41 mg/ml (1.05 mmol/l) and at risk infants considered 'negative' due to LDL-C less than 41 mg/ml (1.05 mmol/l).

The results were as follows:

Mean (sd)	Controls	Positive	p-value vs controls	Negative	p-value vs controls
TC mmol/l	1.9 (0.28)	2.56 (0.38)	p<0.001	1.87 (0.33)	ns
LDL-C mmol/l	0.42 (0.09)	0.34 (0.79)	p<0.005	0.82 (0.10)	ns
HDL-C mmol/l	0.79 (0.15)	1.59 (0.41)	Not done	0.85 (0.13)	ns

Adapted from published paper[31]

Among 19 children from whom later samples were obtained at age 1 to 2¼ years, seven had been considered to have normal LDL-C concentrations at birth and at follow up all seven had LDL-C cholesterols <4.36 mmol/l which was the upper limit for age 1-19 years. Only one of the 12 children considered to have hyperbetalipoproteinaemia at birth had a normal LDL-C at follow up. This infant had been on a strict low cholesterol diet since birth. The correlation between TC and LDL-C improved at follow up.

3.2.3.3 ***Health economic evidence***

Please see the health economic review in Chapter 4 and the full economic modelling in Appendix E.

3.2.4 Evidence statements on coronary heart disease risk of people with suspected FH

Key clinical question:

What is the coronary heart disease risk of people with suspected FH:

- who have a confirmed DNA mutation or
- who do not have a confirmed DNA mutation?

Question 2 of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
Large studies have shown that in individuals with a clinical diagnosis of FH the prevalence of coronary heart disease is significantly higher in those with an identified DNA mutation compared to those without a confirmed DNA mutation [2+]	See comments above on the 'differentiation of risk'.

3.2.5 Evidence summary on coronary heart disease risk of people with suspected FH

3.2.5.1 ***Methods of the clinical evidence review***

The searches for Question 2 were not restricted by study type or age of study participants.

- Identified: 1621
- Ordered: 37
- Included: 8
- Excluded: 29

3.2.5.2 ***Clinical evidence***

The role of DNA testing in determining the risk of coronary heart disease in individuals with FH has been evaluated in six studies which met the inclusion criteria.

Humphries et al[6] examined the effect of mutations in three different genes in the development of coronary heart disease in 409 individuals with clinically defined definite FH. Clinical coronary artery disease was defined as a definite myocardial infarction or having undergone a coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, having angina with an ischaemic resting echocardiogram, or a reported angiogram showing clinically important stenosis. After adjusting for age, sex smoking and systolic blood pressure, compared to those with no detectable mutation, the odds ratio of having CHD for each mutation were as follows: (p=0.001 overall).

- *LDLR* mutation (any) OR 1.84 (95% CI 1.10 to 3.06)
- *APOB* (3500Q) OR 3.40 (0.71 to 16.36)
- *PCSK9* (374Y) OR 19.96 (1.88 to 211.5)

Overall, there was an 84% higher risk of CHD in those with an identified *LDLR* mutation compared with those with no detected mutation. There was also a relatively high frequency and extremely high risk of CHD in carriers of the p.D374Y.

Of particular note was the finding that the post-statin treatment lipid profile in *PCSK9* p.Y374 carriers was worse than in individuals with no identified mutation:

	***PCSK9* p.Y374**	**No mutation**	**p-value**
Mean LDL-C mmol/l (sem)	6.77 (1.82)	4.19 (1.26)	p=0.001
Mean HDL-C mmol/l (sem)	1.09 (0.27)	1.36 (0.36)	p=0.03

Adapted from published paper[6]

Clinical characteristics of index individuals were identified in the study by Damgaard et al[11] reviewed for question 1. Coronary artery disease below the age of 60 was recorded by mutation status as follows:

LDLR	**Apo B**	**No mutations**
24.8%	31.3%	22.3%

Adapted from published paper[11]

The association of genetic mutations typical of FH with atherosclerosis in the coronary vessels in individuals with severe hypercholesterolaemia and a family history of early cardiovascular disease was estimated from a sample of 235 individuals[32]. FH was diagnosed according to a analysis of the *LDLR* or *APOB* genes. Coronary atherosclerosis was evaluated by performing a thoracic CT and exercise stress test. Coronary calcification was present in 75% of FH men compared with 44% of mutation negative men (OR 3.90, 95% CI 1.85-8.18; p<0.001) and in 53% of the FH women compared with 31% in the mutation negative women (OR 2.65, 95% CI 1.14-6.15; p<0.01).

Forty two FH men, 66 mutation negative men, 32 FH women and 36 mutation negative women had an interpretable exercise stress test. Positive exercise stress test was present in 38% of the FH men compared with 9% of the mutation negative men (OR 6.15, 95% CI 2.16-17.49; p<0.01) and in 22% of FH women compared with 6% of the mutation negative women (OR 4.76, 95% CI 0.91-24.85; p=0.06). The exercise stress tests were positive only on the basis of ECG criteria and none of the individuals complained of angina-like chest pain during the test.

Data on another large cohort of individuals with FH and their unaffected relatives were collected through genetic cascade screening and examined for the influence of different mutation of the *LDLR* gene on lipoprotein concentrations and the risk of CVD[33]. In this study cardiovascular disease was defined as angina assessed with electrocardiographic exercise testing, 70% stenosis assessed by coronary angiography, myocardial infarction or performance of coronary bypass or PTCA. The results of interest for this review are as follows:

Table 5 Risk of coronary artery disease in individuals with FH compared to unaffected relatives

		Unadjusted		Adjusted for age and sex	
All mutations	**n**	**RR**	**95% CI**	**RR**	**95% CI**
	608 carriers compared with 1087 non-carriers	4.00	2.83-5.65	8.54	5.29-13.80

Adapted from published paper[33]

Ninety-eight unrelated Belgian individuals with a family history of autosomal dominant hypercholesterolaemia were tested for *LDLR* mutations[34]. When the mutation positive and negative individuals were compared the following results were reported:

	Mutation +ve	Mutation –ve	p-value
Total	24	61	
Coronary heart disease*	7 (29.2%)	19 (31.1%)	ns

*CHD included
1. a medical history of coronary ischaemic heart disease documented by electrocardiography and/or cycloergometry
2. a history of acute MI
3. having undergone a CABG or PTCA.

Adapted from published paper[34]

TC, LDL-C and HDL-C were significantly different between the two groups (p=0.0025, 0.002, and 0.03 respectively).

Two hundred and seventy three individuals with severe hypercholesterolaemia (>95th percentile) and a family history of early cardiovascular disease were genetically tested for FH and evaluated by ultrasonographic measurement of intima media thickness in the carotid and femoral arteries[35]. The mean age of mutation negative

men was 46.6 (sd.3) years and FH men was 44.8 (sd 10.8) years; NS. The mean age of FH women was 46.0 (sd 11.9) years and 51.5 (sd 11.0, p=0.01) years.

Table Results for mutation positive FH and mutation negative individuals

	Mutation +ve	**Mutation –ve**	**p-value (unadjusted)**
Men			
Mean carotid artery IMT (mm) ± sd	1.27±0.47	1.00±0.40	p<0.001
Mean femoral artery IMT (mm) ± sd	1.30±0.53	1.08±0.46	p=0.01
Women			
Mean carotid artery IMT (mm) ± sd	1.04±0.45	0.93±0.33	p=0.15
Mean femoral artery IMT (mm) ± sd	1.05±0.49	0.84±0.32	p=0.01

Adapted from published paper[35]

Another study which evaluated carotid intima-media thickness and plaque as predictors of cardiovascular events in individuals with FH was conducted by Tonstad et al[36]. Participants were non-smoking men and women between the ages of 26 and 46 years with a DNA based diagnosis of FH and no known cardiovascular disease. Controls were non smoking individuals from the locale who were matched to each case by age (±3 years) and sex and BMI. The results were as follows:

	Men		**Women**	
	FH n=41	**Controls n= 41**	**FH n=38**	**Controls n=38**
Carotid IMT				
Mean far wall (mm)(sd)	0.61(0.13)	0.55 (0.14)*	0.52 (0.09)	0.63 (0.07)
Max far wall (mm) (sd)	0.74 (0.15)	0.68 (0.16)	0.65 (0.11)	0.65 (0.09)
Carotid bifurcation IMT				
Mean far wall (mm) (sd)	0.81 (0.15)	0.74 (0.19)**	0.74 (0.17)	0.66 (0.15)**
Max far wall (mm) (sd)	1.08 (0.27)	0.97 (0.35)**	0.99 (0.31)	0.85 (0.23)**
Carotid plaque (yes/no)	22/19	8/35***	21/17	3/35***

*p=0.03; **p=0.01; ***p=0.0001 compared with FH

Adapted from published paper[36]

A study among 120 French Canadian men aged <60 years who were heterozygous for FH and a group of 280 men without FH provides some data on CAD risk among diagnosed individuals with FH[37]. All individuals in this study were screened for *LDLR* mutations .

1 The outcomes of interest include:

	Mutation+ve (n=120)	Mutation –ve (n=280)	p-value
Number of diseased vessels	**n (%)**		
0 vessels with >50% stenosis	6 (5%)	31 (11%)	p=0.0001
1 vessel with >50% stenosis	27 (22.5%)	98 (35.0%)	p=0.005
2 vessels with >50% stenosis	30 (25%)	72 (25.7%)	p=0.96
3 vessels with >50% stenosis	28 (23.3%)	58 (20.7%)	p=0.65
4 vessels with >50% stenosis	29 (24.1%)	21 (7.5%)	p=0.0001

2 Adapted from published paper[37]

3 Other outcomes of interest were:

	Mutation +ve (n=120)	Mutation –ve (n=280)	p-value
Mean BMI (sd)	26.0 (0.3)	27.9 (0.3)	p=0.0001
Mean waist circumference (sd)	92.3 (0.8)	97.6 (0.7)	p=0.0001
Mean waist-to-hip ratio (sd)	0.92 (0.01)	0.96 (0.01)	p=0.0001
Fasting insulin (mμ/L) (sd)	16.2 (0.8)	19.0 (0.7)	p=0.02

4 Adapted from published paper[37]

5 *3.2.5.3* ***Health economic evidence***

6 Please see the health economic review in Chapter 4 and the full economic modelling
7 in Appendix E.

4 Identification strategies

4.1 Introduction

The prevalence of FH in the UK population is estimated to be 1 in 500, which means that approximately 110,000 people are affected. Most people with FH are undiagnosed. However, it is clear that early detection and treatment can reduce morbidity and mortality. It is therefore important to determine which system of case finding for FH is the most clinical and cost effective.

4.2 Comparison of identification strategies

4.2.1 Recommendations

Unless otherwise indicated, recommendations are relevant for individuals with possible or definite FH. Recommendations are also applicable for individuals with both heterozygous and homozygous FH, unless otherwise indicated.

Please note, numbering is as in the NICE guideline.

1.2 Identifying individuals with FH using cascade testing

1.2.1 Systematic methods should be used for case identification of FH.

1.2.2 All individuals with FH should be referred to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing.

1.2.3 Healthcare professionals should discuss the implications of cascade testing with individuals.

1.2.4 Cascade testing using a combination of lipid concentration measurement and DNA testing should be used to identify relatives of index cases with a clinical diagnosis of FH.

1.2.5 In families in which a mutation has been identified, the mutation should be used to identify affected relatives.

1.2.6 In the absence of a DNA diagnosis, cascade testing using lipid measurements should be undertaken.

1.2.7 To diagnose FH in relatives, the gender and age-specific probabilities based on LDL cholesterol concentrations in Appendix E (of the NICE guideline, or Appendix F of the full guideline) should be used. Simon Broome LDL-C criteria should not be used.

1.2.8 The establishment and use of a nationwide family based follow-up system is recommended to enable comprehensive identification of affected individuals.*

* See also the Department of Health FH Cascade Testing Audit Project, available at www.fhcascade.org.uk

4.2.2 Evidence statements on the effectiveness of different identification strategies

Key clinical question:

What is effectiveness (defined as case identification and cost-effectiveness secondarily) of the following strategies for identifying people with FH:

- GP note searching using electronic data bases identifying individuals with
  (i) history of early MI (<60 years) and total cholesterol (TC) >7.5mmol/l
  (ii) family history of ischemic heart disease and hypercholesterolemia, or
- secondary care registers (i) within coronary care units through identifying individuals with
  (i) history of early MI (<60 years) and total cholesterol (TC) >7.5mmol/l or
  (ii) identification of individuals through pathology registers aged <60 years and TC>9 mmol/l and LDL-C>5.5mmol/l or;
- cascade testing?

Question 3 of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
A single retrospective study[38] in approximately 12,000 individuals in one GP practice demonstrated that electronic note searching identified 402 records that upon case note review found 2 previously unidentified individuals with definite FH and 4 previously unidentified individuals with probable FH [2+] No evidence using secondary care registers was identified. A report[21] of the first 5-years of a national screening programme based in the Netherlands using a computerised register of pedigrees found that in relatives of probands with a positive DNA diagnosis 2039 out of 5442 were identified as having the same FH mutation as their proband. On average, 20 1st and 2nd degree relatives were tested per proband in whom the diagnosis of FH was confirmed in 8 (37%). At the time of identification of the mutation, 667 of these adults with FH (39%) received some form of lipid-lowering treatment; 1 year later, this had increased to 93%. [2+] A Health Technology Assessment report[39] which compared modelling of cascade testing of lipid measurements of 1st degree relatives vs population screening concluded that cascade testing is an efficient and cost effective means of case finding for FH [1+] A retrospective study[40] of cascade testing using lipid measurements in two specialized hospital clinics identified 285 1st degree relatives from 259 probands with definite FH. 200 relatives were tested of whom 121 (60%) were found to have FH, demonstrating the feasibility of cascade testing using direct contact by a clinic nurse. [2+] A prospective study[41] using cascade testing of lipid measurements from a specialized hospital clinic covering a defined geographical area identified 227 eligible adult index cases who had 1075 1st degree relatives. Using indirect contact via the probands 23% of adult relatives who lived within the catchment area were tested of whom 29% had lipid concentrations indicative of FH. 97% of children/young people under 18 years, where the parents were directly approached were tested, of whom 32% had lipid concentrations indicative of FH [2+]	<u>Primary care registers</u> There is currently no evidence that note searching in primary care is effective. Because of the high proportion of expected cases already identified in this particular practice the results may not be generalisable to the wider NHS. Primary care has a key role in the diagnosis and identification of individuals with FH and the NICE guidelines on cardiovascular risk modification can only increase the importance of this role. It is therefore necessary to identify the most effective way of finding individuals with FH in a primary care setting and a research recommendation was drafted on the use of primary care records for case finding. <u>Secondary care registers/records</u> No evidence was identified and a research recommendation was drafted. <u>Cascade testing</u> A national programme of cascade testing is feasible and would result in an improvement in clinical practice (with associated higher rates of treatment). Two studies showed the feasibility of cascade testing in the UK, and also showed the value of approaching relatives directly. The average age of diagnosis is reduced using this strategy. Overall, the evidence supported the use of national cascade testing as this would not then be limited by geographical boundaries. The evidence supported a direct approach to relatives. A nationwide, proactive, systematic approach to cascade testing is recommended but will need to be evaluated.

1

4.2.3 Evidence summary on the effectiveness of different identification strategies

4.2.3.1 Methods of the clinical evidence review

The searches for this review were not restricted by study type or age of individuals.

- Identified: 380
- Ordered: 16
- Included: 6
- Excluded: 10

4.2.3.2 Clinical evidence

GP note searching

A study[38] was conducted to assess the utility of combined computer and notes-based searches in a GP practice to identify index cases of FH. This retrospective chart review used computer searches in a South London practice with 12,100 individuals. Four searches were done using practice coding levels:

1. for ischaemic heart disease (IHD) in the record
2. for lipid disorder in the record
3. for statin prescribing in the record, and
4. for cholesterol search in the record.

Selected notes were reviewed by a GP and consultant lipidologist to give a Dutch score for the probability of FH.

Case finding for FH in this practice identified 12 individuals scoring more than 8 (definite), eight individuals scoring between 6 and 8 (probable) and after exclusions, 47 scoring between 3 and 5 (possible) on the Dutch scale. Of the 12 definite cases 2/12 (16.6%) and 4/8 (50%) of the probable cases were not already known to a secondary care lipid clinic. A combined search of IHD, lipid diagnosis or statin use showed a sensitivity of 100% and a yield of 5.83%. In this study the combined search plus the use of cholesterol >7.0mmol/l showed a sensitivity of 100% and a

yield of 4.98%. A total of 3.3% of the registered practice population had their notes searched. It took approximately half an hour to search a set of notes. The combined and cholesterol search required 20.1 sets of notes to be searched to find one case of definite or probable FH.

This study demonstrated that is it possible to use note searching to define a population of FH individuals in primary care. Although results showed that the combined search resulted in the highest sensitivity and yield, the authors did not recommend ignoring the cholesterol search as, "… there are bound to be individuals in other practices whose elevated cholesterol is the only marker of the diagnosis." The authors also recommended that where records are incomplete face to face interviews would be required to establish a diagnosis. In addition, the effect of variable practice coding levels and information derived from individuals must be considered.

Secondary care registers

No evidence was identified.

Cascade testing

Targeted testing of relatives of index cases of individuals with definite FH is known as cascade testing.

A well documented active case finding program for individuals with FH was established in the Netherlands in 1994. In a narrative paper Defesche et al[42] described the Dutch method for identification of individuals with FH which incorporates active family testing supported by DNA diagnostics. The program is based on principles for large scale screening programs which include the following:

- The condition should be recognizable at a latent or early symptomatic stage
- The natural history of the condition should be understood
- The condition must be considered to be an important health hazard
- A suitable diagnostic test should be available
- The diagnostic test should be acceptable
- The cost of case finding should be economically balanced
- Facilities for diagnosis and treatment should be available

- There should be consensus on whom to treat
- Acceptable treatment for individuals with recognized disease should be available
- Case finding should be an ongoing process.

Individuals in the Netherlands with a clinical diagnosis of FH are referred for DNA testing. Once a mutation has been identified the individual becomes an index case. With the help of the index case, information is collected on all family members and these individuals are tested for the mutation of the index case and for non fasting lipid concentrations. During the years 1994 to 1998 over 5400 individuals were enrolled in the identification program. In this group, starting from 237 index cases, more than 2000 individuals were diagnosed as having FH.

The Umans-Eckenhausen et al[21] (also reviewed for Question 1 on the diagnosis of FH) described the Dutch program of active family testing supported by DNA diagnostics. A clinical diagnosis was made according to a uniform diagnostic protocol which included LDL-C, physical signs, and personal and family history in a scoring system. All individuals with clinical FH were tested for DNA mutations. Index cases were those with both a clinical diagnosis and a confirmed DNA mutation. First degree relatives of index cases were contacted by a specialist nurse after written consent was obtained; 5442 relatives of 237 people with FH were tested; 2039 individuals were identified as heterozygous by LDL-C receptor gene mutation analysis. At the time of examination, 667 of these adults with FH (39%) received some form of lipid-lowering treatment; 1 year later, this percentage had increased to 93%.

A Health Technology Assessment[39] evaluated screening for hypercholesterolaemia versus case finding for FH. Danish population screening of school entrants by testing capillary blood samples was shown to be more efficient than screening for FH by first identifying children with a positive family history. However, the prevalence of FH in this population was higher (about 1 in 300) compared to the UK (1 in 500). Population screening in an American study was not considered cost effective. Population screening cost US $1600 per new case identified while tracing relatives of identified index cases cost US $400. Data reviewed for family tracing /case finding (cascade testing) was poorly described and the paucity of studies made it

difficult to reach firm conclusions about relative effectiveness or cost of different strategies. However the HTA economic model concluded that cascade testing would be the most effective and least costly option of identifying undiagnosed FH. Screening all 16 year olds using clinical methods of diagnosis appeared to be similarly cost-effective, assuming that such screening was acceptable and that at least 55% of those invited for screening attended. See also Section 4.2.3.3 and Appendix E for further details.

Researchers at the University of Manchester[40] used detailed family history records of FH probands to identify first degree relatives. Two hundred first degree relatives were tested and 121 (60%) were found to have inherited FH. To detect a similar number by population screening over 60,000 tests would be required and only a few of these individuals would have been detected had cholesterol testing been restricted to those with other risk factors for coronary heart disease. The newly diagnosed individuals were younger than the probands and were generally detected before they had clinically overt atherosclerosis. Concentrations of serum cholesterol were respectively 8.4 (1.7 SD) mmol/l and 8.1 (1.9 s) mmol/l in affected men and women and 5.6 (1.0 sd) mmol/l and 5.6 (1.1 mmol/l in unaffected men and women. Screening for risk factors would have failed to identify most of the affected relatives in whom hypertension, diabetes mellitus, cigarette smoking and obesity were uncommon.

Another UK based study[41] conducted cascade testing among individuals attending the Oxford lipid clinic and meeting the diagnostic criteria of the Simon Broome Familial Hyperlipidaemia Register for definite or probable FH. Index cases in this study were asked to contact their first degree relatives. The positive diagnostic rate among those resident in the Oxfordshire area was 29% (15/52) in adults and 32% (36/113) in children. DNA testing was not done. Testing increased prevalence by 14.4% from 0.58/1000 (95% CI 0.52-0.65) to 0.67/1000 (95% CI 0.60-0.73), representing 33.5% of predicted cases. The authors concluded that cascade testing conducted by a specialist hospital clinic within its population catchment area did not substantially increase the prevalence of diagnosed FH. For cascade testing to identify most individuals with FH, a comprehensive national programme would be needed.

A study conducted by Starr et al[10] aimed to demonstrate that the plasma LDL-C concentrations used as diagnostic criteria for FH probands in the general population are too stringent for use when cascade testing in 1st degree relatives, given that they have a 50% probability of having FH. A Bayesian model of LDL-C cut offs for 1st degree relatives was shown to have a higher sensitivity than MedPed for identification of potential FH individuals. Serum LDL-C results of 1st degree relatives of FH probands in the Netherlands, Denmark and Norway were compared according to both the Bayesian model and the MedPed model. In the Netherlands, the cut offs performed best for the youngest cohort (aged under 15 years) where sensitivity was 85% and specificity 93%. Sensitivity decreased with age from 85% in the younger cohort to 38% in over 55 year olds. This means that specificity dropped rapidly after 14 years of age (93% to 85%) and then remained fairly constant at between 83-86%. The accuracy (as assessed by Youden's index) was 0.53, but the cut offs performed significantly better amongst younger 1st degree relatives (aged under 45 years) compared to those older (Youden's Index, 0.59 vs. 0.33 $p<0.001$). The Norwegian and Danish values were adjusted to take into account the higher concentrations seen in these countries. The pattern of greater accuracy in younger age groups seen in the Dutch cohort was mirrored in the Norwegian data whilst for the Danish cohort the pattern was reversed and sensitivity increased with age. Overall the Youden's index in the Norwegian data was 0.68 and in the Danish data was 0.64, 84% and 81% accuracy respectively. Overall the LDL-C cut offs gave a significantly better performance ($p<0.001$) than the MedPed cut offs when tested on the Dutch sample and at least as well for the Norwegian and Danish data sets. The sensitivity was higher for all datasets when using the LDL-C cut offs and specificity consistently lower.

4.2.3.3 ***Health economic evidence***

Published analyses

The literature search retrieved 185 abstracts and 10 papers were ordered for further consideration. Only five papers met the inclusion criterion, all of which were published between 2000 and 2004. One of the publications[43] was a follow up to the Health Technology Assessment report undertaken in 2000[39] by the same authors, and only the updated version is reported here.

Marks et al[43] undertook a cost-effectiveness analysis from the NHS perspective which considered the different approaches to screening for FH patients aged between 16 and 54 years. Strategies considered were universal screening, opportunistic screening of patients consulting for unrelated reasons in primary care, opportunistic screening of patients admitted to hospital with premature myocardial infarction and systematic screening of first degree relatives of people with diagnosed familial hypercholesterolemia. They used life table analysis to construct the life years gained and data from the Simon Broome Register[44] aided in the construction of life tables. Tracing of family members was the most cost-effective strategy with an estimated ICER of about £3,097/LY. Universal population screening was the least cost-effective strategy with an estimated ICER of £13,029/LYG. They also found that it was more cost-effective to screen younger people and women. There was no incremental analysis comparing these strategies against each other or comparing clinical versus diagnostic testing.

Marks et al[45] also undertook a cost-effectiveness study over a 10 year period of the different strategies for FH screening. The strategies compared were family tracing strategy, in which a clinic nurse collects family histories from index cases, and universal screening of 16 year olds. They used a combination of life table analysis and decision analysis to estimate the life years gained from each strategy. They concluded that screening 16 year olds will avert 11.7 deaths over 10 years from 470 new cases identified. The cost per case identified and treated was £13, 141 and cost per death averted was about £1.6m. Family tracing would result in 13,248 new cases identified and 560 deaths averted over 10 years. The cost per case identified and treated was £3,505 and cost per death averted was £3,187. This result was explained by the fact that using family screening only needed 2.6 people to be screened in order to identify one positive case, whereas for universal screening of 16 year olds, about 1370 people were needed to find one positive case. The analysis was assessed using the Drummond checklist as being well conducted with appropriate methodology used by the authors. However an incremental analysis between the two methods was not undertaken. However, in previous work, the authors had shown that the two identification methods have a similar lifetime cost per life year gained.

Wonderling et al[46] evaluated the cost-effectiveness of a Dutch genetic screening programme of FH patients compared to no screening. They used data from the Dutch screening programme in the year 2000. New cases identified by the screening programme gained an average of 3.3 years of life (undiscounted) and 0.9 years discounted. The model estimated that 26 myocardial infarctions would be avoided for every 100 persons aged between 18 and 60 years who were treated with statins. The cost per new case identified was US$7, 500. The cost per life-year gained was US$8, 800. The result was sensitive to the price of statin treatment and the number of life-years gained. If all of these parameters were set to the value most unfavorable (worst case scenario), within their respective range, the incremental cost-effectiveness ratio (ICER) of the genetic identification programme relative to no intervention rises to rises to $38, 300 per life-year gained. This study was assessed as being of good methodological quality, with excellent internal validity. However, the generalisability of the result to the context of the NHS is unclear due to different resource use valuations between countries.

Marang-van de Mheen et al[47] evaluated the cost-effectiveness of five DNA-based genetic screening programmes in FH patients compared no screening. The methods compared were 1) treating all individuals with a cholesterol level above the 95th percentile of the general Dutch population, 2) individuals who fulfil the treatment criteria in the Dutch Institute on Health Care Improvement (CBO) consensus guideline on hypercholesterolemia, 3) as in 1, but only if untreated at screening, 4) as in 2, but only if untreated at screening, 5) all FH positive patients. The authors used data from the Dutch screening programme and combined this with Framingham risk functions to estimate patient survival and costs. Results were evaluated for each strategy using cost per life year gained (LYG). Treating all FH positive patients had an estimated ICER of about €31,260/LYG. All FH positive patients with elevated cholesterol concentrations above the 95th percentile of the Dutch general population had an estimated ICER of €29,957 per LYG, individuals who fulfil the treatment criteria in the Dutch Institute on Health Care Improvement (CBO) consensus guideline on hypercholesterolemia had an estimated ICER of €24,376. Those individuals with a cholesterol level above the 95th percentile of the general Dutch population and untreated at screening had an estimated ICER of €30,558 and lastly untreated FH+ as in cholesterol consensus had an estimated ICER of €27,700. The

paper was assessed as being of fair quality using the Drummond checklist, but had weaknesses, including the lack of discounting. Also, the generalisability of the result to the NHS is unclear. Furthermore, the lack of incremental analysis between options is not justified.

In conclusion, screening programmes using DNA based methods have been found to be cost-effective.

Modelling of cascade testing - analysis

Above we have summarised the results of four studies, found in a literature search, which compared the cost-effectiveness of different identification methods in patients with FH. The GDG requested a de novo economic analysis with an NHS costing perspective to help inform the guideline recommendations about cascade screening. The following is an overview of this economic modelling analysis. The details the model and the economic analysis can be found in Appendix E.

A decision tree was constructed in Excel to estimate the numbers of "affected patients". The standard method of clinical diagnosis and identification of affected relatives using elevation of LDL-C concentrations is the base line comparator, and is referred to in this model as the Simon Broome criteria, "Cholesterol" method. The UK FH Cascade Audit Project (FHCAP) has shown that, 30% of the patients currently being treated in lipid clinics have definite FH (DFH), 60% have possible FH (PFH), and 10% fail to meet either criterion[48]. Only patients meeting the criteria of DFH or PFH were included for cascade testing. The second method is based on the identification of an FH-causing mutation by molecular genetic methods, called the "DNA" method in this model. Here, only patients with an identified mutation were included for cascade testing, and the relatives tested for the family mutation. This is the model used in the Netherlands[21].

- Strategy 1:
  Cascade testing is carried out from all DFH and PFH probands. All relatives with elevated LDL-C concentrations are offered appropriate treatment and used as secondary index cases for further cascade testing .

- Strategy 2:
  Following DNA testing of the probands, cascade testing of relatives is undertaken in all mutation-positive probands i.e. using the DNA information to offer appropriate lipid-lowering treatment and to select those from whom secondary cascading will be undertaken.
- Strategy 3:
  Following DNA testing of the probands, cascade testing of relatives is undertaken in all mutation-positive probands , and cascade testing is also undertaken in the relatives of DFH probands using measures of LDL-C concentrations to identify “affected” relatives for treatments and for secondary cascading (DNA+DFH method).
- Strategy 4:
  Cascade testing is undertaken in all mutation-positive probands as above and additionally from both DFH and PFH probands using measures of LDL-C concentrations to identify “affected” relatives for treatments and for secondary cascading (DNA+DFH+PFH method[L1]).

In each strategy, all individuals with elevated LDL-C are offered lipid-lowering therapies. For the purposes of the analysis a true-positive index case is defined as one who has a monogenic cause of FH who is selected for cascade testing, while a false-positive case is defined as one who does not actually have a monogenic cause but who is selected for cascade testing (i.e. fulfils the clinical criteria of FH but the cause is due to polygenic plus environmental causes). A false-negative subject is one who is not selected for cascade testing but who actually does have a monogenic cause of FH, and a true-negative subject is defined as one who does not actually have a monogenic cause, and who is not selected for cascade testing (i.e. does not fulfill the clinical criteria of FH).

For relatives, a true-positive is defined as one who has a monogenic cause of FH who is correctly identified by the strategy in use (i.e. by elevated LDL-C concentrations or by being a carrier for the family mutation) and who is offered treatment and selected for cascade testing, while a false-positive case is defined as one who does not actually have a monogenic cause but who is offered treatment and selected for cascade testing (i.e. has LDL-C concentrations above the diagnostic cut-

off for age and gender but the cause is due to polygenic plus environmental causes). A false-negative subject is one who actually does have a monogenic cause of FH but who is not offered treatment or selected for cascade testing (i.e. with LDL-C concentrations below the diagnostic cut-off for age and gender due to "protective" polygenic plus environmental causes), and a true-negative subject is defined as one who does not have a monogenic cause, and who is not offered treatment or selected for cascade testing (i.e. with LDL-C concentrations below the diagnostic cut-off for age and gender or who does not carry the family mutation).

In the model it is assumed that 65% of the first degree relatives and 60% of the second degree relatives will agree to testing. In FHCAP, these values were 85% and 80% respectively. Data on sensitivity and specificity of the Cholesterol method were taken from Hadfield 2007 and for the DNA method, the mutation detection rate in DFH was taken to be 80%[8,6,49]. Unit costs for health care professional time, blood tests, and invitation letters were taken from PSSRU[50] and GDG estimates.

All index cases, and all relatives with elevated LDL-C levels were offered statin treatment. True and false positives were offered high intensity statins while true and false negatives were offered low intensity statins for their elevated lipids for both index cases and relatives. A Markov model was developed to estimate the incremental cost per quality adjusted life year (QALY) of lifetime treatment with high intensity statins (atorvastatin 80mg and simvastatin 80mg) compared with low intensity statins (simvastatin 40mg) from a UK NHS perspective. The baseline age for the index case was 50 years and the age for the relative was 30 years.

The intermediate outcomes included in the model include MI, stroke, heart failure, revascularisation, angina and death from CVD and other causes. Effectiveness data were drawn from the updated Simon Broome register[51]. We also used data from TNT[52] and IDEAL[53] which were meta-analysed. The model makes the conservative assumption that the all cause mortality rate in the modelled population, is twice that of the general population. Health state utility values were taken from published sources (Appendix E). All cause mortality rates are from the Government Actuarial Department[54]. The model makes the conservative assumption of no adverse events from treatment using high intensity statins. Costs of drugs were taken from Drug tariff Dec 2007[55]. Costs of cardiovascular events were taken from the NICE TA94 on Familial hypercholesterolaemia: full guideline DRAFT (February 2008)

statins[31]. In order to reflect social values for time preference as is standard in economic models; costs and QALYs have been discounted at 3.5% as recommended by NICE[56]. All of these and other model assumptions have been tested in sensitivity analyses.

Modelling of cascade testing - results

The base case results are presented below, and cost-effectiveness is assessed against a threshold of £20,000/QALY. The table below shows the lifetime costs and QALY gains per patient by strategy.

The Cholesterol method, using LDL-C levels for identification of affected and non affected relatives is ruled out by simple dominance; compared to DNA, this method results in more cost and fewer QALYs (£27,768 vs. £17,092 and 4.40 vs. 7.28 QALYs respectively). The model results indicates that DNA with cascading from both mutation negative definite FH individuals and individuals with possible FH is cost effective when compared to DNA and cascading from mutation negative definite FH individuals alone (strategy 4 compared with strategy 3). The estimated ICER is about £17,000/QALY.

The second most cost effective strategy is that of using DNA mutation information for identification in all families where it was available and cascading only from mutation-negative definite FH individuals using LDL-C concentrations.

The least efficient strategy is the use of the Cholesterol method, i.e. LDL-C concentrations alone.

The cost effectiveness was however somewhat sensitive to assumptions about age and the costs of the drug combinations used. Assuming a £20,000/QALY threshold, using DNA plus cascading from both mutation negative definite and possible FH individuals would not be cost effective, if the initial age of index cases was increased to 65 years, with a concomitant increase in the age of the identified relatives to 50 years, as the ICER will rise to about £41,300/QALY. The model was also slightly sensitive to the price of drugs which is determined by combination of drugs used and the proportions of patients taking each drug.

Table 6 Base case results for the Incremental cost effectiveness of the four strategies for cascade screening

Strategy	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (QALY)	ICER (£/QALY)
DNA (strategy 2)	£17,092	7.28	-	-	-
DNA + Chol M-ve DF (strategy 3)	£18,617	7.53	£1,526	0.25	£6,034
Cholesterol (strategy 1)	£27,768	4.40	-	-	-
DNA + Chol M-ve DF +PFH (strategy 4)	£30,265	8.21	£11,648	0.68	£17,021

In conclusion, using a threshold of £20,000/QALY, the most cost effective method for cascade screening was using DNA mutation information and cascading from both definite and possible FH mutation negative individuals using LDL-C levels with an estimated ICER of about £17,000/QALY compared with DNA and cascading from mutation negative definite FH individuals alone. All methods involving DNA testing are cost effective when compared to using LDL-C levels.

5 Management (pharmacological treatment)

5.1 Introduction

Current clinical management of FH routinely includes drug treatment with HMG CoA (hydroxymethylglutaryl co-enzyme A) reductase inhibitors or statins. When statins are not tolerated bile acid sequestrants, fibrates, nicotinic acid and dietary measures may be used. Most recently ezetimibe has been introduced for the treatment of FH. Although the heterozygous condition affects about 1 in 500 of the UK population, there is little published data about the risks of coronary heart disease in treated heterozygous individuals and it would no longer be ethical to conduct placebo controlled trials to obtain more data. Therefore, it is necessary to rely upon the few studies conducted before the use of statins became usual practice to evaluate the effectiveness of monotherapy in adults with FH in randomized control trials.

In 1999, the Scientific Steering Committee of the Simon Broome Register published statistics on the largest cohort of individuals with heterozygous FH (FH) to date[57]. This report divided the person-years observation into two periods: before 1 January 1992 and from 1 January 1992 onward, by which date statins were being widely prescribed for people with FH. Although there was no evidence of a substantial decline in coronary mortality across all ages at that time, there was a large reduction in mortality in individuals aged 20-59 with relative risk declining from 8 (95% CI 4.8-12.6) to 3.7 (95% CI 1.6-7.2) (not statistically significant however, $p<0.081$). This corresponded to an absolute reduction from 523 to 190 in the annual excess number of deaths per 100,000.

5.2 Pharmacological treatment

5.2.1 Recommendations

Unless otherwise indicated, recommendations are relevant for individuals with possible or definite FH. Recommendations are also applicable for individuals with both heterozygous and homozygous FH, unless otherwise indicated.

Please note, numbering is as in the NICE guideline.

1.3.1 Drug treatment

Adults

1.3.1.1 Statins should be the initial treatment for all adults with FH.

1.3.1.2 Prescription of a potent statin should usually be considered when trying to achieve a reduction of LDL-C concentrations of greater than 50% (from baseline).

1.3.1.3 Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who would otherwise be initiated on statin therapy but who are unable to do so because of contraindications to initial statin therapy[*].

1.3.1.4 Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who are intolerant to statin therapy (as defined in section 1.3.1.8)*.

1.3.1.5 Ezetimibe, coadministered with initial statin therapy, is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who have been initiated on statin therapy when*:

- serum LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy and
- consideration is being given to changing from initial statin therapy to an alternative statin.

1.3.1.6 When the decision has been made to treat with ezetimibe coadministered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost*.

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[*] Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. London, National Institute for Health and Clinical Excellence (NICE). Technology Appraisal 132, 2007. www.nice.org.uk/page.aspx?o=289446.

1.3.1.7 For the purposes of this guidance, appropriate control of cholesterol concentrations should be based on individualised risk assessment in accordance with national guidance on the management of cardiovascular disease for the relevant populations (see 1.1.10) [*].

1.3.1.8 For the purposes of this guidance, intolerance to initial statin therapy should be defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised. Adverse effects include evidence of new-onset muscle pain (often associated with levels of muscle enzymes in the blood indicative of muscle damage), significant gastrointestinal disturbance or alterations of liver function tests*.

1.3.1.9 Prescribing of drugs for adults with homozygous FH should be undertaken within a specialist centre (see 1.1.2).

1.3.1.10 Individuals not achieving a reduction in LDL-C concentrations of greater than 50% from baseline should be referred to a specialist centre.

1.3.1.11 Individuals with FH should be referred to a specialist with expertise in FH if they are assessed to be at high risk, that is, they have

- established coronary heart disease; or
- a family history of premature coronary heart disease; or
- two or more other cardiovascular risk factors (for example, smoking, hypertension, diabetes, male sex).

1.3.1.12 Individuals with intolerance or contraindications to statins or ezetimibe should be referred to a specialist with expertise in FH for consideration for

[*] Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. London, National Institute for Health and Clinical Excellence (NICE). Technology Appraisal 132, 2007. www.nice.org.uk/page.aspx?o=289446.

treatment with either a bile acid sequestrant (resin), nicotinic acid, or a fibrate to reduce LDL-C concentrations.

1.3.1.13 Caution must be exercised when adding a fibrate or nicotinic acid to a statin due to the risk of muscle-related side effects including rhabdomyolysis. Gemfibrozil and statins should not be used together.

Children and young people

1.3.1.14 Children and young people diagnosed with, or being investigated for a diagnosis of, FH should be referred to a specialist with expertise in FH in an appropriate child focused setting.

1.3.1.15 The decision to defer or offer drug therapy for a child or young person should take into account their age, the age of onset of cardiovascular disease within the family, and presence of other cardiovascular risk factors including LDL-C concentrations greater than 6mmol/l in the child or young person.

1.3.1.16 Where the decision to initiate statins has been made in children and young people (aged 10 years upwards), those licensed for use in the appropriate age group should be chosen.

1.3.1.17 Statin therapy for children and young people with FH should usually be prescribed at the doses specified in the BNF for children.

1.3.1.18 In children with homozygous FH, LDL concentration may be lowered by lipid modifying medication and should be considered.

1.3.1.19 In exceptional instances (for example, where there is a family history of cardiovascular disease in early adulthood) a higher dose of statin, or more than one lipid modifying treatment, may be considered for the child/young person at a younger age.

1.3.1.20 In children and young people with FH who are intolerant of statins, other drug therapies capable of reducing LDL-C (bile acid sequestrants [resins], fibrates, or ezetimibe) should be considered.

1.3.1.21 Routine monitoring of growth and pubertal development in children and young people with FH is recommended.

Adults and children

1.3.1.22 Decisions about the choice of treatment should be made following discussion with the individual, and be informed by consideration of concomitant medication, co-morbidities, safety, and tolerability.

1.3.1.23 The decision to add a bile acid sequestrant (resin), nicotinic acid or a fibrate should be taken in a specialist centre following consideration of the need for a further reduction in LDL-C concentrations.

1.3.1.24 Vitamin supplementation should be considered for individuals on long-term treatment with bile acid sequestrants (resins).

1.3.1.25 Individuals experiencing unusual side effects should be referred to a specialist with expertise in FH.

1.3.1.26 Individuals prescribed nicotinic acid should receive advice on strategies that reduce flushing. This includes taking low initial doses with meals and/or non -steroidal anti-inflammatory drugs (NSAIDs) or aspirin 30 minutes prior to the first daily dose.

1.3.1.27 Baseline liver and muscle enzymes, including transaminases and creatine kinase respectively, should be measured before initiation of a statin. However individuals with raised liver or muscle enzymes should not routinely be excluded from statin therapy.

1.3.1.28 Monitoring of creatine kinase is not routinely recommended in asymptomatic individuals treated with a statin.

5.2.2 Evidence statements on the effectiveness of monotherapy in adults

Key clinical question:

What is the effectiveness in improving outcome in adults with FH of the following monotherapies (i.e.: statins versus placebo, resins (bile acid sequestrants) versus placebo, nicotinic acid versus placebo, fibrates versus placebo, fish oils (omega 3 fatty oils) versus placebo, ezetimibe versus placebo) in improving outcome in adults with FH?

Questions 8a-f of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
Statins lower LDL-C and TC in people with FH. There was no statistically valid data quantifying side effects in the FH population. [1+] The biochemical responses to statins in people with FH are comparable with those of other hyperlipaedaemic individuals. [1+] Bile acid sequestrants significantly reduce total cholesterol and LDL-C concentrations when compared with placebo. [2 studies; quality ratings 1+ and 1+][58;59] Nicotinic acid significantly reduces LDL-C, TC, and triglyceride concentrations when compared with placebo. HDL-C concentrations are also raised significantly with nicotinic acid therapy. [One study; quality rating 1+][60] There is good supportive evidence, based on a published systematic review, for the use of acetyl salicylic acid in reducing the severity of flushing related to the use of nicotinic acid. Indomethacin 100mg was also shown to significantly reduce the incidence of flushing due to nicotinic acid.[61] Fibrates significantly reduce LDL-C, TC, and triglyceride concentrations when compared with placebo. HDL-C concentrations are also raised significantly with fibrate therapy. [Two studies; quality ratings 1+ and 1+][62;63] No studies were identified for the use of omega 3 acid ethyl esters treatment in the FH population. Evidence from the post MI population showed that advice to increase consumption of oily fish reduced all-cause mortality [1++].[64] There was no evidence for the use of ezetimibe monotherapy in the FH population. See also NICE	Adults with FH should be treated with statins as initial therapy. The reviewed evidence showed that statins reduce both TC and LDL-C in adults with FH and adverse events are rare in the general population (based on evidence reviewed in the NICE TA[65]). Similarly, extrapolating from the general population, statins were associated with a lowering of coronary mortality. Evidence showed that nicotinic acid and fibrates affect outcomes other than LDL-C, including TG and HDL-C, so these may be additional factors in the clinical decision making around drug choice. The BNF states that: • resins affect the absorption of other medication, and this must be taken into account when prescribing, and • resins may affect vitamin absorption. However, these issues are similar to those as in the general population and are not specific to the use of these drugs for adults with FH. Recommendations were drafted to include the NICE TA ezetimibe recommendations[66] and to give clear and practical guidance to prescribers, recognising that clinicians need to be able to choose the most appropriate drugs in conjunction with the individual. A > 50% reduction in LDL-c was recommended on the basis of the ASAPS study (this being the therapeutic response associated with lack of progression of atherosclerosis). However, lipidologists should use their expert judgment when individualising treatment. Recommendations on the sequencing of different drugs were based on the consideration of indirect evidence and clinical experience, as no head-to-head trials were identified. Efficacy, safety, and tolerability were key factors considered.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
TA[10] The health economic model showed that high intensity generic statins are cost effective in the management of FH patients compared with low intensity statins. High intensity non generic statins are cost effective in the management of FH patients who are aged below 60 years.	The draft recommendations were written so as to alert prescribers to clinical factors (risk) and the response of LDL-C (biochemical response). It should be noted that people with FH may be prescribed drugs for lipid lowering at much earlier ages (see recommendations for drug use in children) and therefore, although the side effects may be rare, the duration of drug treatment may be much longer that in the general population. Therefore, safety and tolerability were key to the discussions on drug use and strategies were recommended to prevent and manage adverse effects based on both BNF guidance, and clinical and individual experience. <u>Ethnic groups</u> All FH patients are considered as high risk so no distinctions between subgroups should be made when treating with statins. .

5.2.3 Evidence summary on the effectiveness of monotherapy in adults

5.2.3.1 Methods of the clinical evidence review

For this review we included only randomised controlled trials conducted in the FH population. Search for statin monotherapy:

- Identified: 1113 studies
- Ordered: 166 studies
- Included: 16 studies
- Excluded: 150 studies

Search for monotherapy with bile acid sequestrants, fibrates, nicotinic acid, fish oil:

- Identified: 789 studies
- Ordered: 62 studies
- Included: 11 studies
- Excluded: 51 studies

5.2.3.2 Clinical evidence

Statins versus placebo

One systematic review met the agreed inclusion criteria. Marks et al (2002)[67] reviewed the evidence on diagnosis, natural history and treatment of FH. There were no placebo controlled trials identified which studied statin use in people with FH. A review of rosuvastatin treatment (Chong & Yim, 2002)[68] included abstracts, proceedings and unpublished data on file from the manufacturer and therefore did not meet NICE quality criteria for systematic reviews. Several of the studies specific to individuals with primary hypercholesterolemia or heterozygous familial hypercholesterolemia included in the Chong and Yim review also did not meet GDG inclusion criteria. Studies which did meet criteria have been reviewed individually.

Four studies were identified which included a simvastatin versus placebo phase in the treatment of individuals with FH. Phase 1 of a study conducted by Berger et al (1989)[69] in 44 South African individuals included a 4 week randomised placebo controlled dose response trial in which six different doses (2.5mg-80mg) were administered and then compared to placebo.

After 4 weeks of therapy the placebo group showed a 4.6% reduction in LDL-C; the simvastatin groups showed reductions of 14.9% (2.5mg), 31.7% (20mg), 44.6% (40mg) and 46.5% (80mg) (significance levels not given).

In a placebo controlled trial (LeClercq, 1989)[70]19 individuals received placebo or simvastatin tablets ranging from 2.5mg up to 80mg daily. On 20 mg simvastatin there was a 50% decrease at week 12 ($p<0.005$), a 47% decrease at week 77 ($p<0.05$) and a 42% decrease at week 104 ($p<0.04$). On 40mg simvastatin LDL-C concentrations were lowered by 37% ($p<0.005$), 41% ($p<0.005$) and 35% ($p<0.05$) at week 12, 77 and 104, respectively.

An Italian research team (Valerio et al, 1990)[71] evaluated the efficacy and tolerability of simvastatin 10mg versus placebo in a double blind RCT of 12 individuals with FH. At the end of treatment, the simvastatin treated group showed a significant ($p<0.001$) decrease in LDL-C (35%), and a 26% decrease in total cholesterol.

McDowell et al (1991)[72] studied the effect of simvastatin 10mg in 27 individuals with severe primary hypercholesterolaemia in a double blind randomised placebo controlled parallel group trial. LDL-C fell by 39% and total cholesterol fell by 32% ($p<0.05$ for both LDL-C and TC).

Simvastatin was well tolerated in all trials and appeared to be uniformly effective in reducing LDL-C as well as total cholesterol, triglycerides and Apo B concentrations.

A further double blind parallel, placebo controlled study (Hunninghake et al, 1990)[73] evaluated the safety and efficacy of pravastatin 40mg (on various dosing schedules) versus placebo. One hundred and ninety six individuals with primary hypercholesterolaemia were randomised to treatment or placebo. Significant reductions in both total and LDL cholesterol were observed in all three pravastatin treatment groups throughout the study ($p<0.001$). Pravastatin treatment reduced mean total cholesterol more than 15% from baseline and mean LDL cholesterol more than 19% from baseline as early as the end of the first week of treatment.

Bile acid sequestrants versus placebo

Cholestyramine versus placebo was evaluated by Wiklund et al in a Swedish study[58]. One hundred and twenty individuals with FH were randomized into three groups: pravastatin (10 mg for 6 weeks; 20 mg for 6 weeks), cholestyramine (24 g or highest dose tolerated) or placebo. The cholestyramine versus placebo group showed an LDL-C reduction of approximately 30%

after 12 weeks (mean±sd: 5.6±1.8 mmol/l versus 8.3±2.3 mmol/l). In the pravastatin group LDL-C was reduced by 28% after 12 weeks (5.9±1.5 mmol/l versus 8.3±2.3 mmol/l). At 12 weeks total cholesterol was reduced 24% in the cholestyramine versus placebo group (7.3±1.7 mmol/l versus 10.1±2.15 mmol/l and by 23% in the pravastatin versus placebo group (7.6±1.5 mmol/l versus 10.1±2.2 mmol/l). HDL-C concentrations were increased for the pravastatin group only and there were no significant changes in triglyceride concentrations. The differences between the placebo group and the two treatment groups were highly significant for reduction of LDL-C and TC ($p<0.001$). However, after 12 weeks there was no significant difference between the treatment groups. HDL cholesterol increased significantly on pravastatin ($p<0.01$); TGs were variable with no significant increase in any group at 12 weeks.

Another placebo controlled parallel study of cholestyramine and pravastatin 40mg per day was carried out by Betteridge et al[59] in 128 people with heterozygous FH. Pravastatin 40mg/day led to a 25% reduction in total cholesterol (mean±sem: 9.9mmol/l±1.3 baseline) and a reduction in LDL-C of 30% (mean±sem: 7.8mmol/l±0.3 baseline). Cholestyramine 24g/day led to similar reductions in concentrations of TC (23%; baseline mean±sem: 9.51mmol/l±1.23) and LDL-C (31%; baseline mean±sem: 7.6mmol/l±0.2). No consistent changes occurred in HDL-C. There was a small rise (18%; baseline 1.4mmol/l± 0.1) in TG with bile acid sequestrant therapy. The reductions in TC and LDL-C were similar when compared with placebo, $p<0.001$. There was no change in the concentration of high density lipoprotein cholesterol. Plasma triglyceride concentration fell but was not significantly different from placebo; however it was significantly different from baseline ($p<0.05$).

Nicotinic acid versus placebo

In a multicentre placebo controlled trial[60] 158 individuals with type IIa or IIb primary hypercholesterolaemia (115 FH individuals) were randomised to either placebo, nicotinic acid extended release 500mg bid, pravastatin 40 mg at bedtime or a combination of nicotinic acid 500 mg bid and pravastatin 40 mg for 8 weeks. Percent change was reported. LDL-C concentrations were 21% lower than placebo with nicotinic acid, 33% lower than placebo with pravastatin 40 mg, and 49% lower with combination therapy. At week 8 HDL-C concentrations were increased in relation to placebo by nicotinic acid (12%), pravastatin (13%) and combination therapy (16%). Total cholesterol decreased by 11.3% with nicotinic acid, 23.1% with pravastatin and 31.6% with combination therapy. TG decreases were as follows: 11.4% with nicotinic acid, 14.38 % with pravastatin and 34.9% with combination therapy. In

comparison with placebo, nicotinic acid, pravastatin and combination therapy was associated with significantly lower TC and LDL-C ($p<0.05$) and combination therapy was significantly lower than the other 3 treatments at all weeks measured ($p<0.05$). HDL-C was significantly higher at week 8 in all treatment groups ($p<0.05$) but there were no between group differences. Adverse events were less frequent in the pravastatin and placebo groups ($p\leq0.05$). Treatment with nicotinic acid had no statistically significant effects on triglyceride concentrations in relation to placebo but treatment with pravastatin and with combination therapy resulted in significantly lower triglyceride concentrations ($p<0.05$).

At the request of the GDG a systematic review on the use of acetyl salicylic acid (ASA) to control flushing related to nicotinic acid treatment was reviewed[61]. This review identified four studies specifically exploring the utility of ASA in preventing flushing due to nicotinic acid in healthy volunteers. Twenty-three studies using nicotinic acid where ASA was mandatory or optional within the protocol and four studies where ASA therapy was reported in most participants were also identified. Discontinuation rates with nicotinic acid commonly reported in the literature were up to 40%. However with the use of ASA discontinuation rates due to flushing were low (mean 7.7%). Indomethacin 100mg was also shown to significantly reduce the incidence of flushing following intravenous nicotinic acid.

Fibrates versus placebo

Two studies were identified which evaluated fibrates versus placebo in people with FH.

Brown et al[62] randomised 227 individuals with type IIa and IIb hypercholesterolaemia (181 and 46 respectively) to double blind treatment with either fenofibrate (100 mg three times a day) or matching placebo for 24 weeks. For the 92 type IIa individuals receiving fenofibrate there were significant reductions ($p<0.01$) in total cholesterol from 8.0mmol/l in placebo to 6.4mmol/l in the treatment group (18%); LDL cholesterol 5.7mmol/l in placebo to 4.5mmol/l in the treatment group (20%) and TG 2.3mmol/l in placebo to 1.3 in treatment group (38%). Mean plasma HDL-C increased by 11% ($p<0.01$) 1.2mmol/l in placebo to 1.4 in treatment group. Fenofibrate significantly ($p<0.01$) reduced mean plasma concentrations of TC, LDL-C and TG. Mean plasma HDL-C increased significantly ($p<0.01$).

The hypolipidaemic efficacy of ciprofibrate was evaluated in individuals with type II hypercholesterolaemia by Illingworth et al[63]. Twenty seven of the 31 participants were classified with type IIa phenotype. Individuals were randomised to placebo or ciprofibrate 50mg or 10 mg

for 12 weeks. Total and LDL cholesterol decreased 11% (8.0mmol/l to 7.2mmol/l; p<0.05) and 13% (6.1mmol/l to 5.3mmol/l; p<0.025) on the 50mg dose whereas HDL-C increased 8% (1.1mmol/l to 1.4mmol/l; p<0.01). TG fell by 22% (1.9mmol/l to 3.2 mmol/l; p<0.025). In individuals receiving 100 mg ciprofibrate total and LDL cholesterol fell by 20% (to 6.9mmol/l; p<0.005) and 24 %(to 5.1mmol/l; p<0.005) respectively. HDL-C increased 9.8% (1.4mmol/l; p<0.01) and TG decreased by 30% (to 0.8mmol/l; p<0.05).

Fish oils versus placebo

No studies were identified.

Ezetimibe versus placebo

No studies were identified.

5.2.3.3 ***Health economic evidence***

No relevant health economic studies were identified.

5.2.4 Evidence statements on the effectiveness of monotherapy in children

Key clinical question:

What is the effectiveness in improving outcome in children with FH of the following monotherapies (i.e.: statins versus placebo, bile acid sequestrants versus placebo, nicotinic acid versus placebo, fibrates versus placebo, fish oils (omega 3 fatty oils) versus placebo, ezetimibe versus placebo) in improving outcome in children with FH?

Questions 8a-f of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
Statins are effective in lowering LDL and TC, and raising HDL-C in children aged 8-18 years (numbers of children aged below 10 years were very small). [1+] In short-term studies of statin use in children there were no adverse effects in terms of growth rate or pubertal development. [1+] In short-term studies (up to 2 years) statins have not been associated with significant adverse effects in children aged 8-18 years. Longer term studies are not available. [1+] Bile acid sequestrant therapy is effective in lowering and LDL-C and TC in children aged 6-15 years. [1+] The palatability and side effects of bile acid sequestrants reduces compliance with therapy. [1+] The safety of bile acid sequestrants in children has not been evaluated for greater than 5 years. No studies were identified for nicotinic acid use in children. Fibrate therapy lowered TC and raised HDL-C concentrations in children ages 4-15 years in one small short-term study. [1+][74] In a short-term study[74] fibrates have not been associated with significant adverse effects with children ages 4-	Treatment for children with heterozygous FH should be started early, with general agreement that this should be at aged 10 years (based on the median age of the included study populations, and very limited data on the use of drugs in younger children). Evidence from post-mortem studies (not reviewed in this guideline) showed that atherosclerosis is not evident in children younger than 10 years, but is evident in older children so treatment should be initiated before significant atherosclerosis has developed. The evidence for children was more limited than for adults, so the recommendations were drafted to allow for the use of different drugs as first line, based on clinical judgment and patient and parent/carer preference. The age of onset of cardiovascular disease within the family and presence of other cardiovascular risk factors including LDL-C greater than 6 mmol/l in the child/young person should also be taken into account. As for adults, safety and tolerability were considered paramount and monitoring recommendations were agreed to be the same as for adults. Routine monitoring of growth and pubertal monitoring was also recommended, although the limited evidence does not show any disturbances in growth or pubertal development. This is standard paediatric care, as is monitoring of BMI/weight in adults, but the reasons for monitoring of growth/weight are different in children and adults (the effect on growth compared with overweight/obesity respectively). Parents may be concerned that the drugs will affect the child's growth, so any drug should be initiated in children only after a full, informed discussion. The use of nicotinic acid in children was not recommended as these drugs are not licensed in this age group.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
15 years. [1+] Longer term studies are not available. No studies were identified for fish oils use in children. No studies were identified for ezetimibe use in children.	

5.2.5 Evidence summary on the effectiveness of monotherapy in children

5.2.5.1 Methods of the clinical evidence review

Inclusion criteria for Q7b, 8a-f, 9a-f specified randomised controlled trials conducted in the FH paediatric population. The paediatric population was included in the original search terms for statins (1113) and the searches for other cholesterol lowering drugs (789).

- Identified: 1902 total
- Ordered: 34 studies
- Included: 7 studies
- Excluded: 27 studies

Studies for each comparison were as follows:

- statins versus placebo – 4 studies
- bile acid sequestrants versus placebo – 2 studies
- nicotinic acid versus placebo – no studies identified
- fibrates versus placebo – 1 study
- fish oils (omega 3 fatty oils) versus placebo – no studies identified
- ezetimibe versus placebo – no studies identified.

5.2.5.2 Clinical evidence

Statins versus placebo

Researchers from the Department of Public Health and Primary Health Care, University of Oxford (Arambepola et al, 2007)[75] recently conducted a systematic review and meta analyses of clinical trials and observational studies to assess the evidence for efficacy and safety of statin therapy in children and adolescents with heterozygous FH. Eight RCTs were included in the review which evaluated statin therapy against placebo. Two other trials used active treatment control groups. Statin therapy varied by type and dosage. In total 947 individuals (548 males) were included in the RCTs with an age range of 8-18 years. Median duration of the trials was 27 weeks (6-96). Total exposure was estimated at 850 person-years.

All trials measured mean changes in LDL-C, HDL-C and total cholesterol and triglycerides from baseline to the end follow up point as primary efficacy outcome measures. Five studies were included in a pooled analysis of LDL-C and HDL-C outcomes. The pooled reduction in LDL cholesterol due to statins was 1.89mmol/l (95% CI 1.58-2.19) compared to placebo ($p<0.0001$). There was a significant heterogeneity within the pooled LDL cholesterol changes ($p=0.04$). All reduced LDL-C but efficacy varied by the statin used and dose. Due to this variability, individual studies are described Table 7 which has been expanded from the systematic review paper and the original studies. Table 8 reports the outcome data for each of these studies.

Eighteen studies in total (11 trials and 7 prospective case series) provided information on safety outcomes for an estimated total exposure of 1162 child-years. There were no significant adverse events. In the RCTs, adverse events were equally distributed between statin treatment and placebo. Adverse events did not appear to vary by type or dose of statin when groups were compared within trials.

Table 7 Included studies on statin treatment in children with FH - description (Adapted from published review[75])

Study	Study design	Follow up	Characteristics of participants			Intervention	Control	Jadad score (quality assessment
			Age range	n (males)	Criteria of LDL-C (mmol/l) for inclusion			
Wiegman (2004)	RCT	96w	8-18 years	214 (100)	≥ 4.0	Pravastatin 40mg/d if ≥14 y of age; 20mg/d if <14 y of age	Placebo	5
de Jongh (2002a)	RCT	48w	10-17 years	175 (99)	4.9-13.0	Simvastatin10mg/d for 8w; 20mg/d/ for 8w; 40 mg/d	Placebo	4
Stein (1999)	RCT	48w	10-17 years	132 (132)	≥ 4.9	Lovastatin 10mg/d for 8w; 20mg/d for 8w; 40mg/d	Placebo	4
de Jongh (2002b)	RCT	28w	9-18 years	50 (26)	Above 95th percentile for age and sex	Simvastatin10mg/d for 8w; 20mg/d for 8w; 40mg/d	Placebo	1
McCrindle (2003)	RCT	26w	10-17 years	187 (120)	> 4.1	Atorvastatin 10mg/d; 20mg/d if LDL-C ≥3.4 at week 4	Placebo	3
Clauss (2005)	RCT	24w	10-17 years post menarche females	54 (0)	4.1-10.3	Lovastatin 20mg/d for 4w; 40 mg/d	Placebo	5

Study	Study design	Follow up	Characteristics of participants			Intervention	Control	Jadad score (quality assessment
			Age range	n (males)	Criteria of LDL-C (mmol/l) for inclusion			
Knipscheer (1996)	RCT (4 randomised arms)	12w	8-16 years	72 (25)	Above 95th percentile for age and sex	Pravastatin: (1) 5 mg/d (2) 10 mg/d (3) 20 mg/d	Placebo	3
Couture (1998)	RCT	6w	8-17 years	63 (37)	Above 95th percentile for age and sex	Simvastatin 20 mg/d (for 3 groups according - gene mutations)	Placebo	3
McCrindle (2002)	Randomised cross over trial	18w	8-18 years	40 (25)	> 4.15	Pravastatin 10mg/d + colestipol5g/d	Colestipol 10g/d	-
Stefanutti (2005)	Non-randomised parallel matched trial	48w	4-11 years	16 (7)	Not stated	Simvastatin 10mg/d + step II AHA diet	Step II AHA diet	-
Lambert (1996)	Time series comparison (4 randomised arms)	8w	≤ 17 years	69 (69)	Above 95th percentile for age and sex	Lovastatin: (1) 10 mg/d (2) 20 mg/d (3) 30 mg/d (4) 40 mg/d	Placebo/4w prior to randomisation	-

1

Table 8 Included studies on statin treatment in children with FH (FH) – results (Adapted from published review[75])

Study	Mean absolute changes (±sd) in lipid profiles from baseline (mmol/l)	Mean percent changes(±sd) in lipid profiles from baseline (mmol/l	Endothelial function	Carotid IMT (mm)
Wiegman (2004)	2 year follow-up: TC: pravastatin 20mg (under 14yrs) and 40mg over 14 years +1.44 (±1.1), p<0.001. LDL-C: pravastatin 20mg (under 14yrs) and 40mg over 14 years +1.46 (±1.0), p<0.001 HDL-C: pravastatin 20mg (under 14yrs) and 40mg over 14 years +0.03 ns			2 year follow-up: pravastatin 20mg (under 14yrs) and 40mg over 14 years -0.010 (±0.048) p=0.02
de Jongh (2002a)		Week 48: TC: simvastatin 40mg -30.9% (±11.5); LDL-C: simvastatin 40mg -40.7% (±39.2) HDL-C: simvastatin 40mg +3.3% (±14.9).		
Stein (1999)	Week 48: TC: lovastatin 40mg +0.51 (±0.5), p<0.001 vs placebo; LDL-C: lovastatin 40mg +0.64 (±0.5), p<0.001 vs placebo; HDL-C: lovastatin 40mg +0.01 ns			

Study	Mean absolute changes (±sd) in lipid profiles from baseline (mmol/l)	Mean percent changes(±sd) in lipid profiles from baseline (mmol/l	Endothelial function	Carotid IMT (mm)
de Jongh (2002b)	Week 28: TC: simvastatin 40mg -2.16 (±1.04), p=0.0001; LDL-C: simvastatin 40 mg -2.13 (±0.99) p=0.0001; HDL-C: simvastatin 40 mg -0.05 (±0.17) p=0.08.		Week 28: FMD significant increase in simvastatin FH group (p<0.0001).	
McCrindle (2003)		Week 26: TC: atorvastatin 10-20mg titrated depending upon response, -31.4% (± 1.0); LDL-C: atorvastatin 10-20mg titrated depending upon response, -39.6% (± 1.1); HDL-C: atorvastatin 10-20mg titrated depending upon response, +2.8% (± 1.3);		
Clauss (2005)]		Week 24: TC: lovastatin 40mg -21.8% (±2.5); LDL-C: lovastatin 40mg -26.8% (±3.4); HDL-C: lovastatin 40mg +2.5% (±2.5);		

Study	Mean absolute changes (±sd) in lipid profiles from baseline (mmol/l)	Mean percent changes(±sd) in lipid profiles from baseline (mmol/l	Endothelial function	Carotid IMT (mm)
Knipscheer (1996)		Week 12: TC: pravastatin 20mg -24.6% (95% CI 21.0 to 28.1); LDL-C: pravastatin 20mg -32.9% (95% CI 28.6 to 37.0); HDL-C: pravastatin 20mg + 10.8% mean change (95% CI 3.4 to 18.8).		
McCrindle (2002)	Week 18: TC: colestipol 10g only -0.63±0.80; colestipol 5g + pravastatin 10mg -1.06±1.11 p=0.041; LDL-C: colestipol 10g only -0.65±0.80; colestipol 5g + pravastatin 10mg -1.07± 1.06 p=0.066; HDL-C: colestipol 10g only -0.01±0.18; colestipol 5g + pravastatin 10mg +0.03± 0.13 p=0.63;			
Stefanutti (2005)		Month 12 TC: simvastatin 10mg -24%; LDL-C: simvastatin 10mg -29% p<0.01; HDL-C: simvastatin 10mg +7% (no sd reported)		

Study	Mean absolute changes (±sd) in lipid profiles from baseline (mmol/l)	Mean percent changes(±sd) in lipid profiles from baseline (mmol/l	Endothelial function	Carotid IMT (mm)
Lambert (1996)		Week 8: TC: lovastatin 40mg +29% (26-32); LDL-C: lovastatin 40mg +36% (33-39) ; HDL-C: lovastatin 40mg +3%		

1

Duplaga (1999)[76] published an early review of literature regarding the safety and efficacy of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) when used during childhood and adolescence. Six clinical studies were reviewed after a Medline search of the literature (children aged 0-18 years), including case series and RCTs (Stein, 1989;Ducobu et al, 1992; Sinzinger et al, 1992; Lambert et al, 1996; Stein et al, 1999; Knipscheer et al, 1996). Three of these studies are included in the 2007 Arambepola et al review (Lambert et al, 1996; Stein et al, 1999; Knipscheer et al, 1996). This review suggested that the addition of statins to diet therapy in children aged >10 years may be effective when diet therapy alone has failed to reduce LDL-C. In children and adolescents TC and LDL-C can be expected to decrease by 25% when statins are used in conjunction with lipid lowering diet but HDL-C is not significantly improved. Statins appear to be well tolerated and generally safe to use in children and adolescents who took part in these studies, including growth parameters of male children before and after puberty. Effects on girls are not known.

Two guidelines for the treatment of children with FH were also reviewed. The Finnish Medical Society (2004)[77] guideline, based on a systematic review and quality assessment of the literature made the following recommendation regarding drug therapy in children with FH:

'The need for drug therapy is decided mainly on family history of coronary heart disease. Drug therapy (a bile acid sequestrant is the first line drug; a statin may be used as an alternative) is initiated by an experienced paediatrician.'

The evidence base for this recommendation is Wiegman et al, 2004[78] and is summarized as follows:

'Two years of pravastatin therapy appear to induce a significant regression of carotid atherosclerosis in children with familial hypercholesterolemia.'

An American guideline from the Institute for Clinical Systems Improvement (2005)[79] based on a 'search of electronic databases' also cites Wiegman et al, 2004[78] regarding treatment of children and adolescents with familial hyperlipidaemia:

'A long-term study demonstrates that statin therapy for FH is safe and effective in children.'

Bile acid sequestrants versus placebo

Two studies on the effects of bile acid sequestrants in children with FH were identified. Groot et al (1983)[80] studied 33 children aged 7-15 years, who were matched on age, sex and serum cholesterol and received either colestipol or placebo in a 16 week crossover trial. The treatment effects for colestipol v placebo were:

- TC -0.89 (p<0.001); percent change -12.8%
- LDL-C +VLDL -0.91(p<0.001); percent change -15.7%
- HDL-C +0.02 (ns); percent change +1.7%
- TG -0.10 (ns); percent change -9.3%
- Apo B -0.18 (p<0.001); percent change -13.5%
- Apo A +0.02 (ns); percent change +1.7%.

Five children did not complete the study because of aversion to the sandy tasting medication. There were no other complaints.

Tonstad et al (1996)[81] conducted a one year RCT comparison of 8gm cholestyramine versus placebo among 72 children with FH and a mean age of 8.4±1.4* years. Percent change was reported; absolute values were not given. After one year of treatment the following percent changes were reported for the cholestyramine versus placebo group:

- TC -11.5% (p<0.001) (further statistics not provided in paper)
- LDL-C -16.9% to -18.6% versus 0 to +1.5% in placebo (p<0.0001)
- HDL-C +8.2% to +13.4% versus +2.4% to +8.8% in placebo (not significant)
- Mean triglyceride remained unchanged in both groups
- Apo B was reduced from 2.1±0.4gm/l to 1.8±0.4 gm/l (p value not given).

Mean height velocity standard deviation scores during 1 year for the children in the cholestyramine and placebo groups who had not started puberty were 0.24±1.14 and 0.11±0.68, respectively (not significant). Mean levels of 25-hydroxyvitamin D in the

* Assumed to be mean±sd throughout, but not reported explicitly in paper

cholestyramine group decreased. Unpalatability of the drug caused 21 withdrawals. Abdominal pain and/or loose stools or nausea were reported in 3 placebo and 5 treatment individuals. One case of intestinal obstruction after taking two doses of cholestyramine was reported.

Nicotinic acid versus placebo

No studies were identified.

Fibrates versus placebo

One study was identified which evaluated the use of bezafibrate in 14 children, aged 4-15 years, with FH (Wheeler, 1985)[74]. Bezafibrate was given twice daily in a dose of 10 to 20 mg/kg/day in a 6 month double placebo randomised crossover trial. LDL-C was not reported. The results of other lipid values were as follows:

- TC:
  mean baseline TC: 9.3 (sd 1.5); mean TC on bezafibrate 7.8 (sd 3.0); mean placebo TC 10.0 (sd 1.6). Mean plasma total cholesterol while on bezafibrate was 22% lower than during the placebo period and 16% lower than in the period before the trial.
- HDL-C:
  mean baseline HDL-C: 1.44 (sd 0.2); mean HDL-C on bezafibrate 1.30 (sd 0.36); mean placebo HDL-C 1.43 (sd 10.2). There was a mean rise in HDL-C on bezafibrate of 15% compared with placebo and 25% compared to pre-trial values. There was a mean rise in HDL-C on bezafibrate of 15% compared with placebo and 25% compared to pre-trial values.
- TG:
  mean baseline TG:1.00 (sd 0.26); mean TG on bezafibrate 0.67 (sd 0.37); mean placebo TG 0.87 (sd 0.35). There was a mean fall of TG on bezafibrate treatment of 23% compared with placebo and 33% compared with pre trial values. This was not statistically significant.

One child had an elevated alkaline phosphatase due to intercurrent infection and a second child had a transient rise in alanine transaminase . Both of these children returned to normal at the end of the third month and there were no other abnormal blood results. Growth was satisfactory and no reported clinical side effects.

Fish oils versus placebo

No studies were identified.

Ezetimibe versus placebo

No additional studies were identified.

*5.2.5.3 **Health economic evidence***

No relevant health economic evidence was identified for any comparison.

*5.2.5.4 **Drug safety***

At the request of the GDG chair and clinical advisor an additional search was carried out for studies of 'long term' bile acid sequestrant and fibrate safety in children. 'Long term' was determined to be five years or greater.

- Identified: 107 total
- Ordered: 26 studies
- Included: 1 study
- Excluded: 25 studies

Only one reference study followed children for more than five years. Hansen et al (1992)[82] evaluated 30 children for the effects of low fat diet alone or diet and colestipol. The median age at the start of the study was 3.0 years in the diet only group and 5.0 years in the diet and colestipol group. The median duration of treatment was 8.5 years in 13 children on diet only and 5.5 years in 17 children treated with diet followed by diet and colestipol. The children were not randomized to treatment. The decision to prescribe colestipol was based upon the concentrations of serum lipids and the response to dietary measures, the age and sex of the child and the family history of early ischemic heart disease. The scores for both height/age and weight/age decreased by approximately 0.4 during dietary treatment ($p<0.05$), but were not affected by treatment with colestipol.

5.2.6 Evidence statements on the effectiveness of combined therapy in adults

Key clinical question:

What is the effectiveness of adjunctive pharmacotherapy with statins (statins and bile acid sequestrants, statins and nicotinic acid, statins and fibrates, statins and fish oils, statins and bile acid sequestrants with nicotinic acid, statins and ezetimibe, or statins plus bile acid sequestrants versus statins plus fibrates) in adults with FH?

Question 9 of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
The use of statin and bile acid sequestrant in combination significantly reduces LDL-C and TC when compared with placebo and appears to have a greater effect when compared with either drug alone. The effect of combination therapy on HDL-C and triglycerides does not appear to be consistent. [1+] The use of statin and nicotinic acid in combination significantly reduces LDL-C, TC, and triglycerides and increases HDL-C when compared with placebo. The combination appears to have a greater effect when compared with either drug alone. [1+] The use of statin and fibrate in combination significantly reduces LDL-C, TC, and triglycerides and increases HDL-C when compared with placebo. (Reduction in total cholesterol (29.0%), LDL-C (37.1%), TG (41.7%) and increased HDL-C by 16.8%). The combination appears to have a greater effect when compared with either drug alone. [1+] There was no evidence for the use of a combination of statins and omega-3-ethyl esters treatment in the FH population. There was no evidence for the use of a combination of statins and bile acid sequestrants with nicotinic acid in the FH population. One RCT showed that the addition of fibrates or bile acid sequestrants to statin therapy, showed similar reductions in LDL-C or TC. In this trial fibrates were more effective than bile acid sequestrants in reducing TG and raising HDL-C concentrations. [1+][83] See the NICE TA for evidence on the use of ezetimibe in adults with heterozygous FH[66]. No evidence on the use of ezetimibe in individuals with	Clinical practice on the use of combination therapy or more potent agents may differ depending on the side effect profile for the individual statin, the results of monitoring, and the response of the individual (where the dose response curve may flatten off considerably). None of the included studies titrated to maximal dose. There was no direct evidence for the differential choice of drugs within the treatment pathway, so recommendations were made based on clinical judgment and considerations of efficacy, safety, and tolerability. The combination of statin with fibrates has specific safety issues which have been highlighted in the recommendations.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
homozygous FH, or children with FH was identified. In summary, combination therapy is superior to monotherapy in the treatment of FH individuals to lower LDL-C and TC.	

5.2.7 Evidence summary on the effectiveness of combined therapy in adults

5.2.7.1 Methods of the clinical evidence review

For this review we included only randomised controlled trials conducted in the FH population.

- Identified: 789 studies
- Ordered: 62 studies
- Included: 11 studies
- Excluded: 51 studies

5.2.7.2 Clinical evidence

Statins in combination with bile acid sequestrants

An early randomised follow on study from 1988[84] evaluated the response of 60 individuals with heterozygous FH to treatment with cholestyramine (8-16 g) or simvastatin 20mg for 6 weeks then on 40mg for a further 6 weeks. At the end of 12 weeks 50 of 60 participants were placed on 40mg simvastatin in combination with 8-16 g cholestyramine. There were significant differences ($p<0.05$) between each treatment. Percent changes in lipid concentrations were reported:

	TC	LDL-C	HDL-C	TG
Cholestyramine	-23%	-30%	+9%	+11%
Simvastatin	-36%	-43%	+16%	-21%
Combination	-45%	-54%	+20%	-17%

A study conducted in Holland in 1990[85] randomised 40 heterozygous FH individuals to pravastatin 40mg and 22 individuals to placebo. If serum LDL-C concentrations did not fall below 5.0mmol/l 8 weeks after randomization, bile acid binding bile acid sequestrants were added starting 10 weeks after randomization. These were given at the maximum tolerable dose per individual. After 8 weeks of treatment, TC had decreased from 10.6 (sd±1.7 mmol/l to 7.6±1.3 mmol/l (28%; $p<0.01$). When pravastatin was supplemented with bile acid

sequestrants, there was an additional reduction in TC of 8% (p<0.01) by week 24. LDL-C decreased after 8 weeks from 8.7±mmol/l to 5.8±1.3 mmol/l (33%, p<0.01). In 30 individuals treated with combination therapy the LDL-C decreased an additional 12% (p<0.01). HDL-C was not affected by bile acid sequestrants. The addition of bile acid sequestrants to pravastatin caused TG concentrations to increase by 7% compared to pravastatin monotherapy.

Tsai et al[86] conducted a randomized parallel group study comparing pravastatin 20mg/day with a combination of pravastatin 10mg/day plus cholestyramine 8g/day for 24 weeks in 30 individuals with primary hypercholesterolaemia. The low dose combination of pravastatin and cholestyramine was significantly more effective than pravastatin alone in higher doses in terms of LDL-C reduction (mean±sem): 25% reduction with pravastatin alone (4.7mmol/l±0.3 to 3.5mmol/l±0.3); 34% reduction (4.7± 0.3 to 3.1±33) with the pravastatin/cholestyramine combination (p<0.01 between groups). There was no significant change in total cholesterol or in HDL-C. TG increased by 18% (4.9±0.6 to 3.1±0.3) in the combination treatment group (between group p-value not reported).

Pravastatin was studied at doses of 20 or 40mg twice daily alone or 20mg twice daily with cholestyramine, 12g twice daily vs. placebo in an 8 week RCT in 311 individuals with primary hypercholesterolaemia[87]. TC and LDL-C reductions were substantially greater than with either drug alone (p<0.001). At 8 weeks pravastatin 20mg bid reduced TC by 23.8% (7.9 mmol/l±0.18 placebo versus 6.0mmol/l± 0.16); pravastatin 40mg bid reduced TC by 29.8% (7.9mmol/l±0.18 placebo versus 5.7mmol/l±0.13);cholestyramine 12g bid reduced TC by 18.3% (7.9 mmol/l±0.18 placebo versus 6.6mmol/l±0.20); pravastatin 20mg bid plus cholestyramine 12g bid reduced TC by 32.2% (7.9 mmol/l±0.18 placebo versus 5.4mmol/l±0.15). LDL-C reductions were as follows: placebo 5.9 mmol/l±0.18; pravastatin 20mg bid 31.7% change (4.1mmol/l±0.13); pravastatin 40mg bid 38.9% change (3.7mmol/l±0.13); cholestyramine 12g bid 28.3% change (4.4mmol/l±0.19); pravastatin 20mg bid plus cholestyramine 45.4% change (3.3 mmol/l±0.14). For the study as a whole, HDL-C concentrations increased about 5% with either drug alone or in combination. Both pravastatin regimes after eight weeks of therapy reduced plasma TG concentrations by 13-14% (p<0.01) versus placebo. Cholestyramine significantly elevated plasma TG from baseline (12.1%, p<0.01).

The effect of the combination of low dose lovastatin and low dose colestipol versus placebo was studied among 57 individuals with moderate to severe primary hypercholesterolaemia[88].

Subjects received either colestipol 5g at breakfast and lovastatin 20mg at bedtime; colestipol 10g and lovastatin 20mg; or placebo. Compared to placebo, 20mg of lovastatin and 5g of colestipol reduced TC concentrations from 7.9±0.8mmol/l to 5.6±0.7mmol/l after 8 weeks of treatment ($p<0.0001$). LDL-C concentrations were reduced from 5.9±0.8mmol/l to 3.9±0.7mmol/l (34%; $p<0.0001$). In the lovastatin 20mg and 10g colestipol group TC was reduced to 5.5mmol/l and LDL-C was 3.6±0.8mmol/l representing a 35% decrease ($p<0.0001$ in both groups). Triglycerides and HDL-C remained unchanged.

Statins in combination with nicotinic acid

See Nicotinic acid versus placebo

Statins in combination with fibrates

Only one study of pravastatin and gemfibrozil alone and in combination for the treatment of primary hypercholesterolaemia was identified[89]. Individuals with primary hypercholesterolaemia (n=266) were randomised to either pravastatin 40mg once daily, gemfibrozil 60 mg twice daily, combination therapy with pravastatin and gemfibrozil or placebo. Pravastatin reduced total cholesterol more than gemfibrozil (26.3% versus 15.2%, $p\leq0.01$) and LDL-C (16.8%, $p\leq0.01$). Gemfibrozil reduced triglycerides (42.2% versus 14.2%, $p\leq0.01$) and increased HDL-C (15.2% versus 5.9%, $p\leq0.01$) more than pravastatin. The combination significantly ($p\leq0.01$) reduced total cholesterol (29.0%), LDL-C (37.1%), TG (41.7%) and increased HDL-C by 16.8%). The absolute mean values (sem) were as follows:

- TC: placebo 7.13mmol/l (0.12), -1.72% change; pravastatin 5.44mmol/l (0.11), -26.25% change; gemfibrozil 6.20mmol/l (0.12), -15.18% change; combination 5.10mmol/l (0.12), -28.98% change
- LDL-C: placebo 5.02mmol/l (0.13), -1.88% change; pravastatin 3.44mmol/l (0.11), -33.54% change; gemfibrozil 4.29mmol/l (0.11), -16.80% change; combination 3.17mmol/l (0.10), -37.06% change
- VLDL: placebo 0.65mmol/l (0.05), +2.17% change; pravastatin 0.49mmol/l (0.04), -21.85% change; gemfibrozil 0.32mmol/l (0.02), -49.06% change; combination 0.32mmol/l (0.03), -49.43% change
- TG: placebo 1.83mmol/l (0.10), +1.87% change; pravastatin 1.53 mmol/l (0.08), -14.17% change; gemfibrozil 1.03mmol/l (0.05), -42.16% change; combination 1.01mmol/l (0.06), -41.68%change

- HDL-C: placebo 1.16 mmol/l (0.03), -4.44% change; pravastatin 1.32mmol/l (0.04), -5.93% change; gemfibrozil 1.39mmol/l (0.04), 15.21% change; combination 1.46mmol/l (0.05), 16.81% change.

Statins in combination with fish oils

No studies identified. The GDG extrapolated from evidence reviewed in the Clinical Guidelines and Evidence Review for Post Myocardial Infarction[64].

Statins in combination with bile acid sequestrants and nicotinic acid

No studies were identified.

Statins in combination with ezetimibe

For a review of the evidence in adults with heterozygous FH, see the NICE TA on the use of ezetimibe[66]. No evidence on the use of ezetimibe in adults with homozygous FH was identified.

Statins in combination with bile acid sequestrants versus statins in combination with fibrates

It was decided to review one additional study by Leitersdorf et al[83] as it contributed to the evidence base for determining second and third line treatment options in FH. This study was a double blind, double placebo randomized parallel group investigation in 38 individuals with heterozygous FH. During weeks 13-18 of this study 18 individuals (Group 1) received 8g cholestyramine and 40mg fluvastatin daily and 20 individuals (Group 2) received 40 mg bezafibrate and 40mg fluvastatin. Percent change (mean±sd) from baseline was reported in both groups. Total cholesterol in Group 1 changed by 23.9±10.7% and in Group 2, 28.6±11.7%; TG increased in Group 1 by 14.2±35.8% and decreased in Group 2, 25.1±29.7%; HDL-C increased in Group 1 2.9±11.0% and in Group 2 13.0±13.4%; LDL-C decreased by 21.3±7.9% in Group 1 and 25.0±13.5%. There was no significant difference in total cholesterol or LDL-C between groups; however, there were significant differences between triglyceride and HDL-C concentrations ($p<0.001$ and $p<0.05$ respectively).

*5.2.7.3 **Health economic evidence***

No studies were found looking at high versus low dose statins or any lipid lowering drug compared with placebo from the literature search. However there was one cost utility analysis found comparing fluvastatin 80mg versus simvastatin 40mg. in FH patients by Metcalfe[90] for PHARMAC a pharmaceutical management agency established by the New Zealand Public

Health and Disability Act of 2000. The authors of the report used data from the Simon Broome register, other observational data and effectiveness data from the 4S trial. Most of the data was presented as graphs, but the authors were transparent with the sources of data and the methodology used except for utility data which was not well reported.

The authors reported that simvastatin 40mg resulted in more QALYs compared to fluvastatin 80mg. (1.03 vs. 0.89 discounted QALYs respectively) The estimated ICERs were approximately $32,947 for those aged 35-59. The ICERs ranged between $28,112 in men aged 55-59 years, to about $77,000 in children. The cost effectiveness improved with age.

The authors did not undertake a sensitivity analysis which weakens their study. In their base case model they assumed fluvastatin will cause a disutility of 0.01 (compared to a disutility of 0.00 for simvastatin), while in their discussion they acknowledge that published studies did not find any difference in utility between the two statins. The implications, which the authors acknowledge, are to exaggerate the QALY gains by simvastatin; hence making the ICERs favourable. It would be more helpful if they had fully explored this in sensitivity analysis or assumed no difference in the base model.

In conclusion, simvastatin 40mg compared with fluvastatin 80mg used in patients with FH appears to have value for money; this finding is weakened by a lack of sensitivity analysis and, especially, the assumptions about utility loss between the two statins. Their finding seem to contradict our finding that in FH patients, cost effectiveness is favourable for those aged less than 60 years compared to those aged over 60 years.

Modelling the cost effectiveness of high intensity statins compared with low intensity statins in the management of FH

When initial searches were undertaken, no studies were found which compared cost-effectiveness of higher intensity statins with lower intensity statins in patients with FH. Consequently, the GDG requested the development of a de novo economic model to help inform the guideline recommendations.

A Markov model was developed to estimate the incremental cost per quality adjusted life year (QALY) of lifetime treatment with high intensity statins (atorvastatin 80mg and simvastatin 80mg) compared with low intensity statins (simvastatin 40mg). The base case models a cohort of hypothetical patients aged 50 years of age.

The intermediate outcomes include MI, stroke, heart failure, revascularisation, angina and death from CVD and other causes. Effectiveness data were drawn from the updated Simon Broome register[51]. We also used data from TNT[52] and IDEAL[53] which were meta-analysed. The model makes the conservative assumption that the all cause mortality rate in the modelled population is twice that of the general population. Health state utility values were taken from published sources (Appendix E). All cause mortality rates are from the Government Actuarial Department[54]. The model makes the conservative assumption of no adverse events from treatment using high intensity statins. Cost of drugs were taken from the Drug tariff Dec 2007 (atorvastatin 80mg £367.74/year, simvastatin 80mg £64.01/year, simvastatin 40mg, £17.08/year)[55]. Costs of cardiovascular events were taken from the NICE TA94 on statins[31]. In order to reflect social values for time preference as is standard in economic models; costs and QALYs have been discounted at 3.5% as recommended by NICE[56]. All of these and other model assumptions have been tested in sensitivity analyses.

Results

The base case results are presented below, and cost-effectiveness is assessed against a threshold of £20,000/QALY. We report the results separately for atorvastatin 80mg and simvastatin 80mg.

Results for patients with FH effectiveness data from Simon Broome

Table 9 indicates the modelled number of events for the hypothetical 1,000 patients who are taking high intensity or low intensity statins. The table indicates that fewer cardiovascular events occur in the population treated high intensity statins. More people will die from other causes and fewer people will die from cardiovascular mortality. This translates to a gain of 0.72 discounted QALYs when compared with low intensity statins. The additional cost of achieving this gain in QALYs depends on the statin being used.

Table 9 Lifetime event outputs modelled for a cohort of 1,000 patients high intensity statins compared with low intensity treatment strategy for patients with FH

Health state	Low intensity	High intensity (treatment effect from Simon Broome)
MI	297	176
Stroke	188	146
Heart failure	115	62
Revascularisations	149	90
Unstable angina	98	61
Cardiovascular mortality	252	166
Death from other causes	748	834

- cost effectiveness results using the price of atorvastatin 80mg

  The incremental cost per patient on atorvastatin 80mg needed to achieve the net gain of 0.72 QALYs is estimated to be about £4,010.when compared with low intensity statins. The estimated ICER is about £5,600/QALY suggesting that high intensity statins are cost effective.
- cost effectiveness results using the price of simvastatin 80mg

  For people on simvastatin 80mg, there are cost savings of about £600 per patient for the estimated gain of 0.72 QALYs. Thus high intensity statins dominate the low intensity statins since they result in fewer costs (i.e. give savings) and more QALYs. The model results are stable in sensitivity analysis.

Results for patients with FH using effectiveness data from post MI patients with stable coronary artery disease (CAD)

Table 4 indicates the modelled number of events for the hypothetical 1,000 patient who are taking high intensity or low intensity statins. The table indicates that fewer cardiovascular events occur in the population treated high intensity statins and less people are dying from cardiovascular death while more are dying from other causes. This translates to a gain of 0.23 discounted QALYs when compared with low intensity statins. The additional cost of achieving this gain in QALYs depends on the statin being used.

Table 10 Lifetime event outputs modelled for a cohort of 1,000 patients high intensity statins compared with low intensity treatment strategy for patients with stable coronary disease[52;53]

Health state	Low intensity statins	High intensity statins (treatment effect from TNT and IDEAL)
MI	297	231
Stroke	188	153
Heart failure	115	76
Revascularisations	149	112
Unstable angina	98	82
Cardiovascular mortality	252	220
Death from other causes	748	779

- cost effectiveness results using the price of atorvastatin 80mg
  The incremental cost per patient on atorvastatin 80mg needed to achieve the net gain of 0.23 QALYs is estimated to be about £4,364. The estimated ICER was about £19,000/QALY. High intensity statins are borderline cost effective for FH patients. The model results are sensitive to assumptions about treatment effect on cardiovascular mortality; when the upper confidence interval of treatment effect on mortality is used (RR=1.17) high intensity statins are dominated by lower intensity statins, thus they will result in more cost per patient and less quality adjusted life years £4,044 and less QALYs -0.03.
- cost effectiveness results using the price of simvastatin 80mg
  For people on simvastatin 80mg, there are estimated cost savings of about £53 per patient for the estimated gain of 0.23 QALYs. Thus high intensity statins dominate the low statin statins since they result in fewer costs (i.e. give savings) and more QALYs. The model results are stable in sensitivity analysis.

In conclusion, high intensity statins are cost effective for the treatment of FH for all age groups when simvastatin 80mg is used. However when atorvastatin 80mg is used (at current prices), high intensity statins are cost effective for only those aged below 60 years.

5.2.8 Evidence statements on the effectiveness of combined therapy in children

Key clinical question:

What is the effectiveness of adjunctive pharmacotherapy with statins (statins and bile acid sequestrants, statins and nicotinic acid, statins and fibrates, statins and fish oils, statins and bile acid sequestrants with nicotinic acid, statins and ezetimibe, or statins plus bile acid sequestrants versus statins plus fibrates) in children with FH?

Question 9 of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
No evidence was identified.	See also above for issues on ezetimibe.

5.2.9 Evidence summary on the effectiveness of combined therapy in children

5.2.9.1 Methods of the clinical evidence review

Inclusion criteria were randomised controlled trials conducted in the FH paediatric population. The paediatric population was included in the original search terms for statins (1113) and the searches for other cholesterol lowering drugs (789).

- Identified: 1902 total
- Ordered: 34 studies
- Included: 0 studies
- Excluded: 34 studies

A separate search was carried out to review the literature on the use of ezetimibe in children and individuals with homozygous FH. These two populations were not included in NICE ezetimibe TA[10]. For this review we included only randomised controlled trials conducted in the paediatric and homozygous FH population.

- Identified: 82 studies
- Ordered: 7 studies
- Included: 1 study
- Excluded: 6 studies

5.2.9.2 Clinical evidence

Combined therapy (statins with bile acid sequestrants, nicotinic acid, fibrates, fish oils, bile acid sequestrants with nicotinic acid)

No evidence was identified which evaluated combination statin therapy with bile acid sequestrants, nicotinic acid, fibrates, fish oils and bile acid sequestrants with nicotinic acid in children.

Ezetimibe in combination with statins

There were no RCTs identified for the treatment of children alone with ezetimibe.

One study was identified which evaluated the efficacy and safety of ezetimibe in combination with atorvastatin or simvastatin in homozygous adults and children (at least 12 years old or

body weight≥40kg) (Gagne et al, 2002)[91]. Fifty individuals were randomised to ezetimibe 10mg plus 'statin-40' (simvastatin or atorvastatin 40mg) (n=16) or ezetimibe 10mg plus 'statin-80' (simvastatin or atorvastatin 80mg) (n=17) or to statin-80 (n=17). There were 7 participants less than 18 years old in this study (14%). The results were as follows:

- changes in lipid concentrations from baseline (simva-40):
  direct LDL-C absolute change 0.5mmol/l statin-80 and 1.7mmol/l in ezetimibe plus statin 40/80 (p=0.007);
  TC absolute change 0.49mmol/l statin-80 and 1.9mmol/l in ezetimibe plus statin 40/80 (p<0.01).

There were no other significant differences between the two treatment groups. There were reductions of at least 14% to 20.5% in LDL-C when ezetimibe was coadministered with a moderate (40mg) or maximal (80mg) dose statin therapy compared with maximal therapy with statins alone. Ezetimibe plus statin 80mg reduced LDL-C by 26.6% compared to statin 80mg, a reduction of 5.6% from baseline of simvastatin 40mg.

Two individuals in the ezetimibe group discontinued treatment; one due to epigastric and chest pain and another due to increase liver enzymes. There were no significant differences between treatment groups on another other measures of safety.

5.2.9.3 ***Health economic evidence***

No studies were identified.

5.2.10 Evidence statements on the effectiveness of maximal cholesterol lowering in adults

Key clinical question:

What is the effectiveness of aggressive (maximal) cholesterol lowering in adults with FH?

Question 7 of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
Increasing the dose of the statin increases LDL-C reduction [1+] There are differences in efficacy and potency between statins in their LDL-C lowering [1+] Adverse events associated with statins include headache, altered liver function, paraesthesia and gastrointestinal effects (including abdominal pain, flatulence, diarrhoea, nausea and vomiting). Rash and hypersensitivity reactions have been reported but are rare. Muscle effects (myalgia, myositis and myopathy) have also been reported with the use of statins. Severe muscle damage (rhabdomyolysis) is a very rare but significant side effect. Further adverse events are associated with individual statins. For full details of adverse effects, contraindications and interactions, see the Summaries of Product Characteristics. (Statins for the prevention of coronary events. NICE Technology Appraisal 94, 2006; 1++)[65]	Evidence is clear on the effect of statins to reduce LDL-C and TG, but included studies are old, small, and short-term. Therefore, other evidence on the longer term safety and efficacy of statins (including evidence of the effect on clinical outcomes[65]) was considered. In addition, because of the high initial concentrations of cholesterol in people with FH, the need to lower concentrations is of prime importance, so more potent agents may be required to achieve the maximal lowering. In the clinical experience of the GDG, the pattern of side effects tend to show peaks at initiation and when used long term, so rather than define regular monitoring, people experiencing unusual side effects should be referred. However, BNF monitoring recommendations for each drug should be followed.

5.2.11 Evidence summary on the effectiveness of maximal therapy in adults

5.2.11.1 ***Methods of the clinical evidence review***

For this review we included only randomised controlled trials conducted in the FH population. Numbers based on the searches for statins overall.

- Identified: 1113 studies
- Ordered: 166 studies
- Included: 17 studies
- Excluded: 108 studies
- Studies relating to other questions: 41

5.2.11.2 ***Clinical evidence***

High versus low dose statins

The McDowell et al (1991)[72] study, referred to in the review for question 8a, randomised individuals to placebo or 10mg simvastatin during the first month of treatment. The dose of simvastatin was increased monthly for the individuals in the active arm of the treatment and the effects of 10mg, 20mg and 40mg simvastatin on lipid concentrations were compared. Significant decreases in LDL-C, total cholesterol and Apo B occurred at all doses of simvastatin versus placebo. Most of the cholesterol lowering effect was achieved during the first month on a dose of 10mg daily. Mean LDL-C concentrations (±sem) dropped from 6.4±0.5 to 5.6±0.4mmol/l when the dose was increased to 20mg simvastatin (p-values not given). There were no changes in lipid concentrations from 20mg to 40mg. Total cholesterol concentrations changed from 8.3±0.5 to 7.7±0.4mmol/l (no p-value) in conjunction with the change in dosage from 10mg to 20mg. There was no difference between 20mg and 40mg concentrations.

Synvinolin (MK-733 or simvastatin) was studied by Mol et al (1986)[92] who randomised 43 individuals to different doses of synvinolin versus placebo. All doses (2.5mg daily to 80mg daily) produced significant ($p<0.05$) reductions in total and LDL cholesterol than placebo except for treatment with 2.5mg once a day. The 80mg dose was no more effective than 40mg or 20mg in the small treatment groups. However, plotting the log of the dose against the percentage change in LDL-C after 4 weeks gave a straight line with a highly significant correlation ($p<0.001$). From this curve the researchers calculated that in the range of 2.5mg to

80mg synvinolin, every two-fold increase in dose caused an additional reduction in LDL-C of 4 to 6%.

A randomised comparative study (no control group) of pravastatin 20mg, 40mg and cholestyramine 16g was carried out in three lipid clinics in Australia (Simon et al, 1992)[93]. Total cholesterol and LDL-C were reduced significantly by all treatments over the12 week period ($p<0.001$), much of the effect being established within four weeks. There was a greater reduction in total cholesterol with pravastatin 40mg/day compared to 20mg/day (24% $p<0.03$). The reduction in LDL cholesterol concentration did not differ significantly between the treatment groups (range 26% to 34%).

The efficacy of high dose fluvastatin was studied by Leitersdorf et al (1993)[94] in a double blind parallel group trial. A control group taking 40mg fluvastatin was compared to a treatment groups taking fluvastatin in 40mg and 60mg doses. Overall, fluvastatin 40mg was associated with a 20-21% decrease in total plasma cholesterol, and a 25-27% decrease in LDL-C ($p<0.001$). There was a significant decrease in LDL-C when the dose was increased to 60mg ($p<0.01$). Total cholesterol was unaffected.

Raal et al (1997)[95] randomised 12 homozygous people with FH to 80mg simvastatin (group 1) or 40mg (group 2) in three divided doses daily. After 9 weeks the dose in the 80mg group was doubled while the dose in group 2 remained constant. LDL-C concentrations fell by 14% at the 40mg/day dose but were reduced further at the higher doses (25% at the 80mg/day level and by 31% at the 160mg/day dosage ($p<0.0001$).

Statin versus statin

Six studies were reviewed which compared the lipid lowering effects of different statins in heterozygous people with FH.

The hypolipidaemic effects of lovastatin and simvastatin at doses of 10mg, 20mg, and 40mg were compared in a randomised crossover study of 23 people with FH (Illingworth et al, 1992)[96]. Concentrations of total cholesterol and LDL-C decreased significantly for both drugs at all doses. Total cholesterol and LDL-C also decreased significantly as the dose of each drug was increased from 20 to 40 to 80mg/day. In this study, on a milligram per milligram basis the hypolipidaemic effect of simvastatin at a doses of 20mg and 40mg was equivalent to that seen with twice the dose of lovastatin (40 and 80mg).

Simvastatin and pravastatin were compared by Feillet et al (1995)[97] using a 20mg dose in a randomised sample of 26 individuals. Simvastatin was found to be significantly more effective ($p<0.001$) in reducing TC ,28%, and LDL-C, 35.6% than pravastatin (TC, 19.6%, LDL-C, 25.2%).

A study which compared the efficacy of simvastatin 80mg with atorvastatin 80mg (Wierzbicki et al, 1999)[98] in an open crossover trial found that both drugs reduced LDL-C by 47±13%* and 43±16%. Total cholesterol reductions did not differ. However, atorvastatin reduced HDL-C by 2±24% compared with 8±30% increase with simvastatin, which affected the LDL/HDL-C ratio achieved ($p=0.001$). Bo et al (2001)[99] also evaluated atorvastatin versus simvastatin and found that although there were significant reductions in lipid concentrations with both drugs, atorvastatin caused greater reductions in total cholesterol ($p<0.001$) and LDL-C ($p<0.01$).

The ASAP study, conducted by Smilde et al[100] was a randomized, double blind clinical trial of 325 individuals with FH. Participants were given either atorvastatin 80mg or simvastatin 40mg and followed for 2 years. Although the primary outcome measure of this study was carotid IMT the reporting of comparative lipid concentrations in such a large number of FH patients aids the evaluation of high dose therapy in this population. Atorvastatin showed significantly greater reductions (mean [sd])in TC (5.73 [1.31] vs 6.71[1.38] mmol/l; $p=0.0001$) and LDL-C concentrations (3.88 [1.21] vs 4.81[1.38] mmol/l; $p=0.0001$) than did simvastatin. There was also a significant difference in triglycerides ($p=0.0023$) and in apo B concentrations ($p=0.0001$). With regard to the primary outcome of carotid IMT, after treatment with atorvastatin for 2 years, IMT decreased (-0.031mm [95 %CI -0.007 to -0.055]; $p=0.0017$), whereas in the simvastatin group it increased (+0.036 [95% CI +0.01 to +-0.058]; $p=0.0005$). The change in thickness differed significantly between the two groups ($p=0.0001$).

Stein et al (2003)[101] randomised 632 individuals to 20mg/day of atorvastatin or rosuvastatin with forced titration at 6 week intervals to 80mg/day. At 18 weeks, rosuvastatin therapy produced a significantly greater reduction in LDL cholesterol than atorvastatin (57.9% vs 50.4%; $p<0.001$) and a significantly greater increase in HDL-C (12.4% vs 2.9%; $p<0.001$).

5.2.11.3 ***Health economic evidence***

No studies were found looking at high versus low dose statins from the literature search.

One cost utility analysis was found comparing fluvastatin 80mg versus simvastatin 40mg.

This study was done by PHARMAC[90] a pharmaceutical management agency established by the New Zealand Public Health and Disability Act of 2000. The authors of the report used data from the Simon Broome register, other observational data and effectiveness data from the 4S trial. Most of the data was presented as graphs, but the sources of data and the methodology used were generally well reported, except for utility data.

The authors reported that simvastatin 40mg resulted in more QALYs gained compared to fluvastatin 80mg. The estimated ICERs were approximately $28,112 in men aged 55-59 years, to about $77,000 in children. The cost effectiveness improved with age.

The authors did not undertake a sensitivity analysis which weakens their study. In their base case model they assumed fluvastatin will cause a disutility of 0.01 (compared to a disutility of 0.00 for simvastatin), while in their discussion they acknowledge that published studies did not find any difference in utility between the two statins. The implications, which the authors acknowledge, are to exaggerate the QALY gains by simvastatin; hence making the ICERs more favourable. If this had been fully explored in sensitivity analysis or no difference assumed in the base model, the results may have been more useful.

In conclusion, simvastatin 40mg compared with fluvastatin 80mg used in individuals with FH appears to have value for money; this finding is weakened by a lack of sensitivity analysis and, especially, the assumptions about utility loss between the two statins.

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* Assumed to be sd, not reported in paper

5.2.12 Evidence statements on the effectiveness of maximal cholesterol lowering in children

Key clinical question:

What is the effectiveness of aggressive (maximal) cholesterol lowering in children with FH?

Question 7 of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
No evidence was identified.	Recommendation was made to allow prescribing of higher doses, combinations, initiation at an earlier age for children at high risk, in exceptional circumstances only and only by specialists. This was to ensure that appropriate treatment is not denied or deferred inappropriately in the absence of evidence.

5.2.13 Evidence summary on the effectiveness of maximal therapy in children

5.2.13.1 ***Methods of the clinical evidence review***

Inclusion criteria were randomised controlled trials conducted in the FH paediatric population . The paediatric population was included in the original search terms for statins (1113) and the searches for other cholesterol lowering drugs (789).

- Identified: 1902 total
- Ordered: 34 studies
- Included: 0 studies
- Excluded: 34 studies

5.2.13.2 ***Clinical evidence***

No evidence was identified for this question in the paediatric FH population.

5.2.13.3 ***Health economic evidence***

No studies were identified.

6 General treatment – information, lifestyle and assessment and review

6.1 Introduction

6.1.1 Information needs and support

As with any health condition, people with FH have information and support needs. However, due to the genetic nature of FH, and therefore the implications for the wider family, there may be specific needs for people given a diagnosis of FH. Such support and information is particularly key to the success of any cascade testing programme.

6.1.2 Lifestyle interventions, including dietary intervention

Pharmacological treatment is the preferred management strategy for FH. However, lifestyle interventions, including diet, physical activity, and smoking cessation, are important adjuncts to any drug therapy. The aim of such interventions is not to 'treat' FH, that is by lowering LDL-C, but to confer the cardioprotective effect associated with a 'healthy' diet or increased physical activity.

6.1.3 Key components of assessment and review

Assessment and review are key to the management of any long term condition. As with the information and support needs, we have focused on the components of assessment and review specifically related to FH. A key aim therefore of any assessment or review is to identify any new onset, or deteriorating, symptoms of CHD (see also Chapter 7 on CHD assessment and monitoring).

6.2 Information needs and support

6.2.1 Recommendations

Unless otherwise indicated, recommendations are relevant for individuals with possible or definite FH. Recommendations are also applicable for individuals with both heterozygous and homozygous FH, unless otherwise indicated.

Please note, numbering is as in the NICE guideline.

1.4 Information needs and support

1.4.1 General information and support

1.4.1.1 During the assessment and communication of familial risk, individuals should receive clear and appropriate educational information about FH and about the process of family testing.

1.4.1.2 A specialist with expertise in FH should provide information to individuals with FH on their specific level of risk of coronary heart disease, its implications for them and their families, lifestyle advice and treatment options.

1.4.1.3 Individuals with FH should be encouraged to contact their relatives to inform them of their potential risk and to facilitate cascade testing.

1.4.1.4 When considering cascade testing, a specialist with expertise in FH should facilitate the sharing of information about FH with family members.

1.4.1.5 Individuals and families with FH should be offered written advice and information about patient support groups.

6.2.2 Evidence statements on information needs and support

Key clinical question:

What information and support is required for:

- adults
- children and young people?

Question 6 of the key clinical questions – please see Appendix B for details.

1

Evidence statements (grading to be checked for final version)	Evidence into recommendations
No evidence that compared methods of delivery for information and support of individuals with FH was identified. One cross-sectional observational study[102] did not find a significant association between knowledge of FH and adherence to medication.	It should be noted that there is no direct comparative evidence in this population, so generic principles of communication of familial risk were agreed and specific recommendations made based on these. The recommendations reflect information (both information to be gathered and information to be given) for individuals newly identified/diagnosed and also for relatives. This may be therefore different to other risk communication, for example, familial breast cancer. The recommendations also reflect the different information needed at different times in the process of care, for example, where patients are seen in specialist clinics after having had a lipid test in primary care with a possible diagnosis of FH. Recommendations on the need to gather a family history and the ascertainment of key pieces of relevant information, both clinical data and lifestyle factors, were made. This should then be continually added to throughout the patient journey and cascade testing. Although family history may not be totally accurate[103], there was a lack of evidence on the extent of this in FH. A recommendation was made that where possible, the patient should be encouraged to check any information with relatives. As with any confidential information, healthcare professionals should be aware of current guidelines on data protection and best practice for maintaining patient records. The communication of the possibility that a relative may have inherited FH can sometimes be difficult for families and the health professionals involved in their care. Recommendations on how communication could be facilitated and patients be supported were made.

2

6.2.3 Evidence summary on information needs and support

6.2.3.1 Methods of the clinical evidence review

The searches for Question 6 were not restricted by study type or age of patients.

- Identified: 935
- Ordered: 17
- Included: 1
- Excluded: 16

6.2.3.2 Clinical evidence

Communication of familial risk

No studies were identified which addressed communication of familial risk for FH specifically.

The GDG considered that the general purpose and principles of communication of familial risk were covered in the NICE guidance for familial breast cancer[104]. and in guidelines produced by Eurogentest, a European Network of Excellence aimed at harmonising genetic testing services. These reference documents were then reviewed by expert members of the GDG and recommendations agreed.

Information and support

Several observational and qualitative studies have explored the extent to which diagnostic testing and treatment of FH impacts on the psychosocial well-being of those affected. These studies will provide background information to inform the use of specific interventions.

Marteau et al[105] studied the impact of genetic testing for FH within a known FH population. Three hundred and forty one families comprising 341 probands and 128 adults were randomized to either routine clinical diagnosis or to routine clinical diagnosis plus genetic testing. A five item perceived control over FH scale and a six item fatalism about FH scale were administered. Finding a mutation to confirm a clinical diagnosis of FH did not reduce perceptions of control or adherence to risk-reducing behaviours in this population but there was a trend in the mutation positive individuals to believe less strongly in the efficacy of diet (p=0.02 at 6 months) and more strongly in the efficacy of cholesterol lowering medication (p=0.06 at 6 months).

Using qualitative analysis of 23 semi structured interviews, Agard et al[106] found that in general, the interviewees viewed their diagnosis of FH pragmatically. Many did not look upon their diagnosis as a 'disease.' If cholesterol had been normalised and there were no other obvious signs and symptoms of coronary heart disease, they deemed themselves 'healthy.' Apart from a special concern about what to eat, the impact on the interviewees appeared to be minimal. Discussing the genetic implications of FH with family members with whom they had close contact was natural, but informing distant family members was not.

Psychosocial function in 86 boys and 66 girls treated for FH was compared with healthy peers using the Child Behaviour Checklist, Teacher's Report Form and Youth Self Report as well as semi-structured interviews[107]. Scores were similar in the children with FH and the population sample. Scores for family, mood and expression of anger were actually lower than in the population cohort.

Quality of life, anxiety and concerns among statin treated children with FH and their parents was assessed by de Jongh et al[108]using self report questionnaires. The study group consisted of 69 children and 87 parents. FH children and their parents reported no problems with regard to quality of life and anxiety. There were some FH related concerns. One third of the children thought FH could be cured; one third of children did not know what they were allowed to eat. Among parents, 79.3% suffered distress because their child had FH and 37.9% stated that FH as a genetic disease was a burden to the family.

In an attempt to facilitate family communication about FH written information packages were provided to Dutch probands[109] Eight probands and eight relatives were interviewed to evaluate this method of communication. The data suggest that probands approved the family approach for case finding, although reluctantly. The packaged aided family disclosure by reducing hesitation. However, only first degree relatives were informed and only one discussion took place. For relatives the written materials served as a cue for action and a means to gain access to a diagnostic cholesterol test.

One of the social implications of an FH diagnosis may be difficulty in obtaining life assurance. Neil et al[110] sent the same questionnaire to twenty four companies in 1990 and 2002. The mean excess rating increased from 89% (SD52) in 1990 to 158% (SD40) in 2002 ($p<0.000$) but fell to 56% (DS43) on treatment which was 33% lower ($p=0.022$) than the original rating in 1990.

It appears that in 2002 the underwriters assessed risk more realistically and this should encourage at risk individuals to be tested.

Interventions

There is very little literature on interventions to provide information and support for adults and children/young people being considered for a diagnosis of FH. One study which evaluated disease knowledge and adherence to treatment in individuals with FH was conducted by Hollman et al[102] in Sweden. Sixty eight adult patients completed questionnaires (92% response rate). There were no significant differences in demographic data between the male and female respondents. More than 90% of individuals knew about cholesterol and the reasons for drug treatment. However, only 34% of participants had knowledge of the risk of genetic transmission of FH and just 21% had knowledge of their family history; 25% of participants lacked knowledge of CHD as a risk. There was no significant correlation between knowledge and adherence to medication in this study.

No further research was identified relating to education about FH using videos, leaflets, websites or other modalities. No research was identified regarding the role of support groups, family contacts or charities to provide assistance to individuals with FH.

6.2.3.3 ***Health economic evidence***

No published, relevant evidence was identified.

6.3 Dietary interventions (see also Key components of assessment and review)

6.3.1 Recommendations

Unless otherwise indicated, recommendations are relevant for individuals with possible or definite FH. Recommendations are also applicable for individuals with both heterozygous and homozygous FH, unless otherwise indicated.

Please note, numbering is as in the NICE guideline.

1.3 Management

1.3.2 Lifestyle interventions

1.3.2.1 Lifestyle advice should be regarded as a component of medical management, and not as a substitute for lipid-modifying medication.

Diet

1.3.2.2 All individuals and families with FH should be offered individualised nutritional advice from a healthcare professional with specific expertise in nutrition.

1.3.2.3 Individuals and families with FH should be given the same advice as that given to individuals with a high cardiac risk.

1.3.2.4 Individuals and families with FH should be advised to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 10% or less of total energy intake, intake of dietary cholesterol is less than 300 mg/day and saturated fats are replaced by increasing the intake of monounsaturated fats and polyunsaturated fats. It may be helpful to suggest they look at www.eatwell.gov.uk/healthydiet/ for further practical advice

1.3.2.5 Individuals and families with FH should be advised to eat at least five portions of fruit and vegetables per day, in line with national guidance for the general population. Examples of what constitutes a portion can be found at www.eatwell.gov.uk/healthydiet and www.5aday.nhs.uk

1.3.2.6 Individuals and families with FH should be advised to consume at least two portions of fish (one of which should be oily) per week. Pregnant women with FH should be advised to limit

their oily fish to no more than two portions per week. Further information and advice on healthy cooking methods can be found at www.eatwell.gov.uk/healthydiet

1.3.2.7 The range and costs of food products containing stanols and sterols may be discussed. Individuals should be advised that if they wish to take stanols and sterols these need to be taken consistently to be effective.

1.3.2.8 Individuals with FH should not routinely be recommended to take omega-3 fatty acid supplements. For individuals post MI cross refer to NICE guidance on post MI Clinical Guideline 48.

6.3.2 Evidence statements on the effectiveness of dietary interventions

Key clinical question:

What is the effectiveness of dietary interventions to improve outcome in adults and children with heterozygous or homozygous FH?

Question 13 of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
There are no long-term studies that indicate a cholesterol lowering diet significantly lowers lipid concentrations in individuals with FH. There is evidence from short-term studies that foods containing plant sterols and stanols can reduce LDL-C cholesterol concentrations of both heterozygous adults and children with FH.	There was limited evidence in the FH population and all trials were very short term. However, motivation and compliance levels may be high in the FH population, and therefore levels of persistence may be high, trials of longer term (i.e. over 12 months) may not be needed to demonstrate a sustained effect. To corroborate the effectiveness of these interventions, high level, robust evidence from the general population was used to derive recommendations. This is justified as there is evidence that cholesterol concentrations in individuals with FH and treated with statins are lowered to a similar relative degree by dietary interventions as those not taking statins. However, the absolute change in LDL concentrations may not be clinically significant in individuals with FH, so medication should not be delayed in order to fully assess the effect of dietary intervention. Other general recommendations on lifestyle from other NICE guidance were referenced and specific factors stressed as appropriate for individuals with FH. Evidence on the longer term use of stanols and sterols was very limited. This is an important clinical question, particularly the use of these supplements as an adjunct to pharmacological treatments or as the only treatment option for those who are intolerant of all pharmacological treatments. Further research is therefore needed.

1

6.3.3 Evidence summary on the effectiveness of dietary interventions

6.3.3.1 Methods of the clinical evidence review

The searches for Question 13 were restricted to RCT level data.

- Identified: 935
- Ordered: 40
- Included: 5
- Excluded: 35 (13 included in systematic reviews)

6.3.3.2 Clinical evidence

Lipid-modifying diets

A Cochrane review entitled 'Dietary treatment for familial hypercholesterolaemia' was published in 2001[111]. There were seven eligible trials randomised controlled cross over trials. All were short term trials with each arm of the trial lasting between one and three months. The results of the analysis of these studies was as follows:

- Cholesterol lowering diet compared with no dietary intervention:
  One trial with 19 participants. NS difference.
- Cholesterol-lowering diet compared with all other dietary interventions:
  5 trials with 80 participants. NS differences for ischaemic heart disease, death, TC, LDL-C, HDL-C, TG, Apo A and Apo B,
- Cholesterol-lowering diet compared with low fat diet:
  One trial with 16 participants. No significant difference.
- Cholesterol lowering diet compared with increase in plant stanols:
  One trial of 14 children with no significant difference.
- Cholesterol lowering diet compared with increase in plant sterols:
  Two trials but one (Neil) failed to provide data from FH subgroup and the other found NS difference. A review of the Neil trial[112] however revealed that an analysis of statin treated FH individuals was provided in the text of the paper. Plant sterol therapy significantly reduced LDL-C concentration from 4.40 to 3.90mmol/l after 8 weeks ($p<0.0001$, 95% CI 0.28 to 0.72) . Placebo had no effect.

- Cholesterol lowering diet compared to high protein diet:
  Two trials were combined and a non-significant difference was found for ischaemic heart disease, death, TC, LDL-C, HDL-C, TG.

The authors of the review concluded that there was not sufficient data to reach a conclusion about the effectiveness of cholesterol lowering diets or other dietary interventions for FH, and that an RCT was needed to investigate dietary treatment for FH.

Because of the limited evidence for the effect of dietary intervention in patients with FH, high quality meta-analyses of dietary interventions in the general population were reviewed (see question 17 in Appendix B). A Cochrane review "Reduced or modified dietary fat for preventing cardiovascular disease"[113] reviewed RCTs, lasting at least 6 months, which evaluated the effect of dietary advice, supplementation or a provided diet all of which were intended to reduce or modify dietary fat or cholesterol in adults regardless of their cardiovascular status (mixed population). The meta-analysis showed that the average initial total cholesterol concentration was 5.8mmol/l and there was an average reduction of 0.64 mmol/l (a fall of 11.1%) at 6-24 month follow up.

Another Cochrane review on dietary advice "Dietary advice for reducing cardiovascular risk"[114] included RCTs lasting at least 3 months with mixed dietary advice given verbally and/or written to individuals and groups both in person and by telephone in a mixed adult population, including some trials which had screened patients for their risk and cardiovascular status. The review showed that if dietary advice was followed there was an average decrease in LDL cholesterol of 0.18 mmol/l over 3-24 months (difference in means -0.18, 95% CI -0.27 to -0.10).

A meta-analysis by Howell et al "Plasma lipid and lipoprotein responses to dietary fat and cholesterol: a meta-analysis"[115] of single group or multiple-group repeated-measures comparisons of mixed dietary interventions in a mixed adult population supplements the two Cochrane reviews. The meta-analysis showed that, on average, if patients in the high-risk range for LDL cholesterol (>4.14mmol/l) reduced their intakes of saturated fatty acids and polyunsaturated fatty acids there was a 4.5-7.7% reduction in LDL cholesterol concentrations; this study has outcomes based on a typical American diet (described as 385mg of cholesterol per day and 37% of the total energy coming from fat, of which 7% are polyunsaturated fatty acids, 17% are monounsaturated fatty acids and 7% from saturated fatty acids) in 1994.

All 3 meta-analyses were of short term trials with mixed populations and diets; however they did suggest that cholesterol lowering diets can lead to a maximum lipid lowering of 5-10%.

Plant stanols and sterols

A systematic review with meta analysis was conducted by Moruisi et al[116] to investigate the efficacy of phytosterols/stanols in lowering total cholesterol and LDL-C concentrations in FH patients. This review included only controlled, randomized, double blind studies with good compliance and sufficient statistical power. However there was heterogeneity with regard to concomitant drug use. Six trials from 1976 to 2004 qualified to be in the review. Four of these were included in the meta analysis. The results of the systematic review of 6 studies showed LDL-C reduction of 14-15% and TC reduction of 11% in children with the highest dosages of 2.3g/day plant sterol and 2.8g/day plant stanol enriched spreads. Intake of 1.6g/day plant sterol enriched spread by children resulted in reductions of 10.2% in LDL-C and 7.4% in TC concentrations. In the adult group, 2.5g/day plant sterol enriched spread caused a reduction of 10% in LDL-C and 8% in TC concentrations.

The results of the meta analysis of 124 participants on 2.3±0.5 g phytosterols/stanols/day for 6.5±1.9 weeks were as follows: TC reduced by 0.65 mmol/l (95% CI -0.88 to -0.42mmol/l, $p<0.00001$) and LDL-C by 0.64mmol/l (95% CI -0.86 to -0.43mmol/l, $p<0.00001$). I^2 was 0%.

The efficacy of plant stanols and sterols was compared in a study by O'Neill et al[117]. One hundred and thirty nine individuals with FH (most of whom were taking statins) from two medical centres in west London and healthy controls were divided into three treatment groups and randomised to receive plant sterol (Flora Pro Activ) or plant stanol (Benecol spread or Benecol cereal bar). There was no statistical differences in the response to plant sterols or stanols between FH participants taking statins and those who were unaffected. Decreases in LDL-C ranged from 4.8% to 6.6%. Changes in total cholesterol ranged from 3% to 7.5%. Decreases in both concentrations were more marked in the plant sterol group at 1 month and in the plant stanol group at 2 months. In the plant sterol group the decrease at 2 months was only half as great as at 1 month and was no longer significantly different from baseline. Changes in HDL-C were slight but there was a tendency for values to decrease by about 3% in each of the groups.

With sterols there was an increase in serum plant sterols and a significant decrease in 7 alpha-hydroxy-4-cholesten-3-one, a marker of bile acid synthesis. Stanols lowered both LDL-C and plant sterol concentrations significantly and had no effect on bile acid synthesis.

According to the authors the findings suggested that absorption of dietary plant sterols down regulates bile acid synthesis which attenuates their cholesterol lowering efficacy. The authors concluded that plant stanols are preferable for the long term management of hypercholesterolemia.

Another RCT[118] evaluated serum concentrations of lipids and plant sterols in 18 adults with FH taking statins. This double blinded randomised cross over study consisted of two consecutive 4 week intervention periods during which participants either consumed a sterol or stanol spread. The results were as follows (note, table adapted from published paper):

Mean±sem (mmol/l)	Baseline	Stanols	Sterols
TC	6.30±0.24	5.65±0.22*	5.71±0.21*
LDL-C	4.50±0.21	3.81±0.18*	3.86±0.19*
HDL-C	1.26±0.05	1.32±0.04	1.37±0.04**

*Changes in TC and LDL-C were significant from baseline p<0.05

**Changes in HDL-C were significant from baseline p<0.01 for sterols.

Plant sterols were decreased in serum, lipoproteins and red cells by about 25% with stanols and increased by 37-80% with sterols, especially in those on high statin doses.

In this study stanols and sterols both reduced LDL-C but sterols increased serum lipoprotein and red cell plant sterol concentrations in statin treated FH individuals while all the respective values were decreased with stanols.

A study by Jakulj et al[119] examined the effect of plant stanols on lipids and endothelial function in pre-pubertal children with FH. Forty one children between the ages of 7-12 years were randomised to either a low fat plant stanol containing yogurt (2g of stanol) or a low fat yogurt without plant stanol. LDL-C, HDL-C, TC and TG and flow mediated dilation for endothelial function were measured and the results were as follows:

Mean±sd	Stanol	Placebo	Mean change (95% CI)	% change
TC (mmol/l)	6.47±1.35	7.00±1.49	-0.53* (-0.79 to +0.28)	7.5%
LDL-C (mmol/l)	4.77±1.32	5.24±1.45	-0.48* (-0.69 to +0.27)	9.2%
HDL-C (mmol/l)	1.35±0.24	1.38±0.27	-0.03 (-0.13 to +0.06)	Not reported
TG (mmol/l)	0.61±0.51	0.57±0.51	-0.05 (-0.18 to +0.08)	Not reported
FMD %	10.5±5.1	10.5±5.1	+0.05 (-2.40 to +2.51)	Not reported

1 Adapted from published paper[119]

2 Changes in TC and LDL-C were significant compared to placebo p<0.001

3 In this study plant stanols reduced LDL-C concentrations in children with FH but without
4 improving endothelial function.

5 *6.3.3.3* ***Health economic evidence***

6 No published, relevant evidence was identified.

6.4 Key components for assessment and review

6.4.1 Recommendations (see also dietary interventions above)

Unless otherwise indicated, recommendations are relevant for individuals with possible or definite FH. Recommendations are also applicable for individuals with both heterozygous and homozygous FH, unless otherwise indicated.

Please note, numbering is as in the NICE guideline.

1.3 Management

1.3.2 Lifestyle interventions

1.3.2.1 Lifestyle advice should be regarded as a component of medical management, and not as a substitute for lipid-modifying medication.

Physical activity

1.3.2.9 Individuals with FH should be advised to take 30 minutes of physical activity a day, of at least moderate intensity, at least 5 days a week, in line with national guidance for the general population.*

1.3.2.10 Individuals with FH who are unable to perform moderate intensity physical activity at least 5 days a week because of comorbidity, disability, medical conditions or personal circumstances should be encouraged to exercise at their maximum safe capacity.

1.3.2.11 Recommended types of physical activity include those that can be incorporated into everyday life, such as brisk walking, using stairs and cycling. (See 'At least five a week'.).

1.3.2.12 Individuals with FH should be advised that bouts of physical activity of 10 minutes or more accumulated throughout the day are as effective as longer sessions. (See 'At least five a week'.)

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* See: Department of Health (2004) At least five a week: evidence on the impact of physical activity and its relationship to health. A report from the Chief Medical Officer. London, Department of Health. Available from www.dh.gov.uk

Weight management

1.3.2.13 Individuals with FH who are overweight or obese should be offered appropriate advice and support to achieve and maintain a healthy weight in line with the NICE obesity guideline.

Alcohol consumption

1.3.2.14 As for the general population, alcohol consumption for adult men with FH should be limited to up 3 to 4 units a day, and for adult women with FH up to 2 to 3 units of alcohol a day. Binge drinking should be avoided. Further information can be found on the Foods Standards Agency website www.eatwell.gov.uk/healthydiet/.

Smoking advice

1.3.2.15 Individuals, especially children, with FH who do not smoke should be strongly discouraged from starting because of their already greatly increased CHD risk.

1.3.2.16 Individuals with FH who smoke should be advised that because of their already greatly increased CHD risk, they should stop.

1.3.2.17 Individuals who want to stop smoking should be offered support and advice, and referral to an intensive support service in line with the NICE guidance on smoking cessation.[*]

1.3.2.18 Individuals with FH who do not wish to accept a referral to an intensive support service should be offered pharmacotherapy in line with NICE guidance on nicotine replacement therapy, bupropion and varenicline.[†]

[*] 'Brief interventions and referral for smoking cessation in primary care and other settings', NICE Public Health Guidance 1 (2006)

[†] 'Guidance on the use of Nicotine replacement therapy (NRT) and bupropion for smoking cessation', NICE technology appraisal guidance 39 (2002) and 'Varenicline for smoking cessation' NICE technology appraisal guidance 123 (2007)

6.4.2 Evidence statements on key components for assessment and review

Key clinical question:

What are the key components of assessment and review for individuals (adults and children) with homozygous or heterozygous FH including the information and support required for individuals (adults and children) with FH regarding

- diet,
- exercise and/or regular physical activity
- smoking cessation?

Question 16 of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
Components of ongoing assessment and review – see question 12 Diet – see question 13 No studies on exercise and/or physical activity in FH were identified. No studies on smoking cessation were identified. No studies on information content and support for individuals and carers were identified.	No evidence to recommendations documented.

6.4.2.1 ***Evidence summary on key components for assessment and review***

6.4.2.2 ***Methods of the clinical evidence review***

The searches for Question 16 were not restricted by study type or age of patients.

- Identified: 935
- Ordered: 0
- Included: 0
- Excluded: 0

6.4.2.3 ***Clinical evidence***

No published, relevant evidence was identified.

6.4.2.4 ***Health economic evidence***

No published, relevant evidence was identified.

7 Coronary heart disease assessment and monitoring (including referral)

7.1 Introduction

7.1.1 Ongoing clinical assessment of CHD

Individuals with FH are at a greater risk of developing CHD than individual without FH. Assessment of new onset symptoms of CHD and monitoring of any CHD progression is therefore fundamental to any management strategy. Such assessment and monitoring requires clinical judgment and should be undertaken as appropriate for the individual.

7.1.2 Recommendations

Unless otherwise indicated, recommendations are relevant for individuals with possible or definite FH. Recommendations are also applicable for individuals with both heterozygous and homozygous FH, unless otherwise indicated.

Please note, numbering is as in the NICE guideline.

1.5 Ongoing assessment and monitoring

1.5.1 Review

1.5.1.1 All treated individuals with FH should have a regular structured review carried out at least annually.

1.5.1.2 The progress of cascade testing amongst relatives should be recorded. If there are still relatives who have not been tested, further action should be discussed.

1.5.1.3 Family history should be updated and any changes in the coronary heart disease status of relatives should be noted.

1.5.1.4 Review should include assessment of smoking status, a fasting lipid profile, discussion about concordance with medication, side effects of treatment, and any changes that may be required to achieve recommended cholesterol concentrations.

1.5.2 Referral

1.5.2.1 Individuals with FH should be referred urgently* to a specialist with expertise in cardiology for evaluation if they have signs or symptoms of possible coronary heart disease.

1.5.2.2 Individuals with FH should be considered for referral for evaluation of coronary heart disease if they have a family history of coronary heart disease in early adulthood, or two or more other cardiovascular risk factors (e.g. smoking, hypertension, diabetes, male sex).

1.5.2.3 Adults and children with homozygous FH should be referred for an evaluation of coronary heart disease upon diagnosis.

1.5.2.4 In asymptomatic children and young people with heterozygous FH, evaluation of coronary heart disease is unlikely to detect clinically significant disease and referral is not routinely recommended.

* The GDG considered 'urgently' to be within a week, depending on the severity of symptoms

7.1.3 Evidence statements on ongoing clinical assessment

Key clinical question:

What is the effectiveness of investigations to assess the degree of atherosclerosis to improve outcomes in individuals with heterozygous FH?

- Exercise ECG
- Carotid IMT
- Coronary calcium
- Cardiac catheterisation

Question 12 of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
No studies were identified that reported clinical outcomes as a result of routine investigative procedures including the exercise ECG, carotid IMT, coronary calcium, cardiac catheterization.	There was no robust evidence for this question (lack of comparators, no good diagnostic studies, lack of clinical outcomes). Therefore, recommendations were made based on the experience of the GDG on: • differences in non invasive assessment of coronary heart disease or symptomatic vs asymptomatic adults • differences in monitoring for adults with FH vs people without FH • how should results from performance tests be used with other data (such as history, clinical assessment and other factors etc) • referral criteria. Any monitoring should aim to identify those people at medium risk (see also the discussion of risk in Chapter 3 on diagnosis), as people at high risk should be identifiable from diagnosis (i.e. homozygous FH or other clinical data, such as signs and symptoms of CHD). However, concern was expressed that asymptomatic coronary disease may not be detected up without routine investigation. The evidence did not allow the making of specific recommendations (such as frequency of investigations) and it was the view that clinical judgment should be used based on the individual's signs, symptoms, diagnosis, history etc. Children with homozygous FH were considered to be at high risk and therefore monitoring would identify different issues to that for children with heterozygous FH. Children with HoFH should be referred for investigations as CHD should be assumed in those cases. Any recommendations on monitoring have assumed, as in the recommendations, that all people with homozygous FH are evaluated fully at diagnosis.

1

7.1.4 Evidence summary on ongoing clinical assessment

7.1.4.1 Methods of the clinical evidence review

The searches for this question were not restricted by study type or age of individuals.

- Identified: 633
- Ordered: 47
- Included: 3 studies extracted; 16 descriptive studies in table for background information
- Excluded: 28

7.1.4.2 Clinical evidence

This question aimed to identify evidence about ongoing monitoring of coronary heart disease (CHD) risk in individuals with heterozygous FH, and the effectiveness of various modalities used to assess risk.

The literature search did not identify any papers which provided evidence for routine investigations to be used when monitoring CHD risk in individuals with heterozygous FH. A number of papers were identified which described the usefulness of particular tests to assess CHD risk. Three of these papers[120-122] compared various methods of assessment. It is important to note that measures of endothelial function are surrogate markers of vascular function and not used clinically for managing individual patients. No recommendations were made regarding the use of these methods to assess risk over time except in a research setting.

Aggoun et al[120] compared measures of endothelial dysfunction with coronary artery calcium in individuals with FH and healthy controls. Baseline vessel diameter was significantly smaller in individuals with FH compared to controls (3.2±0.3mm*, range 2.7 to 3.6 vs 3.5±0.4mm, range 3.0 to 4.3; p<0.02, respectively). Flow mediated

* Assumed to be mean±sd, not reported in paper

dilation was significantly reduced in individuals with FH compared with controls (10.7±5.3%, range 4.5% to 17.2% vs 17.3±4.6%, range 7.7% to 25.0%; p=0.002). None of the individuals with FH or controls showed calcium of the aortic root or the proximal coronary arteries, resulting in an Agatston score of 0 in every patient. For the whole group (n=26) total cholesterol and LDL-C were inversely correlated with flow mediated dilation (FMD), p=0.0003 and p=0.003 respectively. This study showed that peripheral FMD, a precursor of atherosclerosis, was altered in young heterozygous individuals with FH. This alteration occurred before coronary arterial or aortic root calcium was detected by CT scan and was independently related to hypercholesterolemia.

Another study[121] compared arterial properties in individuals with FH and healthy controls with IMT results. Non invasive ultrasonic measurements were performed of the CCA luminal systolic and diastolic diameters and IMT. Brachial artery diameters were measured after reactive hyperemia and nitroglycerine treatment. In individuals with FH there was significant reduction of systo-diastolic variations in diameter of the CCA (by 20%, p<0.001) without a significant difference in IMT. The wall stiffness was greater in FH subjects than in controls (by 27%, p=0.003). The flow mediated dilation of the brachial artery was smaller in the FH subjects (4.2±2.9%) than in controls (9.0±3.1%, p<0.001). No correlation was evident between the carotid incremental modulus and either IMT or LDL-C.

Four CHD diagnostic models were compared by Jensen et al[122]. These included

- Model A - traditional risk factors including age, sex, cholesterol, hypertension, smoking and BMI;
- Model B-cholesterol year score and
- Models C,D -aortic & coronary calcium measured by spiral computed tomography (CT).

The following variables from models A and B were significantly associated with CHD in individuals with FH:

- age, p<0.001
- treated cholesterol, p<0.05

- BMI borderline, p<0.06
- smoking, p<0.02.

Models C and D were highly significant:

- coronary calcium, p<0.001
- aortic calcium, p<0.001.

The age adjusted ROC curves for coronary calcium score were significantly greater than those for traditional risk factors (p<0.002) cholesterol year score (p<0.0001) and age adjusted aortic calcium score (p<0.0004).

Table 11 below lists papers which describe the various modalities used to assess coronary heart risk in 14 research studies. No direct comparisons are made in these papers.

Table 11 Assessment of CHD risk

Author	Population	Intervention	Results
Beppu et al[123]	25 heterozygotes 6 homozygotes 30 controls	Two dimensional echocardiography of aortic root	In the short axis view plaques were seen in all homozygotes and 5 heterozygotes.
Celermajer et al[124]	10 children with FH 20 smokers 20 adults with CAD 50 controls	Ultrasound detection of endothelial dysfunction	In smokers, FH children and adults with CAD flow mediated dilatation was much reduced or absent (p<0.001) in comparison with each relevant control group. Endothelial dysfunction is present before anatomical evidence of plaque formation in the arteries and may be an important early event in atherogenesis.

Author	Population	Intervention	Results
Cuomo et al[125]	114 subjects (5-30 years) with parental history of premature MI and 114 age and sex matched controls	Ultrasound evaluation of common carotid artery intima media thickness	Individuals with a parental history of premature MI had significantly increased carotid IMT – ages 5-18 (p=0.008) and ages 19-30 p=0.007.
Genda et al[126]	51 consecutive individuals with heterozygous FH and 279 consecutive individuals without FH	Coronary angiography	The coronary stenosis index, and the proportion of subjects with > 75% stenosis vessel subset were almost three times higher in the FH group.
Herrera et al[127]	8 Individuals with FH - 3 on 'standard therapy' (control) and 5 on apheresis	Transesophageal echocardiography	Baseline and follow up at 12 months with TEE was performed. TEE detected plaques and changes after intervention. Changes over time in the control group were not significant. Changes in the apheresis group were significantly improved in total arterial area (p<0.05) and plaque to wall ratio (p<0.05).
Hoffmann et al[128]	10 heterozygous Individuals with FH receiving LDL apheresis; 10 men with confirmed CAD; 10 men with no history of CAD	Coronary imaging by EBCT scanner and calculation of a calcium score for each calcium deposit noted on the scan.	The Individuals with FH displayed median calcification features that were almost three times higher than the medians of CAD individuals (p<0.0001). Quantification of coronary calcium provides independent and incremental information compared to clinical risk assessment or angiography and may be an important, noninvasive screening tool for early diagnosis of CAD in Individuals with FH.

Author	Population	Intervention	Results
Hopkins et al[129]	68 FH-CAD individuals and 194 FH controls with no history of CAD.	Comprehensive examination of risk factors for CAD among individuals with FH	Significant risk factors were as follows: 1. Age (p<0.0001) 2. Gender with men having 5.64 times the risk of women (p<0.0001) 3. Cigarette smoking (OR 2.71, p=0.026) 4. Smaller LDL as determined by the LDL-C/LDL apolipoprotein B ratio (OR 2.60, p=0.014) and 5. High WBC, p=0.014 Lipoprotein(a) and xanthoma were associated with risk only in very early coronary cases. After correction for age, carotid intima thickness was not associated with CAD risk. There were no other significant risk factors. The authors conclude that there is little justification for extensive investigation of risk factors in Individuals with FH. Treatment of LDL-C should be the focus.

Author	Population	Intervention	Results
Lavrencic et al[130]	28 individuals with FH (one homozygous and 27 heterozygous); 28 sex and age matched healthy controls	Use of carotid IMT to assess the extent of early atherosclerotic changes of carotid arteries	The mean carotid IMT was significantly greater in individuals with FH than in controls ($p<0.001$). In all subjects, the mean IMT was significantly correlated with TC, LDL, TG and systolic blood pressure. Thus B mode ultrasonography could provide a useful tool to identify those who are more likely to develop premature atherosclerotic disease.
Mabuchi et al[131]	5 homozygous and 105 male and 56 female heterozygous individuals	Use of coronary angiographic study to predict CV risk.	A coronary stenosis index score (CSI) was calculated based on angiographic results and age. The results were as follows: Mean age mortality: • homozygotes 25.9 years • male heterozygotes 56 years • female heterozygotes 69.2 correlated with coronary stenosis score of 20, calculated at angiogram.

Author	Population	Intervention	Results
Michaelides et al[132]	194 heterozygous individuals	Exercise testing in asymptomatic individuals	22 % (42) of the 194 asymptomatic individuals had a positive ET. A multivariate analysis adjusted for sex, BMI, smoking, diabetes, family history of CAD, presence of xanthomas and lipid concentrations showed that only high fibrinogen concentrations were significantly and independently associated with a positive ET. The adverse effects of FH on the CV system may be partly mediated by coagulability factors.
Riberio et al[133]	3 homozygotes and 32 heterozygotes. 32 age matched healthy normolipidaemic controls were included for comparison.	Use of cross-sectional echocardiography for identifying aortic root lesions and coronary artery ostial stenosis	All three homozygotes showed CV disease on echo and cardiac cath confirmed this. Echo of aortic root in 32 heterozygotes was similar to control but 10 individuals showed abnormal bright echoes within the aortic cusps and four had supravalvular changes similar to but less severe than the homozygotes. Serial cross sectional echo may be useful for monitoring the progress of CV disease and the effect of treatment.

Author	Population	Intervention	Results
Tato et al[134]	59 heterozygous and 6 homozygous individuals with FH	Use of cardiac echocardiography to assess for CAD	Pathological echo changes were found in 59% of heterozygotes and in all homozygotes. In heterozygotes, aortic root sclerosis usually appeared after the age of 30; in homozygotes severe changes were present before the age of 10. A pathological echo correlated strongly with the presence of overt CAD. Echo proved to be a useful non-invasive method for evaluation of individual coronary risk.
Tonstad et al[135]	90 FH children and 30 controls	Assessment of CV risk factors in relation to carotid IMT	Mean carotid IMT was greater in FH than in controls (p=0.03). Mean intima-media thickness in the far wall of the carotid bulb was positively associated with concentrations of apo B, homocysteine and fibrinogen after control for pubertal state. These associations were unchanged after multi-variate analysis. The authors suggest that B-mode ultrasonography may prove to be a useful tool in risk stratification of children with FH.

Author	Population	Intervention	Results
Wendelhag et al[136]	53 individuals with FH and 53 controls with cholesterol below 6.5 mmol/l and matched on sex, age, height and weight	Three year follow up of the progression of intima media thickening in carotid and femoral arteries after therapy with pravastatin, cholestyramine or a combination	Using B-mode ultrasound it was possible to perform a non invasive study of the morphology of large, superficially located arteries, the carotid and femoral arteries , and to determine that there was a net difference in of -0.06 mm in mean carotid intima-media thickness (CI -0.22-0.01) and of -0.09 mm in maximum carotid intima-media thickness (p<0.05, CI -0.16—0.01).
Wittekoek et al[137]	248 Individuals with FH; 106 had CHD with the remaining subjects had no clinical evidence of CHD	IMT measurements of 20 prespecified carotid and femoral arterial wall segments	All IMTs in both groups were severely thickened. In individuals with CHD the distributions of IMT within tertiles for both arterial segments were opposite to those found in those without CHD (p<0.05 for both segments). The largest absolute differences were found in the femoral artery. The OR for clinically manifest atherosclerotic disease for the IMT measurement of the common femoral artery was approximately 3 and highly significant (p=0.007) while for the common carotid artery this was only 1.6 (p value non-significant).

Due to the paucity of evidence to support recommendations for ongoing monitoring in this group of high risk patients, the GDG referred to the National Service Framework (NSF) for Coronary Heart Disease (2000)*, and specifically the

* www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4094275

recommendations on effective policies for both primary and secondary prevention of CHD. Individuals with heterozygous FH clearly meet the NSF criteria for 'high risk' which includes those with multiple risk factors for heart disease who are typically three to five times more likely to die, suffer a heart attack or other major coronary event than people without such conditions or risk factors.

7.1.4.3 ***Health economic evidence***

No published, relevant evidence was identified.

8 Specific treatment

8.1 Introduction

8.1.1 Specialist interventions – apheresis and transplantation

Individuals with homozygous FH and, in exceptional circumstances, those with homozygous FH may need additional, specialist treatments if drug treatment is not able to achieve the necessary LDL-C lowering.

LDL-C apheresis is a mechanical method of removing LDL-C from the blood, similar to that used for kidney dialysis. It is a process that needs to be undertaken approximately every two weeks and requires specialist administration and monitoring.

Liver transplantation (with or without the heart) is a surgical treatment option; again, this is generally only an option for people with homozygous FH, and rarely for those with heterozygous FH. Functioning liver cells that are able to process the LDL-C in the blood are transplanted and this is effectively a cure for FH. However, as with any transplant, there are considerable risks attached.

8.1.2 Contraception and obstetric issues (specifically related to drug treatment)

Girls and women being treated for FH need relevant and up-to-date information on the risks of drug treatment on any pregnancy. This will become increasingly important as girls and women are being treated earlier. Women and their partners should be reassured though, that with appropriate planning and counselling, most pregnancies are successful (see recommendations for details).

8.2 Specialist interventions

8.2.1 Recommendations

Unless otherwise indicated, recommendations are relevant for individuals with possible or definite FH. Recommendations are also applicable for individuals with both heterozygous and homozygous FH, unless otherwise indicated.

Please note, numbering is as in the NICE guideline.

1.3.3 Specialist treatment

LDL-lowering apheresis

1.3.3.1 Adults and children with clinical homozygous FH should be considered for apheresis. The timing of initiation of apheresis will depend on other factors, such as response to lipid modifying medication and presence of coronary heart disease.

1.3.3.2 In exceptional cases, individuals with heterozygous FH with progressive, symptomatic CHD, despite maximal tolerated lipid modifying medication and optimal medical therapy, should be considered for apheresis. This should be undertaken in a specialist centre on a case by case basis and data collected into an appropriate registry.

1.3.3.3 Fistulae are the preferred access in individuals treated with apheresis and individuals should be counselled about possible benefits and complications.

1.3.3.4 Routine monitoring of iron status should be carried out and iron supplementation initiated as required in individuals being treated with apheresis.

1.3.3.5 ACE inhibitors should not be used in individuals being treated with LDL apheresis, and instead substituted with angiotensin receptor blocking agents.

1.3.3.6 All hypotensive agents should be reviewed and considered for discontinuation on the morning of the day of apheresis.

1.3.3.7 Warfarin should be discontinued approximately 4 days before apheresis and substituted with low molecular weight heparin.

1.3.3.8 Anti-platelet therapy should be continued for individuals treated with apheresis.

Liver transplantation

1.3.3.9 Individuals with homozygous FH should be offered liver transplantation as an option following failure of medication and apheresis.

1.3.3.10 The decision to refer for organ transplantation should be undertaken in conjunction with the patient and/or relatives in an appropriate specialist setting, following a discussion of the benefits and potential harms of intervention.

8.2.2 Evidence statements on apheresis

Key clinical question:

What is the clinical and cost effectiveness of the following interventions to reduce LDL cholesterol and improve outcome in individuals with either heterozygous FH or homozygous FH:

- apheresis alone versus no intervention/ usual care?
- apheresis and drug therapy versus drug therapy alone?
- plasmapheresis & drug therapy versus drug therapy alone?
- ileal bypass versus no intervention (heterozygote)?
- apheresis versus plasmapheresis?

Question 10 of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
There are no randomized controlled trials for treatment of FH homozygous individuals. However observational studies of FH homozygous individuals show treatment with apheresis lowered LDL concentrations by 72% compared to use of multiple lipid-modifying maximal drug therapy. Controlled before and after studies showed that LDL apheresis treatment of Individuals with FH who were primarily heterozygous and receiving lipid lowering drugs demonstrated a total percent decrease in LDL-C ranging from 34-81%. In two small studies of individuals with heterozygous FH receiving apheresis and lipid modifying drug treatment, coronary artery disease regressed in 4 individuals (16%) and in 3 individuals (13%).[138;139] A study[139;140] which followed subjects receiving apheresis for up to six years demonstrated a 1.8% incidence of adverse clinical events which included hypotension and a moderate decrease in haemoglobin and ferritin concentrations. Fluctuations in plasma iron and ferritin concentrations were also noted in a case report of two homozygous individuals.[141] There are no trials comparing effectiveness of plasmapheresis & drug therapy versus drug therapy alone. Since the advent of statins there have been no studies comparing ileal bypass versus no intervention. There are no trials comparing effectiveness of apheresis versus plasmapheresis. Although the cost-effectiveness of apheresis remains as yet unproven and no published evidence	Specific issues considered by the GDG included • initiation and discontinuation of treatment • timing of the lipid measurements and changes over time • frequency of apheresis • the measurement of progression of coronary heart disease, specifically in children (see Chapter 7 on assessment and monitoring) <u>Apheresis for patients with homozygous FH</u> Although RCTs were identified, lower level studies were used to corroborate and provide longer term safety/effectiveness data as potentially individuals may be on this treatment for a long time. The evidence statements therefore reflect the lack of robust RCT evidence and recommendations have been made on the observational studies. Clinical experience also supports the effectiveness of apheresis in the reduction of xanthomatosis. A main criticism of the evidence was that most older studies used less well-tolerated drugs or sub-optimal doses, whereas current practice is that all patients undergoing apheresis are on maximal treatment (high dose statins plus nicotinic acid plus another lipid lowering drug plus omega 3 supplements). Generalisability was a concern as there are many factors that differ across countries, for example different criteria for treatment, different marketing/industry, and different financial structures for healthcare. As in most areas, there was minimal evidence for children, but clinical experience is that earlier treatment is better and that progression of coronary heart disease may be slowed, noting as above however that evidence for monitoring in children is also very limited.

was identified, a simple analysis indicates that it is likely to be deemed cost-effective for a treatment with orphan status.	There is no direct clinical evidence on the optimal frequency of treatment, and the patient view was that factors such as time (recovery, travelling etc) and the impact on the family were important. Frequency therefore would be affected by clinical factors and patient acceptability. Apheresis for patients with heterozygous FH Current practice is that individuals with heterozygous FH have access to LDL-C apheresis, and although access is minimal, the GDG agreed that withdrawing this/access was not justified. Apheresis is only carried out in individuals already on maximum tolerated drug therapy who have symptomatically deteriorating CHD, for whom the additional reduction of LDL by the mechanical means of apheresis can reduce CHD. The identified evidence did not directly support definitive entry criteria for this treatment. There were concerns over the low level of evidence, extrapolating from trials in individuals with homozygous FH, and the arbitrary nature of any cut-offs. Apheresis is only therefore recommended in exceptional cases for this population. Although the cost-effectiveness of apheresis remains as yet unproven our simple analysis indicates that it is likely to be deemed cost-effective for a treatment with orphan status. Because of the small numbers of patients involved, we recommend apheresis as a treatment option for the estimated 50 or so patients who would benefit from treatment.

8.2.3 Evidence summary on the effectiveness of apheresis

*8.2.3.1 **Methods of the clinical evidence review***

The searches for this review were not restricted by study type or age of individuals. Studies in languages other than English (specifically Japanese and German) were also scanned on advice from the GDG.

- Identified: 639 English and 157 foreign language
- Ordered: 94
- Included: 21
- Excluded: 73 (studies with less than 20 individuals excluded except where there was no other evidence available)

*8.2.3.2 **Clinical evidence***

Apheresis alone versus no care/usual care

In a before and after study of twenty five homozygous individuals with FH and heterozygous individuals with organ involvement, e.g. xanthomatosis, general atherosclerosis, CHD, were carefully screened and pretreated with diet and drugs for 6 months and then placed on apheresis[142]. No lipid lowering drugs were used during the trial. The effects on lipid concentrations were as follows:

	Before treatment	**After treatment**
Mean TC (mmol/l)	8.35 (7.13-10.9)*	3.54 (2.72-5)
Mean LDL-C (mmol/l)	6.36 (4.77-9.51)	2.10 (1.13-3.31)
Mean HDL-C (mmol/l)	1.13 (0.67-1.92)	0.87 (0.51-1.41)

Table adapted from published paper[142].

* Assumed to be mean and range, not reported in paper

Quantitative measurement of 111 circumscribed coronary stenoses showed a mean stenosis degree of 45±26% at entry and 43±22% at final cineangiofilm demonstrating no significant change. Eight localized stenoses showed a regression of more than 10% and 11 had a progression of more than 10%. An expert panel consensus evaluation for overall coronary atherosclerosis determined that no individual had evidence of regression, there were no changes in 16 individuals, debatable progression in 3 individuals and undecided in one individual.

Apheresis and drug treatment versus drug treatment alone

A systematic review of literature from 1998-2004 which evaluated apheresis and drug treatment versus drug treatment alone was conducted by Moga and Harstall[143]. A thorough search of the literature was done and strict inclusion and exclusion criteria were applied. However, the quality assessment of the literature was not described. Also, only two apheresis systems were included and no studies with mixed heterozygous/homozygous populations were reviewed. A meta-analysis was not done as there was no RCT evidence. The reviewers concluded that there was weak evidence that the DSC Liposorber system in combination with lipid lowering drug therapy lowered LDL cholesterol concentrations in older individuals (>50 years of age) with severe FH when they were treated at least once every two weeks for a minimum of one year. The mean percent decrease in LDL-C ranged from 34%-81%. However, the use of a combined therapy meant that the contribution of LDL apheresis to the treatment effect was unclear.

As there is very little evidence in this area and no meta-analysis could be done in the Moga review[143] due to the variety of study designs, an assessment of the individual included studies which met the GDG inclusion criteria was undertaken.

The LAARS study[144] randomised 42 Dutch men, aged between 30-67 years to treatment for two years with either biweekly LDL apheresis plus simvastatin 40 mg/day or simvastatin 40mg/day alone. Sixteen individuals in each group were heterozygous for FH (76% of study population). All individuals had severe coronary atherosclerosis.

A constant reduction of 63% of LDL-C was found in the apheresis group to an interval mean concentration of 2.95±1.13mmol/l. TC, LDL-C and Apo B showed the same course and were significantly lower in comparison to the medication group.

Mean±sd	Apheresis (n=21)	Medication alone (n=21)	p-value
TC (mmol/l)			
Basal	9.72±1.84	9.85±2.17	
Interval mean	4.63±1.18	5.95±1.60	
% change	-52.60±6.60	-39.50±7.70	0.005
LDL-C (mmol/l)			
Basal	7.78±1.86	7.85±2.34	
Interval mean	2.95±1.13	4.13±1.58	
% change	-62.90±8.3	-47.40±8.10	0.01

Table adapted from published paper[144]

There was no significant difference in the number of clinical events. The mean change per patient in percent stenosis was not different for both groups. However in the apheresis group the total number of lesions was decreased as the result of the disappearance (<20%) of 40 minor stenoses versus 20 in the medication group (p=0.005)whereas 23 versus 32 new stenoses were found respectively (p=0.19). By categorical approach, 9 individuals in the apheresis group and 11 individuals in the medication group were classified as progressors. Two and 5 individuals were regressors respectively and the remaining men showed stable disease. Exercise tolerance was significantly improved in the apheresis group by bicycle exercise tests(p<0.001 for time).

A controlled trial conducted in Japan[138] assessed the difference in frequency of definite progression and regression coronary artery stenosis. Twenty five heterozygous individuals with FH were treated with LDL apheresis and drugs and 11 individuals were treated with drugs alone. Three lipid lowering drugs, pravastatin, probucol and bile acid sequestrants were used in all individuals if tolerated. All underwent follow up angiography 2.3 years later. Mean minimum lumen diameter increased significantly in the LDL apheresis group and decreased in the control group. Progression of coronary stenosis occurred in 64% of controls and 8% of apheresis group. Regression was found in 16% of the apheresis group and in no controls. There was a significant difference in frequency of individuals with progression of coronary artery stenosis,

those unchanged and those with regression between the two groups (p<0.004). Three individuals in the apheresis group had clinical coronary events and four individuals in the control group had an event. Lipid concentrations were also reported. The mean (±sd) differences in lipid concentrations between the groups averaged over the follow up period were a lowering of both TC by 17% (5.07±0.92mmol/l versus 6.10±1.87; p<0.05) and of LDL-C by 18% (3.59±0.78 versus 4.36±1.49; p<0.05).

A small controlled trial[145] in Japan studied the long term effects of LDL apheresis on carotid atherosclerosis in two groups of individuals. In the LDL apheresis and drug group there were 2 homozygotes and 9 heterozygotes; the control group on drugs alone consisted of 10 heterozygotes. All apheresis individuals were taking a statin;10 were on probucol and one on cholestyramine. Eight of the control individuals were taking statins and 7 on probucol. The two groups were compared for changes in lipid concentrations and the development or progression of carotid atherosclerosis over 4 years time.

Table 12 Results for the LDL apheresis group

	Mean baseline (±sd)	**Time average value (±sd)**	**Change**
Homozygous			
TC (mmol/l)	17.0±3.95	7.42±0.40	56.4%
LDL (mmol/l)	16.0±3.60	6.43±0.07	60.5%
Heterozygous			
TC (mmol/l)	12.9±2.47	5.63±1.26	56.5%
LDL (mmol/l)	11.5±2.46	4.32±1.20	56.8%
Control			
TC (mmol/l)	7.18±1.14	5.62±0.79	21.7%
LDL (mmol/l)	4.81±1.26	3.71±0.58	22.9%

Table adapted from published paper[145]

In the LDL apheresis group, progression of plaques occurred in nine of the 11 individuals; one patient remained unchanged and one patient showed regression. In the control group all

individuals showed progression. The difference between the two groups was not statistically significant. The annual progression rate of mean maximum IMT was a mean of 0.0002mm/year in the LDL apheresis group. This was significantly lower than the mean of 0.0251 mm/year in the control group ($p<0.005$). In the LDL apheresis group the mean maximum IMT in heterozygous individuals with FH was -0.0023mm/year. Although progression occurred in the homozygous individuals it was markedly slower than in the control group (p value not reported).

The long term effects of LDL apheresis were studied in 29 individuals who participated in the follow-up phase of a controlled trial[146]. In the original trial all homozygous individuals received apheresis but individuals with heterozygous FH were randomly assigned to diet, drug therapy (not described) and LDL apheresis (n=45) or to diet and drug therapy alone (n=9). Results for individuals with data at the 4 year follow-up time point are presented below. Controls received apheresis only after the initial controlled phase of the study ended at 18 weeks.

	Homozygotes (n=7)	**Treated heterozygotes (n=19)**	**Control (n=3)**
LDL-C baseline (mmol/l)	12.31	6.23	6.18
4 years	9.03	5.95	6.21
p-value	p=0.059	p=0.22	
HDL-C baseline (mmol/l)	0.46	0.49	1.54
4 years	0.55	0.48	0.58
p-value	p=0.33	p=0.82	

Table adapted from published paper[117]

A total of 24 unique cardiovascular events occurred during the 5 years before initiation of LDL apheresis whereas only 7 events occurred during the period of treatment with LDL apheresis, a drop of 44% from 6.3 events per 1000 patient-months to 3.5 per 1000 patient-months.

There were no clinically important changes in laboratory values over time. Hypotension was the most common adverse event in 0.9% of procedures. One episode of blood loss with anaemia occurred.

A comparison of LDL apheresis with bile acid sequestrants and statins in decreasing lipid concentrations was carried out in a multicentre study in Wales and London[147]. The study was a randomised angiographic trial of the effects on coronary atherosclerosis of fortnightly LDL apheresis plus 40mg simvastatin daily or colestipol 20g plus simvastatin daily. Changes in lipid concentrations and in coronary stenosis were reported.

	Apheresis (n=20)		**Drugs alone (n=19)**		
	Mean baseline (sd)	**Interval mean (sd)**	**Mean baseline (sd)**	**Interval mean (sd)**	**p-value**
TC (mmol/l)	9.0 (2.0)	5.2 (0.7)	8.1 (1.7)	5.3 (1.0)	ns
HDL-C (mmol/l)	1.1 (0.2)	1.1 (0.2)	1.1 (0.3)	1.15 (0.3)	ns
LDL-C (mmol/l)	6.8 (2.2)	3.2 (0.8)	6.1 (1.8)	3.4 (1.1)	p=0.03

Table adapted from published paper[147]

The interval means between apheresis procedures did not differ significantly from the mean values in the drug group for TC and HDL. The LDL value was significantly lower in the apheresis group (p=0.03).

Diameter stenosis	**Apheresis (n=20)**	**Drugs alone (n=19)**	**p-value**
Mean % per patient (sd)	-1.80 (4.00)	-2.25 (5.50)	ns
Mean % lesion change (sd)	-1.91 (9.38)	-2.06 (9.21)	ns

Table adapted from published paper[147]

The mean changes in percent diameter stenosis after 2 years treatment did not differ significantly between the apheresis and drug groups on either a per patient basis or per lesion basis.

Several studies followed small cohorts of individuals who did not adequately respond to drug treatment and were subsequently treated with LDL apheresis.

Thirty four heterozygous FH individuals in Germany with angiographically proven coronary heart disease who had not responded to maximum tolerated doses of simvastatin were treated with regular LDL apheresis by differing systems for (mean and SEM) 3.5±2.5 years[139]. Lipid concentrations changed as follows:

	Immunoadsorption	**Dextran sulphate adsorption**	**HELP apheresis**
Mean TC (mmol/l) ±sd			
Baseline	7.69±3.07	7.79±1.82	9.43±1.84
Mean of final 5 treatments	5.02±0.87	4.95±1.12	5.33±0.53
Mean LDL-C (mmol/l) ±sd			
Baseline	6.63±1.41	5.92±2.02	6.51±1.43
Mean of final 5 treatments	3.17±0.58	3.25±0.68	3.56±0.51
Mean HDL-C (mmol/l) ±sd			
Baseline	1.05±0.31	1.05±0.12	0.99±0.15
Mean of final 5 treatments	1.28±0.25	1.18±0.18	1.23±0.21

Table adapted from published paper[139]

In 23 individuals followed for more than 2 years, there was a regression of coronary atherosclerosis in 3 individuals and in all other cases there was a stop in progression of coronary lesions (that is, no change). Three individuals died of coronary complications after 6 and 9 months of therapy; one after 6 years. One patient suffered a non fatal MI.

34 individuals with FH, of whom 31 were refractory to conventional drug therapy (three individuals could not tolerate lipid lowering drugs), were maintained on pharmacotherapy if tolerated and also treated with LDL apheresis[148]. A comparison of lipid concentrations before and after treatment and of four different apheresis systems was done.

The results of laboratory studies showed the following:

	Baseline	Under treatment	Mean % change
Mean TC (mmol/l) ±sd*	10.5±1.92	5.42±1.52	-51.9%
Mean LDL-C (mmol/l) ±sd	7.42±1.95	3.70±1.72	-49.8%
Mean HDL-C (mmol/l) ±sd	1.05±0.19	1.10±0.33	+4.4%
Mean TG (mmol/l) ±sd	5.63 (sd not given)	3.26 (sd not given)	-57.8%

Table adapted from published paper[148]

Fibrinogen decreased by 73.3%.

In a study of the long term (6 years) efficacy of LDL apheresis on coronary heart disease[149] 87 individuals received intensive drug therapy and 43 individuals received medical therapy and LDL apheresis. LDL apheresis was compared with aggressive drug therapy which included 10-20mg/day pravastatin or 5-10mg/day simvastatin and then 500-1000mg/day of probucol and/or 4-12g/day of cholestyramine or 400mg/day of bezafibrate.

Using time averaged concentrations of LDL, because the rebound curves of TC and LDL after apheresis are not linear, it was shown that LDL apheresis significantly reduced LDL cholesterol from 7.42±1.73 to 3.13±0.80mmol/l (58%) compared with the group taking drug therapy (6.03±.32 to 4.32±1.53mmol/l (28%), p<0.0001). TC decreased by 53% from baseline concentrations (9.28±1.71mmol/l to 4.40±0.78mmol/l) with LDL apheresis and by 25% (from 7.94±1.24 to 5.92±1.58mmol/l) with drug therapy (p<0.0001).

The proportion of individuals without any coronary events was significantly higher in the LDL apheresis group (90%) than in the drug therapy group (64%) by 72% (p=0.0088).

Thirty individuals with FH resistant to diet and maximum lipid lowering drugs (not identified) were treated for up to 6 years with LDL apheresis[150]. Prior to treatment 23 of 30 individuals suffered from coronary heart disease. Twenty nine were heterozygous and 1 was homozygous.

* Assumed to be sd, not reported in paper

Lipid concentrations changed as follows after treatment:

	Baseline	**Under treatment**	**% change**	**p-value**
Mean TC (mmol/l) ±sd	10.4±1.9	5.5±1.5	-47.2%	p<0.0001
Mean LDL-C (mmol/l) ±sd	7.42±1.95	3.8±1.67	-48.7%	p<0.0001
Mean HDL-C (mmol/l) ±sd	1.05±0.02	1.16±0.29	+10.5%	p<0.0001
Mean TG (mmol/l) ±sd	5.63	3.4	-39.8%	p<0.0001

Table adapted from published paper[150]

Fibrinogen dropped by 25.6% (p<0.001). These results were confirmed in a second study published in 1997[151].

The K-LAS II study was carried out in Japan[152] among 37 individuals who continued for a mean of 5 years on LDL apheresis. All individuals received concomitant treatment with lipid lowering drugs including daily doses of 10-20mg pravastatin, 1-2g probucol, 18-27g cholestyramine and/or 600-750mg nicotinic acid. In this study group there were no significant differences between mean pre-treatment concentrations of TC, HDL-C, LDL-C, TG from the end of the phase 1 study and the end of phase 2.

	Phase 1	Phase 2	% change	p-value
TC (mmol/l)				
Mean pre-treatment ±sd	7.18±1.64	6.79±1.56	-5.4%	p=0.071
HDL-C (mmol/l)				
Mean pre-treatment ±sd	0.87±0.28	0.79±0.22	-8.8%	p=0.112
TG (mmol/l)				
Mean pre-treatment ±sd	1.43±0.87	1.40±0.92	-1.6%	p=0.255
LDL-C (mmol/l)				
Mean pre-treatment ±sd	5.4±1.5	5.13±1.38	-5.3%	p=0.156

Table adapted from published paper[152]

Overall 7 (18%, 7/38) cardiovascular events were observed during a mean of 5 years of LDL apheresis. One additional patient experienced new unstable angina.

Two studies describe the results of the HELP-LDL-apheresis multicentre study[153;154]. Seidel et al[153] reported on the evaluation of safety and cholesterol lowering effects of apheresis during the first 12 months. Ten German centres participated and 51 individuals aged between 28 and 65 years were recruited. Patients continued on a variety of lipid lowering drugs including bile acid sequestrants, fibrates, nicotinic acid and sitosterol. All individuals had severe CHD and type IIa hypercholesterolaemia. A distinction between individuals with heterozygous and homozygous FH was not made. Forty six individuals completed 12 months of regular treatment. At 12 months the following results were reported:

	Baseline	12 months	p-value
Mean TC (mmol/l) ±sd			
Pre-apheresis	9.18±2.3	7.10±1.05	p<0.001
Post-apheresis	4.62±1.46	3.51±0.67	
Mean LDLC (mmol/l) ±sd			
Pre-apheresis	7.26±2.2	5.21±1.05	p<0.001
Post-apheresis	3.08±1.36	1.95±0.62	
Mean HDL-C (mmol/l) ±sd			
Pre-apheresis	1.04±0.28	1.24±0.28	p<0.001
Post-apheresis	0.94±0.36	1.06±0.31	
Mean TG (mmol/l) ±sd			
Pre-apheresis	2.07±1.46	1.66±0.01	p<0.05
Post-apheresis	1.69±0.64	1.38±0.39	

Fibrinogen concentrations fell 19-24% over the course of therapy and plasminogen concentrations were unchanged.

Schuff-Werner et al[154] then published the final evaluation of the effect of regular treatment on LDL cholesterol and the course of coronary heart disease. The mean±sd pre/post apheresis LDL-C concentrations decreased from 7.33±2.26/3.10±1.41 mmol/l at first apheresis treatment to 5.21±1.03/1.97±0.62 mmol/l after 1 year to 5.26±1.1 /1.97±0.51 mmol/l after 2 years. The angiographies from 33 individuals obtained before and after 2 years of regular treatment were evaluated blindly and the mean degree of stenosis of all segments decreased from 32.5% (sd=16) to 30.6% (sd=16.8) over the 2 years. A regression >8% was observed in 50/187 (26.7%) segments whereas 29/187 (15.5%) segments showed progression. In 108/187 (57.8%) segments the lesions were stable (<8% deviation) over 2 years.

Thirty seven individuals were treated by 13 institutions registered as member of the Japan LARS group; the group consisted of 7 homozygous FH and 25 heterozygous FH 2 familial combined hyperlipidemia and 3 individuals with high cholesterol not confirmed as FH[155]. Most of the individuals had been treated with cholesterol lowering drugs such as probucol, pravastatin and cholestyramine in combination with LDL apheresis. Angiography was performed at intervals of 49 months for homozygotes and 32 months for heterozygotes to assess for changes in CHD. The evaluation of regression of no change and of progression in a lesion for each patient was defined as follows:

- individuals with at least one regressed segment and without any progressed segment were represented as regression;
- individuals with only unchanged segments were represented as no change; and
- individuals with at least one progressed segment and without any regressed segment were represented as progression.

Such representation led to the following results:

- regression occurred in 14 of 37 individuals (37.8%);
- no change, in 18 individuals (48.6%) and
- progression occurred in 5 individuals (13.5%).

Plasmapheresis & drug therapy versus drug therapy alone

No evidence was identified for this question.

Ileal bypass versus no intervention (heterozygote)

Two papers on this topic were identified: one case study[156] and one observational study of 11 individuals[157] conducted without the use of statin therapy prior to surgery. The latter study was evaluated to provide background information only. Eleven individuals with heterozygous FH were treated by partial ileal bypass. Postoperatively, mean TC concentrations fell by 26% then rose to 20% below preoperative concentrations at 20-24 months (absolute values not provided). Five individuals had refractory hypercholesterolemia and were then treated with lovastatin. One was treated with lovastatin and LDL apheresis. All individuals experienced diarrhoea which improved with time but two individuals required reversal of their bypass for intractable gas bloat syndrome.

Apheresis vs plasmapheresis

This case study of two South African females aged 17 years with homozygous familial hypercholesterolemi[141] was included due to the paucity of evidence comparing apheresis to plasmapheresis. It is provided for background information only. Pre- and post-treatment lipid concentrations on three differing schedules of apheresis (twice per week, once per week and every two weeks) and after plasmapheresis (biweekly) were presented.

'Quasi steady state' values, i.e. the values just before every procedure representing the least favourable lipoprotein values in the course of therapy, were reported.

Absolute numbers were not provided. Graphs showed a profound reduction in the quasi steady state concentrations of plasma cholesterol, LDL and Apo B in schedules 1 and 2 of apheresis. In the first female the LDL/HDL ratio fell by 74% on schedule 1 (bi weekly treatment), 68% on schedule 2 (weekly) and 37% on schedule 3 (every two weeks) and 46% on plasmapheresis. A similar although less dramatic trend was noted in the second female but in neither was there a significant difference in these ratios comparing schedule 3 of apheresis with plasmapheresis (p-value not given).

Other laboratory parameters remained stable except for iron and haemoglobin concentrations which were reduced with both procedures.

Apheresis alone versus apheresis and statin therapy

This small study of 9 Japanese homozygous individuals with FH[158] undergoing LDL apheresis was included because it is unique in studying the addition of statins in previously untreated individuals receiving apheresis. It is presented for background information only. Five of the individuals were LDL receptor negative and four were receptor defective. Atorvastatin was given in escalating doses of 10, 20 and 40mg/day. The effect of atorvastatin-apheresis therapy in the two groups compared with regular treatment was as follows:

	Regular treatment	Combined treatment	p-value
Mean TC (mmol/l) ±sd			
Negative	11.87±0.27	12.1±2.54	ns
Defective	7.49+2.06	6.54±2.31	p<0.05
Mean LDL-C (mmol/l) ±sd			
Negative	10.08±2.16	10.28±2.15	ns
Defective	6.38±1.91	5.44±2.22	ns
Mean HDL-C (mmol/l) ±sd			
Negative	1.00±0.11	1.08±0.13	ns
Defective	0.77±0.02	0.87±0.09	ns
Mean TG (mmol/l) ±sd			
Negative	1.76±1.03	3.49±2.42	ns
Defective	0.74±0.32	0.52±0.19	p<0.05

Table adapted from published paper[158]

Five of the nine individuals responded well to atorvastatin (20.6% decrease in LDL-C); four of these individuals were receptor defective. Of the five receptor negative individuals only one showed a good response (14.9% decrease in LDL-C).

Apheresis, statins and ezetimibe versus apheresis and statins alone

This case series of six Japanese homozygotes was included because it provided the only information on the treatment of homozygous individuals with FH on apheresis with ezetimibe[159]. It is useful for background information only. Receptor negative homozygous individuals with FH on LDL apheresis were included in this study. These individuals were also being treated with a range of other cholesterol lowering drugs including atorvastatin at varying doses and probucol 500mg or 1000mg/day. Changes in lipid concentrations following treatment with ezetimibe were as follows:

	LDL-C	TC	TG	HDL-C
Mean pre-treatment (mmol/l) ±sd	10.04±1.11	12.17±1.73	1.21±0.59	0.79±0.22
Mean post-treatment (mmol/l) ±sd	9.09±1.22	11.09±2.03	1.28±0.69	0.72±0.19
% change	-9.57%	-9.07%	+18.78%	-7.58%
95% CI (%)	-14.11 to -5.03	-17.43 to -0.72	-42.51 to +80.06	-18.96 to +3.82

Table adapted from published paper[159]

With the exception of one patient, significant decreases in LDL-C and TC at 2 weeks after each apheresis procedure were seen during the period from 4-12 weeks of treatment (p-values not given).

Safety

A retrospective analysis of laboratory and clinical safety data was reported by Sachais et al[160]. Data from 34 Americans receiving LDL apheresis treated from 1996-2003 were collected. The average length of treatment was 2.5 years. Adverse reactions were rare. The most common reactions were light-headedness (1.5%), nausea/vomiting (1.2%), hypotension (0.73%), and chest pain (0.58%). Examination of BUN, creatinine, AST, ALT, total protein, albumin and PT, PTT revealed that all values were within normal range and none were significantly altered by long term treatment. All individuals had markedly decreased LDL-C and triglycerides after each treatment without a significant change in HDL-C. All individuals had decreased time averaged LDL-C (values not provided). After treatment with LDL apheresis for an average of 2.5 years, individuals had a 3.2 fold decrease in cardiovascular events and over a 20 fold decrease in cardiovascular interventions. Subjectively, individuals reported decreased episodes of angina symptoms and improved quality of life.

8.2.3.3 ***Health economic evidence***

No relevant health economics evidence was found in the searched published literature for any relevant comparison. Also, the clinical evidence review indicates that there is a lack of robust clinical evidence of effectiveness, including epidemiological and prognostic data, which would be needed to populate an economic model. There is likely to be a high degree of uncertainty around the cost effectiveness estimates produced by such a model.

From the limited clinical evidence, based on small numbers in observational studies, apheresis appears to be an effective intervention for lowering LDL-C in patients with FH, specifically in those with homozygous FH. Homozygous FH is rare, with a prevalence of about 1 case per million population.

We have not undertaken a formal health economic evaluation of apheresis. However, Tonstad and Thompson[161] indicate a likely procedure cost of £523 in the UK. Assuming bi-monthly treatments, the estimated annual cost per patient is estimated at approximately £13,600. Assuming that apheresis is an effective treatment, then this cost is likely to be an over-estimate of the net incremental cost of treatment (excludes net savings from reduced need for other healthcare resource use likely to be consumed by FH patients not treated with apheresis).

8.2.4 Evidence statements on the appropriate indications for transplantation

Key clinical question:

What are the appropriate indications for

- i-combined heart and liver transplantation or
- ii- liver transplantation alone in homozygous FH?

Question 11 of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
The evidence, based upon case studies only, suggest the benefit of intervention at an early age, before complications have occurred. [3] If successful liver transplantation will cure homozygous FH, although there may be problems in the long-term with immunosuppression. [3] There is no trial evidence to suggest benefit of combined heart and liver transplantation compared to liver transplantation alone.	Liver transplant can cure homozygous FH but because of the potential for long-term problems, the preferred sequence of treatment should be drugs, apheresis, then transplant but patient/carer preference should be taken into account. Recommendations were made based on this preferred sequence of treatment.

8.2.5 Evidence summary on the appropriate indications for transplantations

8.2.5.1 Methods of the clinical evidence review

The searches for this review were not restricted by study type or age of individuals or language.

- Identified: 108 English, 19 foreign language
- Ordered: 18
- Included: 15
- Excluded: 3

8.2.5.2 Clinical evidence

Transplantation

The only literature available for the review of organ transplant in individuals with FH consisted of case studies, evidence grade 3. These studies were not quality assessed but were summarised in the table presented below.

Table 13 Liver and heart transplant case studies in individuals with FH

Author	Description	Indication	Outcome
Alkofer et al[162]	39 year old male with heterozygous FH and terminal CHF	Double heterozygous mutation with only 20% LDL receptor function and history of CABG x 4 with new onset chest pain and severe coronary lesions and 3 closed by-pass grafts.	The heart lung transplant in this patient was difficult due to severe and prolonged hypercholesterolemia, immediate post op renal failure, an acute heart rejection episode and diabetes secondary to immunosuppressive therapy. The initial cholesterol concentrations were at first normal but 2 years after transplant statins were required to help lower the cholesterol to normal concentrations (5.13 mmol/l)

Author	Description	Indication	Outcome
Barbir et al[163]	33 year old female with homozygous FH	Severe diffuse coronary artery disease and left ventricular outflow tract obstruction secondary to homozygous FH	2 months post liver-heart transplant TC decreased by 60.5%, LDL-C by 68.5%. 3 months post-op all lipoproteins were within normal range; xanthomata had marked regression and at 1 year there were no angiographic signs of accelerated coronary heart disease.
Bilheimer et al[164]	6 year old homozygous female	Severe hypercholesterolemia secondary to homozygous FH with history of MI, CABAG x 2 and mitral valve replacement and continuing angina.	After liver-heart transplant, LDL-C declined by 81% and the fractional catabolic rate of I-LDL, a measure of functional LDL receptors in vivo, increased by 2.5 fold. Thus, the transplanted liver, with its normal complement of LDL receptors, was able to remove LDL-C from plasma at a nearly normal rate.
Castilla Cabezas et al[165]	2 siblings, aged 14 years (male) and 6 years (female)	Diffuse coronary artery disease and severely elevated lipid concentrations.	Spanish study of two homozygous siblings with successful liver transplants. At two years post op TC was normal in both and no cholesterol lowering medication was required.
Cienfuegos et al[166]	12 year old homozygous males	Homozygous FH with severely elevated lipid concentrations and history of aortic valve surgery at age 5; presented with 50% stenosis of left coronary artery and multiple diffuse lesions in the remaining coronary vessels.	Heart and liver transplant done in two stages. One year after the surgeries patient has a normal liver function and TC concentrations. Xanthomas have diminished and patient is on no special diet or hypolipidaemic drugs.
Clinical Nutrition Classes[167]	6 year old female with homozygous FH	Homozygous FH with severely elevated lipid concentrations and acute MI and congestive heart failure.	Post-heart and liver transplant, TC fell to 6.93 mmol/l from 25.64 mmol/l and tendon xanthomata regressed dramatically. Fractional catabolic rate increased from 0.12 pools per day (non receptor level) to 0.31 pools per day (normal mean is 0.43 $\pm$0.06)

Author	Description	Indication	Outcome
Hoeg et al[168]	11 year old male with homozygous FH	Homozygous FH with severely elevated lipid concentrations and history of bruits in carotid and femoral arteries, systolic ejection murmur at the cardiac base, a right parietal CVA.	After liver transplant, TC decreased by 76% and LDL-C by 83% and nearly total regression was seen in many xanthomata 5-6 months after transplantation.
Lopez-Santamaria et al[169]	Brother and sister aged 18 and 16 years with previous ileal bypass and portacaval shunt	Homozygous FH with severely elevated lipid concentrations. Exercise tolerance test and echocardiograms were normal prior to surgery.	Since liver transplantation both individuals are alive, jaundice free with normal liver function at 13 months follow up for brother and 7 months for the sister. TC has decreased from 12.3 mmol/l to 3.31 mmol/l and LDL from 11.6 mmol/l to 2.51 mmol/l in the brother. The sister's values have decreased from TC of 18.46 mmol/l to 5.77 mmol/l and LDL of 17.8 mmol/l to 4.77 mmol/l.
Moyle and Tate[170]	3.5 year old homozygous FH female of Vietnamese descent	Homozygous FH with severely elevated lipid concentrations which continued to increase despite treatment with statins.	Serum cholesterol fell to normal and xanthomata regressed following liver transplantation and she remained well 17 months post-op.
Offstad et al[171]	FH homozygous woman born in 1950 (46 at time of surgery and followed for 4 years)	Homozygous FH with severely elevated lipid concentrations who was treated with plasma exchange but developed end stage calcific left ventricular outflow tract obstruction no amenable to standard valve reconstructive surgery	Heart-liver transplant resulted in immediate lowering of serum lipids; TC decreased from 7.3 mmol/l to 3.5 mmol/l; LDL-C decreased from 5.3 mmol/l to 1.7 mmol/l.

Author	Description	Indication	Outcome
Revell et al[172]	3 boys ages 10-15 years	Homozygous FH with severely elevated lipid concentrations in three boys who all also had angiographic evidence of coronary atheroma and two had exertional angina. One child had a CABG x 4 prior to liver transplant.	All received liver transplants and remained well with normal liver function from 12-45 months after transplantation. Lipid concentrations remained normal without need for any additional diet or lipid lowering drugs. Xanthomata disappeared within one year and one child had reversal of atheromatous coronary artery lesions. Average TC in these boys pre-op was 23.4 mmol/l which decreased to 5.6 mmol/l. Average LDL-C was 22.1 mmol/l which decreased to 4.8 mmol/l.
Shrotri et al[173]	17 year old male with homozygous FH	Homozygous FH with severely elevated lipid concentrations and an occluded right coronary artery with 70% stenosis of the left main stem marginal artery and left anterior descending artery. He underwent CABG and aortic valve replacement and then was listed for liver transplant.	11 years after liver transplant was alive and well. There is also a report of three other individuals, one of whom died 2 years after transplant of an MI and two others who are also alive and well after 9 and 4 years respectively. TC concentrations were described as 'normal' in all survivors.
Sokal et al[174]	47 month old male with homozygous FH	Homozygous FH with severely elevated lipid concentrations. His ECG was normal. Cardiac ultrasound was normal and ejection rate was 66%. No coronary lesions were seen on angiography.	After liver transplant liver enzymes and lipid concentrations were all within normal limits at 12 month follow up (TC 4.46 mmol/l and LDL-C 2.82 mmol/l). Author recommends that transplant be considered early in life before the onset of coronary complications.
Starzl et al[175]	6 year 9month female with homozygous FH	Homozygous FH with severely elevated lipid concentrations and history of double CABG.	In first 10 weeks after transplantation TC fell to 6.92 mmol/l from over 25.64 mmol/l. Visible xanthomata regressed dramatically.

Author	Description	Indication	Outcome
Valdivielso et al[176]	12 year old male with homozygous FH	Homozygous FH with severely elevated lipid concentrations. Cardiac history not provided.	Heart lung transplant was followed by 71% decrease in TC and 79% decrease in LDL-C. Six months post –op the patient leads a normal life.

8.2.5.3 ***Health economic evidence***

No published, relevant evidence was identified.

8.3 Contraceptive and obstetric issues

8.3.1 Recommendations

Unless otherwise indicated, recommendations are relevant for individuals with possible or definite FH. Recommendations are also applicable for individuals with both heterozygous and homozygous FH, unless otherwise indicated.

Please note, numbering is as in the NICE guideline.

1.4.2 Information and counselling on contraception for women and girls with FH

1.4.2.1 When lipid modifying medication is first considered for girls and women, risks to the pregnancy and the fetus while taking lipid modifying medication should be discussed. This discussion should be regularly revisited.

1.4.2.2 Women with FH should be given specific information tailored to their needs and offered a choice of all effective contraceptive methods. Because of the small increased risk of cardiovascular events with the use of combined oral contraceptives, other forms of contraception may be considered initially.

1.4.3 Information for pregnant women with FH

1.4.3.1 Women with FH should be advised that in general, pregnancy is not contraindicated.

1.4.3.2 Lipid-modifying medication should not be taken by women planning to conceive or during pregnancy because of the potential risk of fetal abnormality.

1.4.3.3 Lipid-modifying medication should be stopped 3 months prior to attempting to conceive.

1.4.3.4 Women with FH who conceive whilst taking statins or other systemically absorbed lipid-modifying medication should be advised to stop treatment immediately and be referred urgently to an obstetrician for fetal assessment. This assessment will then inform shared decision making about continuation of the pregnancy.

1.4.3.5 Shared care arrangements, to include expertise in cardiology and obstetrics, should be made for women with FH who are considering pregnancy or are pregnant. Such care should include an assessment of coronary heart disease risk, particularly to exclude aortic stenosis. This is essential for women with homozygous FH.

1.4.3.6 Serum lipids should not be measured routinely during pregnancy.

1.4.3.7 Breast feeding is not contraindicated in women with FH. Potential risks and benefits of re-starting lipid modifying medication for the breast feeding mother and infant should be discussed. Resins are the only lipid modifying medication that should be considered during lactation.

8.3.2 Evidence statements for information/counselling on contraception for women and girls with FH

Key clinical question:

What information/counselling should be provided to girls/women of child bearing potential with FH with respect to contraception?

Question 14 of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
There were no studies specific to girls/women with FH which identified appropriate information or counselling with regard to contraception. Observational studies of coronary risk in healthy women taking third generation OCs indicate that there is no increased risk of MI in these women.[1-] One small study[177] of concomitant use of rosuvastatin and a third generation OC showed no decrease in contraceptive efficacy and significant lowering of LDL-C. (2+)	See also question 15. Recommendations were made on the specific contraceptive choice issues for women and girls with FH. A range of factors were considered, including the lack of direct evidence, the mechanism of action of the different hormones, and the risks of an unplanned pregnancy. The recommendations aim to allow patient-prescriber discussion and informed choice. If treated optimally, women with FH will have normalised lipid concentrations, so combined oral contraception is not routinely contraindicated, Combined oral contraception should therefore be available as an option (based on judgement and choice) after a full, informed discussion between the prescriber and the patient.

1

8.3.3 Evidence summary on contraception for women and girls with FH

8.3.3.1 Methods of the clinical evidence review

The searches for Question 14 included women with FH, women on statins and women at high coronary heart disease risk. The searches were not restricted by type of contraception.

- Identified: 330
- Ordered: 17
- Included: 5
- Excluded: 12

8.3.3.2 Clinical evidence and other information

There were no studies specific to girls/women with FH which identified appropriate information or counselling with regard to contraception. Five studies[177-181] were identified which provide background information on coronary heart disease risk and the use of hormonal contraception in healthy women. One study[177] was identified which describes the effect of combining a statin with an oral contraceptive (OC) in otherwise healthy women.

Four reviews[178-181] were identified which evaluated the association between OC use in healthy women and cardiovascular disease. High risk women were not evaluated. Three[178-180] of these studies included a meta-analysis of observational data. The inherent bias of observational studies makes it difficult to combine studies and obtain a reliable summary statistic. However, the studies have been reported for background information.

Baillargeon et al[178] selected 14 case control studies and calculated summary risk estimates associated with current use of low dose OCs for MI events. The summary risk estimate for MI associated with current use of low dose OCs was odds ratio (OR) 1.84 (1.83 to 2.44). The results were also stratified by generation of OC. Second generation OCs were associated with a significant increased risk of MI, OR 1.85 (1.03 to 3.32);MI for third generation OC use was not significant, OR 1.28 (0.78 to 2.10).

Another meta-analysis of 19 case control studies and 4 cohort studies was carried out by Khader et al[179]. Current OC users had an overall adjusted OR for MI of 2.48 (CI 1.91 to 3.22) compared to never users ($p<0.0005$). The risk of MI for past OC users was not significantly

different from that for never users, overall OR 1.15 (0.98 to 1.35). Stratifying by generation of OCs showed that first and second generation OC users had a significantly higher risk of MI compared with nonusers and the overall ORs were 2.21 (1.30 to 3.76; p=0.004) and 2.17 (1.76 to 2.69; p<0.0005) respectively. Third generation OC users were not significantly different from nonusers in relation to the risk of MI, OR 1.27 (0.96 to 1.67; p=0.094). There was a dose response relationship to estrogen concentrations. Overall OR was 3.62 (2.22 to 5.90; p<0.0005), 1.97 (1.43 to 2.71; p<0.0005) and 0.92 (0.21 to 4.08; p=0.918) for oestrogen dose preparation greater than or equal to 50micrograms, 30-49micrograms and 20micrograms, respectively.

The findings of seven studies (6464 participants in total) on the risk of MI among users of second and third generation OCs were aggregated by Spitzer, Faith and Mac Rae[180]. Compared with non users the aggregated OR for third generation OC was 1.13 (0.66 to 1.92) odds for MI and for second generation OC the odds for MI was 2.18 (1.62 to 2.94).

The association between combined oral contraceptives and cardiovascular disease was studied by Chasan-Taber & Stampfer[181]. All English language human epidemiology studies of OCs that used cardiovascular disease as an end point were reviewed. Descriptive and analytic data was collected. Most of the excess risk for MI among OC users was found to be attributable to an interaction with cigarette smoking. Taken together, case control and cohort studies suggested that current users of OCs who were younger than 40 years of age and did not smoke had little or no increase in risk for MI (9 studies with no significant RRs). Most studies in the literature were too small to address the risk for MI from OCs according to coronary risk factors other than smoking and in many studies smokers and non smokers were not stratified.

Third-generation progestins from the gonane class were recently incorporated into oral contraceptive pill formulations to reduce the androgenic and metabolic side effects that occur with older agents. These new progestins include desogestrel, gestodene and norgestimate.

Oral contraceptive pills containing third-generation progestins reportedly have several benefits. Androgenicity associated with older progestins has been linked to adverse lipoprotein and carbohydrate changes, weight gain, acne, hirsutism, mood changes and anxiety. The third-generation progestins have minimal impact on blood glucose concentrations, plasma insulin concentrations and the lipid profile. Thus, they may be useful for women with lipid disorders or diabetes.

One final study by Simonson et al[177] evaluated the effect of rosuvastatin on oestrogen & progestin concentrations in 18 healthy women taking a third generation OC (orthotricyclen). Co-administration of orthotricyclen and rosuvastatin did not result in lower exposures to the exogenous oestrogen or progestin components of the OC. LH and FSH were similar between cycles. There were no changes in the urinary excretion of cortisol. Rosuvastatin significantly decreased LDL-C (-55% [95% CI -59 to -51]), TC (95% CI -27% [-31 to -24), and TG (95% CI -12% [-22 to -3]) and there was a significant increase in HDL-C (11% [95% CI 5-17]).

8.3.3.3 ***Health economic evidence***

No published, relevant evidence was identified.

8.3.4 Evidence statements on information for pregnant women with FH

Key clinical question:

What information or care should be provided to:

- pregnant women or women considering pregnancy with FH with respect to:
  - lipid modifying treatment use or
  - FH related complications around pregnancy/labour/delivery?
- lactating women with FH with respect to:
  - lipid modifying treatment use?

Question 15 of the key clinical questions – please see Appendix B for details.

Evidence statements (grading to be checked for final version)	Evidence into recommendations
There were no studies specific to pregnant or lactating women with FH which identified appropriate information or counselling with regard to lipid modifying treatment or complications in pregnancy, labour or delivery. Observational studies are inconclusive and there may be a small increased risk of a spectrum of congenital abnormalities associated with statin use in early pregnancy	Recommendations were agreed to encourage and support women to breast feed.. The evidence on the safety of statins in pregnancy was reviewed, but due the limited data (often case series or case studies) we were unable to quantify the exact level of risk. The evidence is limited with contradictory results, and is inconclusive. There may be a small increase in the rate of fetal malformations if mothers have taken statins in the first trimester. However the great majority of pregnancies have a normal outcome. There is no clear type or pattern of fetal malformation observed, and most of the fetal malformations would be detectable by ultrasound in utero. The balance and risks to both the woman and the fetus should be carefully considered. Recommendations were made to enable a detailed discussion between the woman and the prescriber leading to an informed choice. It should be stressed that there are no definitive estimates of the levels of risk or the patterns of expected fetal anomalies, so pragmatic recommendations on appropriate referral and monitoring of the pregnancy were agreed. Recommendations were made on shared care and CV assessment for women with established cardiovascular disease. A specific recommendation was also made for women with HoFH and other women with defined pathologies. Serum concentrations should not be monitored as there are usual changes in LDL-c during pregnancy, and these cannot be treated pharmacologically. Routine monitoring of LDL-c concentrations are therefore not recommended, but may be needed in specific cases.

1

8.3.4.1 Evidence summary on information for pregnant women with FH

8.3.4.2 Methods of the clinical evidence review

The searches for Question 15 specifically included women with FH. Studies identified for Question 15 were

- Identified: 252
- Ordered: 8
- Included: 4
- Excluded: 4

8.3.4.3 Clinical evidence

Information and counselling

There were no studies specific to pregnant or lactating women with FH which identified appropriate information or counselling with regard to lipid modifying treatment or complications in pregnancy, labour or delivery.

Pregnancy risk factors in women with FH

The Confidential Enquiry into Maternal Deaths 2000-2002[182] listed cardiac deaths as the most common cause (excluding suicide) of indirect death in pregnancy (up to and including 42 days postpartum) in the UK. In fact, it was more common than any of the direct causes of death in pregnancy. The incidence has been rising in the past two decades reflecting an overall increased mortality from acquired heart disease. Further description of specific cardiac conditions which lead to death was not provided, however according to the Confidential Enquiry, better care could have altered the course of 40% of the deaths from cardiac causes.

Amundesen et al[183] documented changes in plasma lipids and lipoproteins during pregnancy in women with FH. In 22 pregnant women with FH, blood samples were collected at gestational weeks 17-20 (baseline), 24, 30 and 36 weeks and compared with a reference group of 149 pregnant women who did not have FH. Total cholesterol and LDL-C (mean±sd) increased significantly between baseline and gestational week 36 by 29% to 11.6±1.9mmol/l in the first instance and by 30% to 8.6±2.0mmol/l in the case of LDL-C. Changes noted in the reference group were 25.4% increase in TC and 34.2% increase in LDL-C. The relative increases did not

differ (p>0.05) but absolute values in FH women were markedly higher than in the reference group. Of note however is the relatively large number of pre-pregnancy smokers in the FH group (31% compared to 0% in the reference group). Pregnancy outcomes in the FH group did not differ significantly from those in the reference group.

In a further study of the same sample, Amundesen et al[184] again compared risk markers for cardiovascular disease in pregnant women with and without FH. Absolute values of lipids were higher in pregnant women with FH than in healthy women. As pregnancy is also associated with activation of coagulation and possibly also of vascular endothelium, pregnancy might further increase the risk of cardiovascular disease in women with FH. In this study activation markers of hemostasis and endothelium activation were analyzed in a sample of 22 FH women and compared with 149 healthy women. The concentration of prothrombin fragments 1 + 2, a marker of thrombin generation was higher (p<0.05) in the FH group compared with the reference group. The baseline concentrations of the endothelial activation marker VCAM-1 were similar (p>0.05) in the FH and reference groups, VCAM-1 rose markedly (p<0.05) during pregnancy by 120% in the FH group, whereas it remained unaltered in the reference group. The results may be skewed by the large number of pre-pregnancy smokers in the FH group (31% compared to 0% in the reference group). Nonetheless, it is possible that enhanced endothelial activation as well as increased lipid concentrations may confer additional risks of cardiovascular disease among pregnant FH women.

Treatment of pregnant women with FH

Potential teratogenicity of statins in pregnancy has been reviewed and the results of six case series, case study and in vitro study reports are described in the table below.

There was one cohort study identified[185], which included only pregnant women who had a live birth. The cohort was constructed retrospectively from routine data. There were three groups of women: Group A used only statins before and during 1st trimester (n=153); Group B used only fibrates or nicotinic acid before and during 1st trimester (n=29) and group C used only statins between 1 year before and 1 month before pregnancy (n=106). The authors reported the outcome of an infant diagnosed with a congenital anomaly within the first year of life..

The crude OR using Group B as reference group were for Group A 0.18 (95% CI 0.03,1.01) and for Group C 0.43 (95% CI 0.10, 1.91). A multivariate analysis stratified by study group included maternal age, socioeconomic information and education, co-morbidities and health services

utilisation. The adjusted OR for congenital anomalies for group A was 0.79 (95% CI 0.10, 6.02) and for group C 1.74 (95% CI 0.27, 11.27). In a second multivariate analysis which included only groups A and C, using group C as the reference group, the adjusted OR for group A was 0.36 (95% CI 0.06, 2.18). No pattern of type of anomaly was evident in Group A. The absence of outcome data on non-live births and the small sample size, which meant that the study was underpowered, undermine the strength of the results.

Table 14 Statins in pregnancy

Authors	Study	Year	Design	Description	Summary of results
Edison & Muenke[186]	Mechanistic and epidemiologic considerations in the evaluation of adverse birth outcomes following gestational exposure to statins	2004	Case series	170 cases from FDA Medical Products Reporting Program; two cases by literature review and 42 others following requests to manufacturers for clinical data. 70 cases met inclusion criteria.	There were 31 adverse outcomes with 4 cases of IUGR, and 5 cases of fetal demise. 22 infants had structural anomalies. Two major groups of recurrently reported anomalies were noted: 5 central nervous system malformations and 5 limb deficiencies. There were no adverse outcomes reported with use of pravastatin and fluvastatin.

Authors	Study	Year	Design	Description	Summary of results
Kenis et al[187]	Simvastatin has deleterious effects on human first trimester placental explants	2005	In vitro study of human explants	Laboratory data.	Simvastatin sharply inhibited migration of extravillous trophoblast cells from the villi to the mtrigel ($p<0.05$). Simvastatin also inhibited half of the proliferative events in the villi ($p<0.05$) and increased apoptosis of cytotrophoblast cells compared to control. Moreover, simvastatin significantly decreased secretion of progesterone from the placental explants ($p<0.01$). The conclusion is that simvastatin adversely affects human first trimester trophoblast.
Manson et al[188]	Postmarketing surveillance of lovastatin and simvastatin exposure during pregnancy	1996	Case series	Spontaneous reports voluntarily submitted to Merck & Co, reports from clinical trials, postmarketing surveillance studies and regulatory agencies and reports in the literature.	Congenital anomalies were described in 9 reports, spontaneous abortions in 16 reports, fetal deaths/stillbirths in 2 reports, miscellaneous adverse outcomes in 4 reports and normal outcomes in 103 reports. The proportion of prospective reports with normal outcome was 85%. The proportions of prospective reports of spontaneous abortions (8%) and fetal deaths/stillbirths (1%) do not exceed what would be expected in the general population (15 and 3% respectively).

Authors	Study	Year	Design	Description	Summary of results
Petersen et al[189]	Maternal exposure to statins and risk for birth defects	2007	Case Series	National Birth Defects Prevention Study and Slone Epidemiology Center Birth Defects, based on maternal report.	22 mothers of infants with birth defects reported statin use in pregnancy. 12 infants had cardiac defects, 4 infants had orofacial clefts and 2 infants had neural tube defects. Nineteen infants were classified as having isolated defects, 2 had multiple major defects and 1 had a syndrome. There were no limb defects.
Pollack et al[190]	Pregnancy outcomes after maternal exposure to simvastatin and lovastatin	2005	Case series	Merck & Co pharmacovigilance database for reports of exposure to simvastatin or lovastatin.	225 prospective reports resulted in 6 congenital anomalies. The rate of congenital anomalies was 3.8% in the prospectively reported pregnancies and was slightly higher than the US background rate of 3.15% incidence of overall birth defects. Thirteen congenital anomalies (14%) were reported retrospectively. There was no specific pattern of congenital anomalies for either prospectively or retrospectively reported pregnancies. The authors concluded that due to the chronic nature of atherosclerosis the risks in pregnancy of taking a statin continue to outweigh the potential benefits.

Authors	Study	Year	Design	Description	Summary of results
Seguin and Samuels[191]	Fluvastatin exposure during pregnancy	1999	Case report	Physician report.	28 year old woman s/p kidney transplant who continued on all medications during pregnancy including fluvastatin and delivered a healthy female infant. Fluvastatin differs from other statins in that it is entirely synthetic and has essentially no active metabolites, is highly protein bound and is 95% excreted in the liver.

8.3.4.4 ***Health economic evidence***

No published, relevant evidence was identified.

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Appendices A–G are available in a separate file