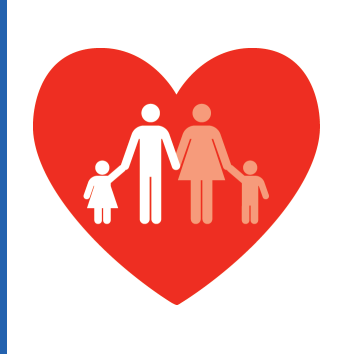


Saving lives, saving families

The health, social and economic advantages of detecting and treating familial hypercholesterolaemia (FH)





About our charity

HEART UK is the nation's cholesterol charity and aims to prevent premature deaths caused by high cholesterol and cardiovascular disease. The charity works to raise awareness of the risks of high cholesterol, lobbies for better detection of those at risk, provides advice and information to patients and clinicians, and supports health care professional training.

About the HEART UK Familial Hypercholesterolaemia Guideline Implementation Team (FHGIT)



The FHGIT was formed after the publication of the NICE guideline on FH in 2008, and aims to help facilitate the implementation of the guideline's recommendations. Activities have included hosting regional events, developing an FH toolkit, advocacy and lobbying.

Target audience for this report:

Key opinion leaders and policymakers in health, the Department of Health, the National Commissioning Board, NHS Trust chief executives, PCT chief executives, PCT chairs, medical directors, emerging clinical commissioning groups, specialised commissioning groups, cardiac and stroke networks, geneticists, a range of clinicians, including GPs, lipidologists, diabetologists, chemical pathologists, and nurses.

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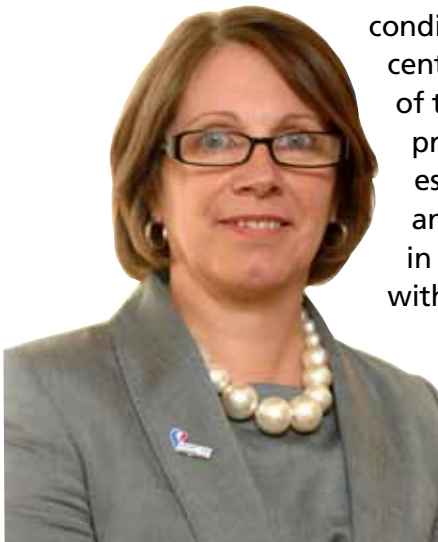
Foreword

Jules Payne, chief executive. HEART UK

Familial hypercholesterolaemia (FH) is a relatively common genetic condition, affecting 1 in 500 people. When FH is undiagnosed and untreated, whole families can needlessly suffer long-term ill health and premature death from heart disease. With effective, affordable means of diagnosing and treating FH readily available, this cycle of early deaths must be stopped.

When NICE published its guideline for the treatment of FH in 2008, HEART UK felt encouraged that more would be done to diagnose and treat people with the condition. The NICE guideline advocates diagnosing FH through a process of blood cholesterol and genetic testing in people with especially high cholesterol, extending through family members in a process known as cascade screening.

Unfortunately, the picture is far from positive in England. The condition has continued to be ignored, with some 80-85 per cent of the FH population still undiagnosed. Other parts of the UK are faring better. This is due in part to the FH programmes and/or clinical standards that have been established to address the condition in Scotland, Wales and Northern Ireland. With no national FH programme in England, health inequalities will soon emerge for those with the condition living in different countries of the UK.



This report recommends the establishment of a national programme for FH in England under the auspices of the National Commissioning Board or similar. This is the best means of ensuring that access to FH services is available beyond the limited boundaries of a PCT or clinical commissioning group.

A UK-wide national patient register and database for FH is also needed to aid better cascade screening across the country.

A national FH programme for England will not only save lives and families, it will also save money. For this report, we commissioned new health economic modelling that demonstrates that the NHS can save money by implementing cascade screening. In fact, since cardiovascular events will be avoided, the more cases of FH that are found and treated, the greater the savings. Indeed, this report shows that by not finding cases of FH, the NHS is actually losing money every year.

HEART UK would welcome the opportunity to work with partners in the development of an England national programme to tackle FH now.

Jules Payne





Executive summary and recommendations

Familial hypercholesterolaemia (FH) is a relatively common genetic disorder, affecting 1 in 500 people. If their condition remains untreated, people with FH suffer a much higher premature death rate from cardiovascular disease than the general population. If untreated, approximately 50 per cent of men and 30 per cent of women with FH will have developed coronary heart disease by the age of 55.

Of the estimated 120,000 people in the UK with FH, only some 15-20 per cent have been formally diagnosed. This is despite the fact that, unlike many genetic conditions, FH can be diagnosed and treated relatively simply. With appropriate treatment, people with FH can lead normal, healthy lives.

The NICE guideline on FH was published in 2008, and recommends the best means of diagnosing and treating people with the condition, through a process called cascade screening or testing, followed by intensive lipid lowering treatment to achieve a reduction in LDL-Cholesterol concentration of greater than 50 per cent from baseline in affected individuals.

Unfortunately, three and a half years on, there is little implementation of the NICE guideline in England. While there is progress on FH in other countries of the UK, England lags behind. As a result, it will soon become apparent that health inequalities emerge between the countries of the UK.

This report highlights the following critical issues that have made implementation of the guideline so difficult:

Critical issues

- Issues associated with the localised commissioning structure have hampered the development of FH services and access to genetic testing
- Lack of clinical awareness and understanding of FH
- Lack of appropriate IT software that would aid the process of cascade screening and registering patient data
- Lack of lipid clinics to help treat people with complex lipid disorders

The NICE guideline shows that cascade testing, using a combination of cholesterol and DNA tests in affected families, followed by intense statin therapy, is cost-effective and delivers optimum health outcomes. This report has commissioned new economic modelling to further analyse the costs/benefits of cascade screening.

The key findings of our research

- Treatment with high intensity statins, compared to low intensity statins or no treatment results in greater reduction of LDL-C and major cardiovascular events, which translates into more quality adjusted life years and life years gained
- Reduction in mortality - 101 cardiovascular deaths will be avoided per 1,000 FH patients (aged 30 to 85 years) who are treated with high intensity statins to achieve optimal LDL-C reductions of more than 50 per cent from baseline, when compared with no treatment
- The greater the number of FH patients identified and treated, the greater the comparative and accrued health benefits and cost savings to the NHS





- The UK could save **£378.7 million** from cardiovascular events avoided if all (100 per cent) relatives of FH index cases are identified and treated optimally over a 55 year period, or **£6.9m per year**
- If, more realistically, 50 per cent of patients with FH are diagnosed and treated, **£94.7 million** (i.e. **£1.97m per 1,000 cases**) can be saved by the NHS over the same period, or **£1.7m per year**
- By not fully implementing cascade screening as recommended in the NICE guideline (identifying 50 per cent of potential relatives cases), the NHS is losing approximately **£1.4m per year**
- The costs of a national FH register are small when considering the gains that could be made from a national FH programme. Costs would vary depending on whether the NHS decides to fund one or two people per PCT to maintain the registers. The costs are estimated to range from **£87,860 to £149,000 per year in total**.

At present, there is an international momentum towards developing national services to address FH, including the Netherlands (since 1994), Norway, Spain, and increased activities in Australia and New Zealand.¹

Given the complexities of providing services for family members living in disparate places, England must develop a national programme to tackle FH properly. The premature loss of a family member can have serious emotional and financial consequences across the generations. When the FH genetic mutation is discovered in families, it is important not just for the health and wellbeing of those living today, but to future generations who will be aware of the importance of DNA testing in their families.

HEART UK recommends the following to improve the implementation of the NICE guideline on FH:

Our recommendations

- 1 A national programme for FH in England under the National Commissioning Board. This is the best means of ensuring that access to FH services is available beyond the limited boundaries of a PCT or clinical commissioning group. A national programme should have ring-fenced funding and include the following:**
 - A dedicated network of involved professionals, including lipid clinics, primary care and genetic services
 - Clear referral pathways at local level
 - Employing of FH nurses to rollout the cascade screening process
 - Measurement of outcomes as the programme is rolled out at local level
- 2 A UK-wide national patient register and database for FH to aid better cascade screening across the country**
- 3 Improved capacity of lipid clinics to manage patients with possible or definite FH.**
- 4 Increased education and training programmes, that have been developed to nationally agreed standards and contain nationally agreed content, such as those developed by the NHS National Genetics Education and Development Centre for other healthcare professional groups. These programmes would aim to improve primary care awareness of FH and local care pathways for lipid management. This would also facilitate much of the long-term care and review of FH patients to be appropriately carried out in primary care.**





CHAPTER 1:

What is is familial hypercholesterolaemia and how should it be treated?

This chapter provides an introduction to familial hypercholesterolaemia (FH) and the recommended means of diagnosing and treating the condition.

What is familial hypercholesterolaemia?

Familial hypercholesterolaemia (FH) is a genetic condition that leads to a high concentration of cholesterol in the blood. It is caused by genetic alterations in the genes that encode for the proteins that are involved in the pathway that clears LDL-C (low-density lipoprotein cholesterol) from the bloodstream, usually in the LDL-C receptor. The genetic alteration and its consequent increase in LCL-C is present from birth, leading to the early onset of atherosclerosis and coronary heart disease. As it is an autosomal dominant genetic condition, children of FH patients have a 50 per cent chance of inheriting the gene alteration, and therefore developing the condition. If untreated, approximately 50 per cent of men and 30 per cent of women with FH will have developed coronary heart disease by the age of 55 years.²

There are two main types of FH. Heterozygous FH patients have inherited an altered gene from only one parent and have a 50 per cent chance of passing it on to their own children. Homozygous FH occurs when someone inherits a gene alteration from both parents and can be due to alterations in two copies of the same gene, or an alteration in two different genes associated with the condition. Symptomatic atherosclerosis or sudden death can occur in childhood.

Prevalence of FH

The estimated prevalence of familial hypercholesterolaemia (FH) is 1 in 500, suggesting 120,000 affected individuals in the UK. The condition is massively under diagnosed. It is difficult to ascertain the exact numbers diagnosed, though this is believed to be around 15-17 per cent of the FH population.^{3,4} Homozygous FH is rare, with around one case per one million of the population.⁵





The NICE guideline on FH (CG 71)

The NICE guideline⁶ sets out the following key elements for a successful service for FH testing and management:

- **Diagnosis**
- **Identifying people with FH using cascade testing**
- **Management for adults, children and young people**
- **Information needs and support**
- **Ongoing assessment and diagnosis.**

A critical component of the NICE guideline is advocacy of the process known as cascade testing (or screening). This process begins with blood cholesterol measurement and/or DNA tests to determine whether FH is 'probable' or 'definite' in an index case. If a genetic mutation is found, the process can then be carried out with first and subsequent other appropriate relatives of the index case – in other words, 'cascaded' through the family.

Key recommendations of the NICE guideline include:

Diagnosis

- The Simon Broome criteria (for assessing FH), including a family history of premature coronary heart disease, should be used to diagnose FH
- Where appropriate, all individuals should be offered a DNA test to confirm a clinical diagnosis of FH, and to assist in cascade testing of relatives
- Cardiovascular (CVD) risk estimation tools, such as those based on the Framingham algorithm and QRISK, should not be used in FH patients, as they are already at high risk of CVD
- In children at risk of FH because of one affected parent, the following diagnostic tests should be carried out by the age of 10
 - A DNA test if the family mutation is known
 - LDL-C concentration measurement if mutation is not known.

Identifying people with FH using cascade testing

- Healthcare professionals should offer all people with FH a referral to a specialist in FH for confirmation of diagnosis and initiation of cascade testing of relatives
- For cascade testing, a combination of DNA testing and LCL-C concentration measurement is recommended to identify affected relatives of index patients with clinical FH. This should be at least the first- and second-degree biological relatives
- The use of a nationwide, family-based follow-up system is recommended to enable comprehensive identification of people affected by FH.





Management for adults, children and young people

- Adults: Prescribe a high-intensity statin/aggressive lipid modifying therapy to achieve a reduction in LDL-C of >50 per cent from baseline (i.e. from before treatment)
As simvastatin 40mg is, in most cases, insufficiently potent to achieve an LDL-C reduction of more 50per cent from baseline, high intensity statin treatment with non-generic statins alone or in combination with other lipid lowering drugs is recommended by NICE CG71 to achieve optimal LDL cholesterol lowering. High intensity statin treatment or aggressive lipid modifying therapy may be defined as any lipid lowering drug or combination which is more potent than simvastatin 40mg, including atorvastatin (20mg or greater) or rosuvastatin (10mg or greater), either alone or in combination with bile acid sequestrants, ezetimibe, nicotinic acid or fibric acid derivative
- Children and young people:⁷ Should be seen by a specialist in an appropriate setting and, using clinical judgement, statin therapy should be considered by the age of 10.

Information needs and support

When lipid-modifying drug therapy is first considered for women and girls, the risk for future pregnancy and the developing foetus while taking lipid-modifying drug therapy should be discussed.

Ongoing assessment and diagnosis

All people with FH should be offered a regular structured review that is carried out at least annually.

Cost effectiveness of cascade testing

The NICE guideline indicates that the cascade testing model (DNA and cholesterol testing) for diagnosing FH is the most cost-effective, with an estimated ICER (incremental cost effectiveness ratio) of £2,700 per QALY (quality adjusted life year). This figure is well below the NICE cost effectiveness threshold of £20,000/QALY. The new economic modelling research included in this paper further demonstrates the financial and health benefits of cascade screening and optimal high-potent statin treatment through QALYs gained and cardiovascular events avoided. In the long run this will actually save money to the NHS (see Chapter 3).

Cascade testing works

NICE guidelines assess evidence and recommend treatment measures for particular conditions. Therefore, the NICE guideline on FH is a recommendation for cascade screening in itself. NICE reviewed the guideline in August 2011 and found that it should not be updated at this time, since no new evidence has been published to alter the recommendations.⁸

Indeed, the evidence from the literature demonstrates the value of cascade screening. A Norwegian review concluded that cascade genetic screening for FH leads to health benefits and is cost effective without causing psychological or social damage. Moreover, cascade genetic screening for FH could serve as a model for case finding of other treatable genetic disorders.⁹ Indeed, the value of the cascade screening model has been demonstrated in other settings, including a Manchester programme for cystic fibrosis.¹⁰ Genetic testing is an important aspect of diagnosing FH patients. This is because patients with a genetic mutation have different clinical characteristics, which can have implications for treatment measures.¹¹ Genetic testing and treatment are also important for children, as FH is a disorder that begins at birth.¹²



Case study:
Rianna Wingett

How failure to use cascade screening led to Rianna's death, aged 11

The failure to implement cascade screening among families with known FH can lead to tragic circumstances.

This was true for Rianna Wingett, who collapsed on 27 November 2009 on the playing fields at her school in Essex.

A post-mortem examination revealed one of the main arteries to her heart was so clogged with cholesterol deposits, that the gap left for the blood to flow through was no bigger than a pin prick.

Starved of sufficient blood, her young heart went into cardiac arrest and, despite the efforts of paramedics and an emergency medical team, it simply refused to start again. It was the day before her 12th birthday. Rianna had fallen victim to FH at an exceptionally young age.

Rianna's mother Amanda, 45, had been diagnosed with the same condition at the age of 18. She had undergone a cholesterol



Rianna Wingett: her parents were never offered cholesterol testing for their daughter despite her family history

blood test after doctors found her own mother Tina, Rianna's grandmother, had dangerously high cholesterol levels and was also affected.

Both Amanda and her mother, who was 38 at the time she was diagnosed, were immediately put on high doses of statins and told they would need to take them every day for the rest of their lives.

Tina is still alive and well and is now aged 65. But details of the family history suggest the

deadly condition has blighted previous generations. "My grandmother had a heart attack at 48," says Amanda. "She survived that but died from a stroke at 72. And my great-grandfather dropped dead in his sixties from a heart attack when he was playing ring-a-ring-of-roses with some of his grandchildren."

Yet despite this gruesome legacy, Amanda and her husband John, 51, were never offered testing for their three

▶ 10





Rianna Wingett

daughters – Rianna and her sisters Sarah, 15, and Becky, 10 at the time of their sister’s death.

In fact, whenever they raised the matter with GPs at their local surgery, they were told the children were too young to be affected and that there was no need to check their cholesterol, or carry out DNA testing, until they were at least 18.

“I often used to bring it up when I was seeing the doctor for something else,” says Amanda. “I would ask what age I should think about



Rianna: keen on horses, and, above on Southend beach

having the girls tested. But they always insisted they were too young to be affected. They said to leave it until they were in their late teens to test them and always assured me

there was nothing to worry about.”

In fact, it is only since Rianna’s tragic death that Amanda and John have discovered that, under the NICE guidance issued in 2008, doctors should screen all children, however young, for signs of this genetic disorder if an immediate family member is known to have the condition.

If Rianna’s dangerously high cholesterol – later estimated to have been as high as 20mmol/l – had been detected she could have been treated with high dose statins. The tragedy of her early death might have been avoided.



CHAPTER 2:

The current position in England and the other countries of the United Kingdom

This chapter highlights the current situation in England with respect to services for people with FH. Here we discuss critical issues that have impeded rollout of the NICE guideline on FH, and compare progress to other parts of the UK.

To understand how well the NICE guideline has been implemented in England, in 2010 HEART UK conducted a study in which Freedom of Information (FOI) requests were sent to primary care trusts (PCTs), asking about their progress.¹³ The study showed that, since the publication of the guideline, little has been done to implement its recommendations in England. This is in contrast with other parts of the UK, where screening programmes are progressing steadily.

The HEART UK study demonstrates that in England there is a lack of formal planning for FH, and incomplete provision of clinical services and education about the condition. There is a lack of specialist services, including provisions for paediatric and obstetric patients.

Key findings of the FOI study

Nearly 70 per cent of PCTs in England responded, with key findings including:

- 60 per cent of PCTs do not have written plans to support implementation of the NICE guidance on FH
- 41 per cent of PCTs admitted barriers to treating FH patients
- 27 per cent of PCTs did not know whether lipid clinics in the area could carry out DNA cascade testing in adult FH patients
- There is a lack of lipid clinics or specialist centres available to children or young people with FH. 41.5 per cent of PCTs indicated that there are no appropriate services in their area, and a further 26 per cent did not know whether there were any appropriate services
- Shared care of discharged FH patients has not been well-developed. 63 per cent of PCTs indicated that there are no written plans for shared care of discharged FH patients, with a further 20 per cent of PCTs saying that they did not know if





- there are shared care arrangements
- This was similarly poor with regard to shared care with obstetrics for care of pregnant women with FH. 64 per cent indicated that there are no such written plans, with a further 21 per cent not knowing whether such plans exist.

The commissioning problem

The commissioning structure is a key aspect of the failure to deliver better FH services in England. Lipid clinics have been traditionally commissioned by PCTs or are funded by the hospital trusts where they are based. In contrast, genetic testing and treatment is often commissioned by specialised commissioners or paid for as part of the infrastructure costs of hospitals.

“The Royal College of Physicians confirms that access to DNA testing is particularly poor in England”

If a lipid clinic wishes to refer a patient for a genetic test, this has funding implications, since the clinic will often need to approach the specialised commissioning group (SCG) for funding.

However, the SCGs largely commission services for conditions much rarer than FH.

In other words, the current commissioning system is not an easy fit for FH cascade screening. This has created problems of access to genetic tests in England. Indeed, the Royal College of Physicians’ (RCP) National Audit on the Management of FH confirms that access to DNA testing is particularly poor in England.¹⁴

Since FH is an issue that affects family members living in disparate locations, the PCT/clinical commissioning group responsibility for FH services is not wholly logical. Not all family members live within the confines of one PCT, which may be one reason for the failure to rollout the NICE FH guideline. Possible solutions to

the commissioning problems are explored in Chapter 4.

Information technology

One of the problems with implementing the NICE guideline on FH is the absence of a widely available IT system to register patients, capture clinical data and assist with patient management. A 2004 study of lipid clinics found that computerisation was patchy, limiting implementation of cascade testing.¹⁵ Several years later, this is still a problem, with the RCP FH Audit confirming a lack of appropriate IT for pedigree drawing in cascade screening. The RCP audit also recommends that a new national register is established that will help facilitate cascade screening among families living in dispersed areas.¹⁶

PASS Clinical software

PASS Clinical is a clinical database with features which make it particularly useful for FH cascade testing programmes. PASS Clinical was originally developed in Holland, where it has been successful in aiding the national cascade genetic screening programme.¹⁷ PASS has now been adapted for use in Wales (see pp 15).

PASS features the ability to help co-ordinate cascade testing at a national level. Families who are spread out over large geographical areas provide a challenge to health professionals carrying out FH cascade testing. However, Pass Clinical allows the co-ordination of whole families by several different co-workers in different geographical locations. It does this by allowing the transfer of specific individuals in a family to colleagues that cover their particular catchment area. The software features pedigree creation and an integrated database. Visual markers and colour coding are used to show genetic status and phenotypical expression, which allows a visual overview of the family.





The programme features workflow management that enables a complete overview of the tasks of other professionals involved, which allows the steps in the cascade testing process to be standardised and controlled.

In its employment and adaptation of PASS Software, the FH programme in Wales concluded that the security and confidentiality aspects are suitable for use in NHS Wales. The system has been shown to work in clinical practice in Wales, which could be extended to other parts of the UK and potentially to other genetic conditions.¹⁸

Recommendation

A national patient register and database should be established to enable better cascade screening across the UK. This register should also include IT capacity to conduct the screening process.

As the Welsh example shows, this IT system is invaluable, and should be included as part of a national programme for FH (see page 33).

Lack of lipid clinics

Lipid clinics are often based in hospitals and provide specialist lipidology and cardiovascular risk-factor management services. Lipid clinics are critical for the assessment and treatment of people with FH and other complex lipid disorders, as they can provide the expertise required to ensure that the correct diagnosis is made and that genetic tests are used cost-effectively.

Access and availability of lipid clinics are important aspects of a comprehensive, equitable health service. A recent paper on cascade testing for FH recommends that a lipid clinic is needed for every 200,000 people.¹⁹ Lipid clinics are currently far too scarce across the UK,

with clinics offering specialist services to children and young people being particularly rare. Additional lipid clinic capacity is required to accommodate adults and children with FH identified through cascade testing. The need for more specialist lipid services is also highlighted in the RCP Audit of FH.²⁰

Recommendation

Improvements are needed to increase the geographical spread and capacity of lipid clinics to manage patients with possible or definite FH. Additionally, other measures, such as training and awareness, could be undertaken to improve primary care management of lipid problems. This would also facilitate much of the long-term care and review of FH patients to be appropriately carried out in primary care.

Lack of awareness of FH

There is evidence that primary health care professions lack awareness of FH and the NICE guidelines to manage and refer possible FH patients. This is important, since GPs are essential in managing patients with elevated cholesterol, and as points of referral to lipid clinics.

A recent study²¹ looked at UK primary care physicians' (largely GPs') knowledge of FH, and found that:

- Most believe that increased education for GPs about FH is the best way to improve FH patient care in their locality
- Evidence shows very little activity on FH, with the vast majority of UK physicians having never received a request from a trust to trace relatives of patients with FH
- Only 7 per cent had awareness of NICE guidelines on FH
- Nearly 20 per cent are unaware of

“The vast majority of UK physicians have never been asked by a trust to trace relatives of patients with FH”





a lipid clinic or specialist in their region

- Nearly one-third have not referred any patients to specialists for challenging lipid disorders
- They believe there is a large population of patients who may have FH but have never been formally diagnosed.

Recommendation

Measures such as education and training should be taken to increase primary care awareness of FH and local care pathways for lipid management. These programmes should be developed to nationally agreed standards and contain nationally agreed content, such as those developed by NHS National Genetics Education and Development Centre for other healthcare professional groups.

Other countries of the UK

England’s FH services remain poorly developed when compared with other parts of the UK. This is largely because the other countries of the UK have better defined national programmes or commitments to tackle the condition.

Critical elements of these programmes – existing or planned – are:

- An IT system to register patients and for clinical management
- A dedicated network of involved professionals
- Clear referral pathways
- The employment of FH nurses.

As the other UK countries develop increasingly accessible and comprehensive FH services, the FH population in England will suffer health inequalities by comparison.

Scotland

In late 2008, after NICE published its

FH guideline, representatives from the Scottish Genetics Consortium (SGC) were invited to the Scottish Lipid Forum to discuss the potential implementation of the guideline in Scotland.

In Scotland, genetic testing for FH had been available from the Aberdeen Regional Genetics Service for some years, but the service had not been advertised widely and was underutilised.

The pathways proposed at the 2008 meeting were put into place during 2009, with testing of individual patients (identified by Scottish lipid clinics), while the genetics service was also developed. As suggested in the ‘Better Heart Disease and Stroke Care Action Plan (2009)’,²² the lipid forum has met annually to discuss progress and further develop the service. In 2010, a process of cascading (using the genetic test) was introduced across Scotland and has built up momentum since then.

By autumn 2011, the SGC had processed more than 1,000 screens and found 252 individuals with FH. There are however, by population estimates, an estimated 10,000 people with FH in Scotland, and so there is a lot of progress to be made. Furthermore, cascading to offer the gene test to relatives of affected individuals has been variable across Scotland, and it is intended to discuss these at upcoming lipid forum meetings.

There are three main outstanding issues in Scotland:

- 1 Remaining areas of Scotland with no lipid clinic provision – Highland, Lanarkshire, and Fife
- 2 Provision of a network of dedicated specialists to facilitate screening across Scotland. This would require a team of about five individuals, working in collaboration with lipid clinics, geneticists and paediatricians;





probably with a nursing background, but with an understanding of FH.

Providing equity across Scotland, such a network could help address point 1

- 3 Availability of a computerised clinical management system to coordinate the process – Glasgow has recently procured a new genetics system, aspects of which could fulfil this role if made available to lipid clinics across Scotland

Wales: FH All Wales Cascade Testing Service

The Wales FH service was launched in December 2010 with the introduction of a diagnostic service for FH combined with family cascade testing. FH is estimated to affect 6,000 individuals in Wales, but prior to the introduction of this service very few had been formally identified or treated.

The need for FH services had been identified in the Welsh National Service Framework (NSF) for Coronary Heart Disease.²³ The NICE guideline issued in 2008 reinforced the evidence base for such a service.

Description of the service

The service is multidisciplinary, and links with elements of current lipid clinic provision, clinical genetics, paediatrics and laboratory testing. The service is hosted by Cardiff and Vale Health Board and managed by the All Wales Medical Genetics Service with oversight from a multidisciplinary all Wales steering group.

The core FH operational team comprises:

- Medical advisor for adult FH (0.2 wte)
- Medical advisor for paediatric FH (0.1 wte)
- 3 FH nurse specialists (3 wte)
- Genetic counsellors (2wte)
- Paediatric nurse specialist advisor

(0.2wte)

Service manager

These staff are based across North, West and South Wales and are supported by a wider team of consultant, senior nurse and genetic counsellor professional support, with managerial, laboratory, IT and administrative input.

The service is funded from the Welsh Government, with an element of pump-priming by the British Heart Foundation for specialist nursing input.

Key benefits of the service to patients and professionals:

The FH Service enables wider availability within Wales for referral to specialist lipid services and for genetic testing for FH. It provides a pathway to assist diagnosing FH for use in primary and secondary care and also sets out a system for family testing for FH. As a result, a Welsh national database of patients with FH is being developed.

Patient pathway

A patient with suspected FH may be referred from their GP to the lipid clinic, where a clinical and lipid assessment is undertaken with a provisional diagnosis of FH using the Simon Broome criteria.

The hyperlipidaemia is treated (with continuing care mostly undertaken within primary care) and if appropriate, the patient is referred to the FH nurse specialist, who will discuss genotyping with the patient. Genotyping criteria have been developed based on a modification of the “Dutch” scoring system. If the patient is genotype positive, they are referred for family cascade testing. This is led by the genetic counsellors and involves taking a full pedigree, family registration, family tracing and first degree relative testing, where consented. Genotype positive relatives are referred





to the lipid clinic for advice on treatment options. Their relatives are also then offered testing and so on, in a cascade fashion.

Based on experience from the Dutch testing programme, the service aims to identify 60 per cent of those affected in Wales over a 10-year period. The main challenge in case finding is to encourage primary care to identify and refer possible index patients for testing and assessment.

Paediatrics

The FH service in Wales includes diagnosis and treatment of children. Paediatricians with a special interest in metabolic disease have been identified across Wales and a system of joint clinics with adult

lipid clinic consultants is being developed.

Software

A bespoke IT system has been purchased to support the service. This is designed by PASS Clinical, who also support the Dutch FH cascade testing service (see

page 15).

Education

Education forms a key part of the FH service, to improve awareness among professionals and to encourage appropriate referral. Events are delivered regularly across Wales by the medical advisors and FH specialist nurses.

FH Family Forum

The FH Family Forum provides a network for individuals and families with inherited high cholesterol and who are affected by FH. The forum holds meetings where members enjoy open discussions with guest speakers. The family forum is affiliated to HEART UK, British Heart Foundation (BHF) and the Genetic Alliance.

Northern Ireland

Northern Ireland (NI) has a population of 1.8m and thus should have about 3,600 cases of FH. However, despite good management of patients with lipid disorders through eight lipid clinics, NI has currently identified only about 800 patients with FH [22 per cent]. All of these patients have the causative genetic mutation defined. In addition, there are several hundred patients with possible and probable FH, according to the Simon Broome criteria, who currently attend lipid clinics but in whom no causative genetic mutation has been identified. Thus, a large group of undetected patients remain.

At present, NI has one specialist nurse, who works between the regional lipid clinic and the regional genetics service to provide support, testing and advice to families with FH. This has enabled NI to increase overall percentage of cases identified by 3 per cent over the past year. There are five health trusts in NI, each with roughly equivalent population bases. Thus, if we had a dedicated FH specialist nurse in each trust the rate of detection of new cases could rise dramatically. The benefits of nurse-centred family screening for FH are considerable and the number of cases we have defined since the introduction of a specialist nurse has more than doubled.

It is important that the FH nurse is seen as a central link between the family and primary and secondary care. This helps to focus attention on the patient and ensures that the family members are given the correct information at a time that suits them, directly from a dedicated professional. The ultimate aim is that the FH nurse ensures that patients are reviewed regularly by the lipid clinic consultant, as required, and that their lipid profiles are monitored on a regular basis. However, this cannot be fully

“Education forms a key part of the FH service to improve awareness among professionals and to encourage appropriate referral”





implemented until we have an effective lipid clinic database in operation.

Lipid clinics in Northern Ireland

Patients with lipid disorders, including FH, are managed through a network of lipid clinics. This includes a central regional lipid clinic at Royal Victoria Hospital, Belfast; with local lipid clinics run at seven hospital sites throughout NI, each attended by a consultant chemical pathologist.

FH genetic testing

NI has had a clinical and research interest in FH for some 15 years or more. Research funding from The NI Chest Heart & Stroke Association, British Heart Foundation and a programme grant from the DHSSPSNI Research and Development Office have led to effective genetic testing services being established. This was recognised by the Regional Specialist Services Commissioning group and revenue funding was provided to enable genetic testing for diagnosis and predictive testing for FH. This service has been available to consultants in the local lipid clinics for eight years.

A research nurse was employed for several years to assist in obtaining samples and clinical information for genetic studies on lipid disorders.²⁴ The benefits of a dedicated nurse quickly became clear in dealing with FH families and NI eventually obtained funding for an FH specialist nurse to be attached to the Regional Lipid Clinic and the Regional Genetics Centre.

The NI strategy is that all potential FH cases, as defined by the Simon Broome criteria, get a basic genetic test first for the most common mutations. Following review by the lipid clinic consultant, a decision is then made as to whether the patients meet the criteria for definite FH or have sufficient family history to

warrant sequence based analysis.

NI currently provides FH testing services to several NHS trusts in England and has identified the causative mutation in more than 200 families referred from outside NI.

Local funding arrangements and service frameworks

In 2009, the DHSSPSNI released a service framework for cardiovascular health and wellbeing. This document recognises the importance of FH and Standard 12 states that: "All people with genetically linked high cholesterol (familial hypercholesterolaemia) should be identified and treated and their names entered on a regional register so that other family members can be identified in order that measures can be introduced to prevent the development of cardiovascular disease."²⁵

This standard has 2 performance indicators

- 1 The percentage of the putative NI FH population identified
- 2 The percentage of adult FH patients achieving a reduction in LDL cholesterol of greater than 50 per cent.

In order to comply with the requirements of the standard a regional FH database is required, along with additional FH specialist nurses.

Future plans

A recent audit in 2010 of FH cases in Northern Ireland has shown that the majority of cases focus on the Belfast clinics [figure 1]. This inequality has been recognised and is the focus of a business case which has been submitted to the Cardiovascular Health and Wellbeing Commissioning Group (CHWCG). This case seeks funding for four part-time specialist nurses and for an updated database

“The NI strategy is that all potential FH cases get a basic genetic test first for the most common mutations”

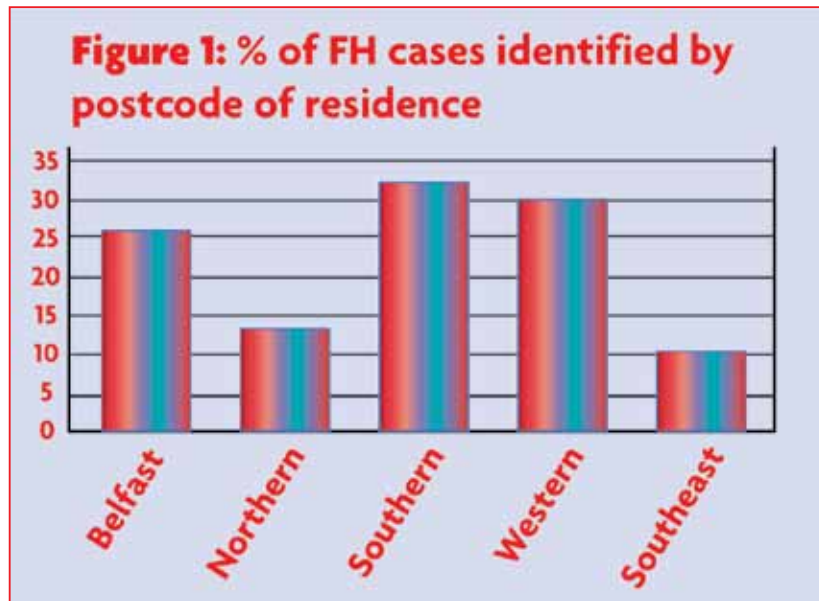




which can be used throughout the region to monitor FH families attending different clinics. IT improvements will also enable accurate audit data to be retrieved annually, helping NI review progress on the framework performance indicators.

The proposal is that specialist FH nurses will be co-ordinated through the Regional Genetics Service, but will be employed

and based in each of the Health Trusts. This will enable them to attend the local lipid clinics to support the consultant staff and to see family members at the lipid clinics and home visits. The project has the support of the CHWCG which is responsible for overseeing implementation of the CVS Framework and hopefully funding will be received in the next financial year.





How cascade testing helped to find FH in several members of my immediate family

Ken Henthorn contributed his story for this report, but sadly passed away on 22 November 2011, before the report was completed. His family has given their consent for his story's inclusion.

Cascade screening is still carried out in a haphazard way in England. When it has been initiated in families with suspected FH, lives can be saved across the generations.

This is the case for Ken Henthorn and his family.

"My story starts back in the late 1970s, when on a doctor's appointment for something totally unrelated, an astute and well-informed GP pointed out some white blemishes around my eyes and suggested I was tested for "high cholesterol".

"At the time, this was a term that I, and the vast majority of people, had never heard before. After the results of the initial blood test I was informed of the potential dire consequences of this condition and duly sent

Case study: Ken Henthorn

off to Manchester Royal Infirmary under the care of Paul Durrington.

After many tests and scans carried out by Deepak Bhatnagar and his team in Manchester, I was prescribed Questran, a lipid lowering agent in powder form, and that was the start of the medication programme to reduce my cholesterol level.

"Over the years I have had some success with the various medications, with the current mix of Atorvastatin and Ezetimibe being the most effective in controlling my FH.

"I suffered my first heart attack aged 36 and another 10 years later.

"Both were traumatic events, and best avoided at all costs.

"After the first event, some

of my brothers and sisters got themselves tested for 'high cholesterol'. Two of my sisters were found to have raised levels of cholesterol and needed medication, while one of my brother's levels was fine.

"My other brother, then in the Army, was not tested, but died suddenly in his sleep at the age of 36 – one could assume this was more than just a coincidence.

"With all this in mind, I have been hugely relieved by the cascade-style testing carried out by Deepak Bhatnagar and his team over the years.

"This has enabled my four children to be tested for FH. My son and one daughter are clear of the problem, while my other two girls are not.

"By early testing and subsequent treatment and advice, it is hoped that the disorder can be controlled so they will not have to suffer the pain and trauma of cardiovascular disease or heart attacks at a relatively early age."





CHAPTER 3:

Estimating the benefits from treatment and increasing the implementation of cascading screening

HEART UK commissioned new health economic modelling for this report, to examine the costs/benefits of different types of cascade screening and different levels of treatment for FH. The full research paper is available at the HEART UK website: www.heartuk.org.uk

Summary

The NICE FH guideline (CG71)²⁶ recommends that people with FH should be treated with high intensity statins to prevent early deaths from coronary heart disease (CHD). Currently, it is estimated that 15 per cent of the expected 120,000 UK FH patients have been identified and treated in primary and secondary care. If the family cascade testing strategy recommended by the NICE guideline is implemented this number is expected to increase to 50 per cent. In this analysis we assumed for every index case there will be five relatives with FH. Thus, out of the 120,000 FH cases in UK, 24,000 are assumed to be index cases and 96,000 are the relatives. In addition to implementing this cascade screening, there is an urgent need for an FH national register, to facilitate follow-up of relatives of affected persons.

We conducted a cost-utility analysis to quantify the benefits of optimal, high intensity statin treatment or sub-optimal statin treatment compared to no treatment. High intensity statin treatment or aggressive lipid modifying therapy may be defined as any lipid lowering drug or combination which is more potent than simvastatin 40mg, including atorvastatin (20mg or greater) or rosuvastatin (10mg or greater), either alone or in combination with bile acid sequestrants, ezetimibe, nicotinic acid or fibric acid derivative.. All of the above drugs and combinations are recommended by NICE CG71 for use as required if optimal LDL cholesterol lowering of greater than 50 per cent from baseline is not achieved. For the purpose of this analysis we used the example of high intensity statins for which long-term outcome data were available however other drug treatment regimes achieving similar LDL-C reductions should be considered equivalent.





We show the benefits of treatment in terms of QALY (quality adjusted life year) gains and cardiovascular (CV) events avoided. We are also able to show the benefits of cascade screening and associated savings from various levels of implementation.

People with FH will incur costs to the NHS over their lifetime, whether they are treated with statins or not treated. These costs include the cost of the intervention; in this case statins, the cost of CV events such as treating MI (myocardial infarction), strokes, revascularisations, and heart failure. The costs of health care professionals such as GPs and specialists are also included. More effective treatments will reduce the incidence of CV events and in the long run save money to the NHS, compared with less effective interventions. When comparing interventions – in this case, high intensity statins with no treatment for instance – high intensity statins result in fewer lifetime costs overall when all cost have been accounted for. High intensity statins also result in better health outcomes such as less CV events and mortality (which will translate to more life years gained and QALYs). This is said to “dominate” the comparator.

Sometimes high intensity statins will result in overall more costs compared with the comparator, but more health benefits. This is the case with high intensity statins when compared with low intensity statins, and a judgment then has to be made whether the additional benefits are worth paying for. The NHS is usually willing to pay £20,000-£30,000 for an additional unity of health benefit measured in QALYs.

The lifetime treatment costs and health benefits have been estimated in line with NICE guidance, which states that both costs and benefits should be discounted

at 3.5 per cent and that health benefits should be estimated in QALYs.²⁷

As mentioned earlier, the overall costs include the cost of drugs and CV events avoided over a lifetime. The lifetime costs for the at-risk relatives of FH index cases who are followed from the age of 30 to 85 years and are not offered statin treatment was estimated to be £18,008.

For those people offered low intensity (sub-optimal) statin treatment the lifetime cost was estimated to be £17,664, and for those offered high intensity optimal statin treatment the lifetime cost is £17,959. The estimated lifetime health benefits in QALY gains from treatment was estimated to be 10.96 for those not offered statins, while those offered sub-optimal and optimal statin treatment gained 11.16 and 11.92 respectively. People who are not offered statin treatment still gain some QALYs. This is because they will be eligible for other treatments such as antihypertensive medication and aspirin, except that in this instance they are assumed not to receive statins.

The analysis shows that both optimal and sub-optimal statin treatment results in greater health benefits at lower overall cost when compared to no treatment. Statin treatment “dominates” no treatment and therefore, statin treatment is preferable to no treatment.

Furthermore, the results show that optimal statin treatment with high intensity statins is more beneficial than sub-optimal treatment, resulting in more costs and greater health benefits. The additional cost and benefits yields an estimated incremental cost-effectiveness

“Optimal and sub-optimal statin treatment results in greater health benefits at lower overall cost”





ratio of about £400/QALY, which is highly cost-effective.

Our analysis was able to demonstrate how the benefits in QALY translate into CV events avoided. For instance, we have demonstrated that by offering affected relatives optimal statin treatment, 101 CV deaths per 1,000 FH patients treated will be avoided compared to no treatment. A further 69 additional CV deaths will be avoided per 1,000 FH patients treated if 1,000 people affected with FH are offered optimal treatment rather than sub-optimal treatment.

We also calculated the cost of screening or diagnosis. Our analysis demonstrated that the cost of diagnosis per patient using the method of LDL-cholesterol

measurement only is £202 for the index cases and £116 for relatives. For DNA diagnosis the cost of for each index case is £125 and £75 for each relative.²⁸

Currently, the cost of DNA testing in England varies and may be higher than that reported in this analysis.²⁹ Lower costs are available through laboratories using the latest technology (such as in Northern Ireland). Using the DNA costs obtained in Northern Ireland the overall cost per patient for cascading relatives using the recommended strategy (combined LDL-cholesterol and DNA based diagnosis) is £160 per relative when 1,000 index cases are screened.

Greater benefits and savings for the NHS will accrue if all eligible FH patients are identified and treated. We have shown that using cascade screening at every level of implementation will yield savings in the form of CV events avoided, and that this translates into QALYs and LYG gained. While it remains aspirational

to achieve 100 per cent identification of the predicted UK FH cases, there is considerable room to improve from the current estimated 15 per cent of cases that have been identified, and we believe a realistic goal is that 50 per cent of the UK FH patients could be found within five years by the cascade testing strategies recommended by NICE.

This analysis has demonstrated that, even if cascade testing were carried out only from the 15 per cent of eligible FH patients currently identified, the CV events avoided would result in savings of £591,647 per 1,000 screened index cases, if identified relatives are offered optimal treatment.

This would translate to £8.5 million nationally for the UK. If, more realistically, 50 per cent of the 96,000 predicted relatives of UK FH index cases were identified by the recommended cascade screening methods, then £1.97 million per 1,000 screened index cases could be saved with optimal treatment. This would translate to £94.7 million nationally for the UK over a 55 year period, or roughly £1.7m per year. By not fully implementing cascade screening as recommended in the NICE guideline (identifying 50 per cent of potential relatives' cases) the NHS is losing approximately £1.4m per year.

To achieve maximum benefit from currently recommended family cascade screening methods, a national disease register for FH will be essential to facilitate efficient use of resources. This does not currently exist in the UK. This analysis has shown that the costs of implementing a national FH register are very small when compared to the expected benefits of identifying relatives of affected index cases. We have estimated that the FH register will cost the whole of the NHS £149,275 per year, or £101,000 if this were used to fund

“ Greater benefits and savings for the NHS will accrue if all eligible FH patients are identified and treated. ”





two staff members or persons per PCT in England respectively to operate the register at the PCT level. Funding two people per PCT will currently cost about £10.37 per person identified per year and would fall to £3.11 per person per year if screening identifies up to 50 per cent of eligible patients. If the PCT decides to fund one person per year, the costs will be £6.10 and £1.83 per person in the database if 15 per cent or 50 per cent of patients are identified respectively.

Methods, modelling benefits of statin treatment

A previous economic analysis using the Markov model³⁰ was used to estimate the benefits of treatment with statins (high and low intensity). An additional analysis was performed to estimate the costs and benefits of no treatment.

The high intensity statin regime used in the analysis was atorvastatin 80mg daily, in comparison with a low intensity statin (simvastatin 40mg daily) and a placebo (considered equivalent to no treatment). Health outcomes were reported as quality adjusted life years (QALYs), life years gained (LYG) and CV events avoided. The model was populated with a hypothetical cohort of 1,000 people with FH. The age at diagnosis was included as a variable. Costs and QALYs were calculated until patients either died or reached the age of 85 years. More details of the methodology are provided in the main report, which can be found on the HEART UK website (www.heartuk.org.uk).

Methods for estimating the numbers screened by different cascading methods

We considered four different cascading methods as described in Nherera et al:³¹

- **Strategy 1:** LDL-cholesterol based diagnosis and cascade testing: Relatives will be cascaded from DFH and PFH (FH genetic mutations) by

LDL-cholesterol testing only

- **Strategy 2:** DNA based diagnosis and family cascade testing: Relatives will be cascaded from DFH and PFH for those mutation positive (Mut+ve) by DNA testing
- **Strategy 3:** DNA diagnosis and combined cascade testing strategy for DFH: Strategy 2 with additional LDL-cholesterol based family cascade testing in DFH mutation negative (DFH Mut-ve). Relatives will be cascaded from DFH and PFH mutation positive (Mut+ve) by DNA testing, while those who have DFH mutation negative (Mut-ve) will be cascaded using LDL-cholesterol testing
- **Strategy 4:** DNA diagnosis and combined cascade testing strategy for DFH and PFH: Strategy 3 with additional LDL-cholesterol based family cascade testing in PFH mutation negative (DFH Mut-ve). Relatives will be cascaded from DFH and PFH mutation positive (Mut+ve) by DNA testing, while all DFH and PFH mutation negative (Mut-ve) will be cascaded using LDL-cholesterol testing.

Results

A Markov model was used to estimate long-term costs and health outcomes (numbers of CV events that will be observed) in FH patients who are:

- Not treated with statins (because they are not identified)
- Sub-optimally treated with generic/low intensity statins
- Optimally treated with high intensity statins

It is important to point out that in this analysis 'no treatment' implies that people are not offered statins or other lipid lowering therapies, but they may be offered treatments other than lipid lowering therapy (e.g. revascularization, antiplatelet therapy). The estimation of benefit from statin treatment was





necessary in order to show what is gained by treating FH patients who are eligible for statin treatment, and conversely what untreated (because they are not identified) FH patients will lose in terms of health benefits and the subsequent costs to the NHS. Our analysis showed that if relatives of FH index cases are identified and treated optimally they will gain 11.92 discounted³² and 21.25 undiscounted QALYs over their lifetime.

If relatives are treated sub-optimally they will gain 11.16 discounted and 19.43 undiscounted QALYs over their life time. If relatives are not screened and identified, they will not be treated with statins. However, they will still accrue some benefits from other interventions other than statins. We estimate that they

will gain 10.96 discounted and 18.84 undiscounted QALYs respectively. The QALY is estimated by weighting the time spent in each health state by the health-related quality of life (utilities) for that health state obtained from the literature.

The lifetime QALY gain from statin treatment is comparable with treatment gain from other therapies. For instance, an economic analysis of screening for pre-diabetes among overweight and obese adults in the US by Hoerger et al estimated treatment benefit in QALYs to be 9.01 for screening compared to 8.9 for no screening.³³ Another economic analysis by Freeman et al estimated the QALY gains of high dose dabigatran to

be 10.84 QALYs and that of warfarin to be 10.28 over a 30 year time horizon.³⁴ If health related quality of life is not considered, i.e. combination of a person's physical, mental and social wellbeing; not merely the absence of disease, the health outcome of the economic model will be measured in terms of life year gained i.e. average years of life gained per person as a result of the intervention. For those patients that are offered optimal statin treatment they will gain 16.24 discounted life years and 30.40 undiscounted life years, while those offered sub-optimal treatment will gain 15.27 discounted life years and 27.87 undiscounted life years. We estimate that those not offered statins will gain 15.16 discounted and 27.32 undiscounted life years.

Healthcare costs are estimated by weighting the time spent in each health state by the expected treatment costs for that health state. If patients were offered statins, we then add the annual cost of statins. Overall, cost of treatment for the relatives will be £17,959 with optimal statin treatment. As mentioned earlier, these costs consist of the cost of events such as MIs, strokes, revascularizations, plus the annual cost of statins. The lifetime costs for sub-optimal statin treatment are estimated to be £17,664. Lastly, the costs of no treatment are estimated to be £18,015 per person; these costs exclude the cost of statins, since we assume they are not treated with statins. Statin treatment either optimally or sub-optimally is a dominant strategy compared to no treatment – that is, it results in more health benefits at less

“ Lifetime QALY gain from statin treatment is comparable with treatment gain from other therapies ”

Table 1: Lifetime treatment costs and benefits (QALY and LYG) for relatives who are followed for 55 years (from 30 years to 85 years)

Intervention	Discounted			Undiscounted		
	Cost	QALYs	LYG	Cost	QALYs	LYG
No treatment	£18,015	10.96	15.16	£34,612	18.84	27.32
Low intensity treatment	£17,664	11.16	15.27	£34,289	19.43	27.87
High intensity treatment	£17,959	11.92	16.24	£35,356	21.25	30.4



costs overall. This is said to be cost-saving. The observed QALY and LYG gained in **table 1** above will translate to the following modelled CV events avoided when no treatment is compared to both sub-optimal and optimal treatment. We have also shown that events can also be

avoided by treating FH patients optimally by reducing baseline LDL-C by more than 50 per cent, with recommended high intensity statins as recommended in the NICE FH guideline. **Table 2** and **figure 1** visually illustrate the observed events avoided below.

Table 2: Base case relative's lifetime events avoided per 1,000 treated patients (followed up from 30 years to 85 years)

Events	Events avoided, sub-optimal treatment with low dose vs. no treatment	Events avoided, optimal treatment with high dose vs. no treatment	Events avoided, optimal treatment with high dose vs. sub-optimal treatment with low dose
MI	94	141	47
Stroke	193	262	69
Heart failure	138	142	4
Re-vascularisation	119	34	-40
Unstable angina	56	41	-15
CV death	32	101	69
Other death*	-11	-31	-20
Total alive**	20	69	49

MI: Myocardial Infarction; CV death: Cardiovascular death

*Negative numbers for other deaths are results of fewer people dying of cardiovascular deaths. Statins have no effect on other causes of deaths – for example, deaths due to car accidents or suicide

** Total people alive is a positive outcome, the more people alive, the better the statin treatment will be

Figure 1: The lifetime observed events avoided for 1,000 FH relatives, assuming they are optimally or sub-optimally treated with either high or low doses of statins or they are not cascaded (hence not treated)

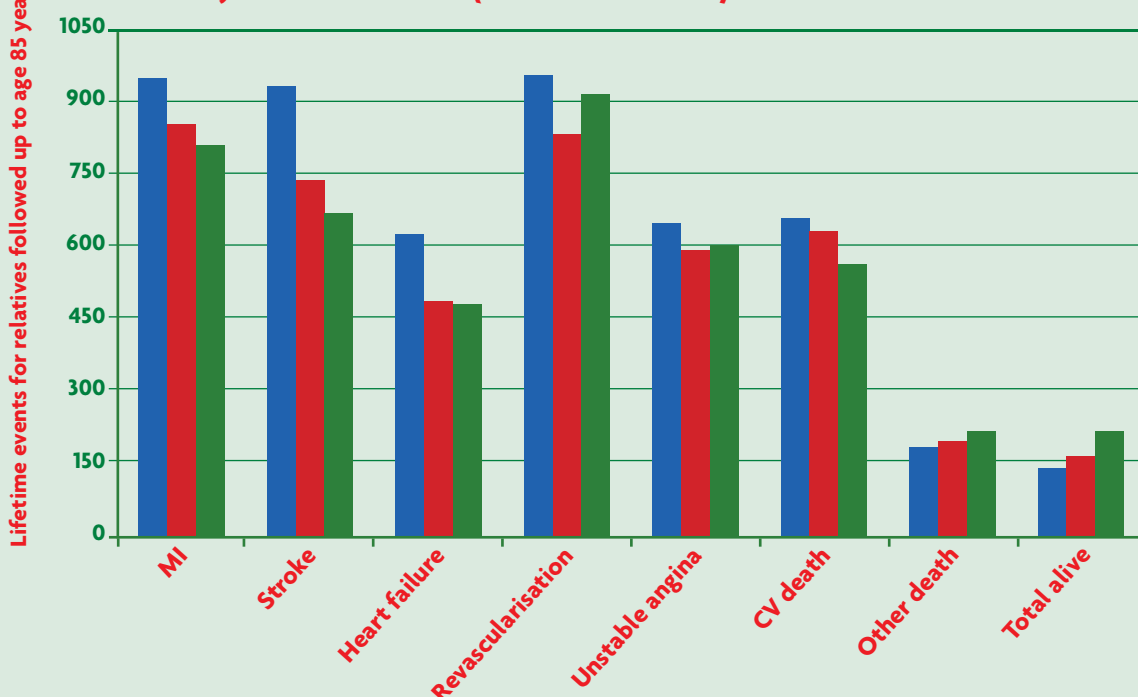




Table 2 and **figure 1** show that there are more benefits to be derived from treating FH patients optimally with high intensity statins to achieve a reduction in LDL-C of more than 50 per cent from baseline, compared with no treatment or sub-optimally with low-intensity statins. Fewer CV events – including CV death – will be observed in those patients offered high intensity statins, compared with no treatment. The **figure** also shows that people treated optimally can expect to live longer and are more likely to die of non-cardiovascular causes. Furthermore, it is clear that by treating FH people even with sub-optimal doses of statins, 20 lives will be saved per 1,000 cases, and if FH people are treated with optimal statin doses, 69 lives will be saved per 1,000 people with FH.

We have estimated the overall savings from treating 1,000 people with FH over a lifetime. We multiplied the events avoided by the cost of treating each event. For those who are alive, we calculated the cost of treating CVD to be a weighted cost of the CVD events

included in the model, weighted by the distribution of these events at baseline without treatment. The cost of treating a CVD event was estimated to be £1,500 including treatment. Overall, treating 1,000 relatives of FH cases will save £3,820,657 when people are offered sub-optimal low intensity statin treatment and £3,944,312 when they are offered high intensity statin treatment. If we consider all relatives of FH index cases in the UK (96,000), the total savings will be estimated to be almost £378 million or £6.9 million per year (96,000 multiplied by the cost-saving per patient of about £3,944). This estimate assumes all FH people are identified and offered optimal treatment.

Modelling cascade screening outputs using different methods

Testing the families of known cases of FH (cascade testing) can identify those with FH. The cost-effectiveness of different cascading methods has been established, and the DNA-based method Strategy 4, has been found to be cost-effective. It has also been demonstrated that any

Table 3: Estimated lifetime cost savings from avoided CV events when true FH relatives of 1000 FH index cases are offered treatment

Events	Cost savings, sub-optimal treatment with low dose vs. no treatment	Cost savings, optimal treatment with high dose vs. no treatment	Cost savings**, optimal treatment with high dose vs. sub-optimal treatment with low dose
MI	£160,304	£239,937	£79,633
Stroke	£2,087,066	£2,828,559	£741,493
Heart failure	£247,904	£255,083	£7,179
Re-vascularisation	£1,304,480	£368,933	-£935,547
Unstable angina	£63,550	£46,910	-£16,641
CV death	£149,788	£475,255	£325,467
Other death	-£2,828	-£7,861	-£5,033
Total lifetime savings per 1,000 treated people	£3,820,657	£3,944,312	-£35,135

** There are no cost savings between optimal treatments compared with sub-optimal treatment as shown by a negative cost. However, the additional payment on optimal treatment has been shown to be worth paying for.





Table 4: Total numbers of index cases identified as TP, FP, FN and TN from 1000 suspected FH cases

Index cases	Strategy 1	Strategy 2	Strategy 3	Strategy 4
True positives – FH	507	446	479	510
False positives – not FH cascaded	0	60	27	0
False negatives – FH not detected	433	434	434	430
*True negatives – no FH, not cascaded	60	60	60	60
Total numbers tested	1000	1000	1000	1000

*No cascading is done in true negative cases, i.e. from those with no FH

cascading method is better than not cascading at all.^{35,36} Cascade testing from 1,000 suspected FH index patients will result in people being classified as true or false positives and true or false negatives. Testing for relatives will be performed from DFH and PFH and if an index case is deemed true negatives (TN), it means they do not have FH and no cascading will be performed in these patients.

Table 4 above shows the numbers of index cases who are true positives (TP), false positives (FP), false negatives (FN) and true negatives (TN) according to the assumptions outlined in the methods section from 1,000 suspected index cases.

Cascading will only be undertaken from those with definite FH (true positives-TP), those incorrectly identified as having FH (false positives-FP) and those incorrectly identified as having no FH when indeed they have FH (false negatives-FN).

From the **table** below, cascading will take place from 940 FH cases, since there are 60 true negatives from each strategy that will not be cascaded from. The **tables** below shows the benefits of cascade screening in terms of the numbers of CV events avoided, life year and QALY gained when relatives are followed for a lifetime.

Cost of diagnosis/screening

We calculated the costs per index and relative case diagnosed or screened, which were divided into clinical confirmation and genetic confirmation costs. All screening methods incurred a clinical confirmation costs i.e. the costs of cholesterol testing. Cholesterol confirmation costs were derived from the unit costs of healthcare professionals obtained from PSSRU³⁷ (physician, dietician and phlebotomy) multiplied by the time that each healthcare professional spent with the patient. The costs of lipid profiles for each patient were then added. Genetic confirmation costs were calculated by multiplying the cost of DNA testing obtained from Bradshaw and Austin³⁸ i.e. £125 for index cases and £75 for relatives by numbers of cases who had DNA testing.

The total cost per index case was calculated by adding the total cost of both cholesterol and genetic confirmation for each method divided by 1,000 index cases that were screened. See **table 5** below for further details.

Results for relatives per 1,000 screened index cases

In this analysis, we assume a PCT has 1,000 index cases that are being seen. Benefits shown in the analysis for cascading



**Table 5: Total costs and cost per index case diagnosed by method of screening**

Index cases	Strategy 1	Strategy 2	Strategy 3	Strategy 4
Clinical confirmation	£201,630	£201,630	£201,630	£201,630
Genetic confirmation	–	£117,500	£117,500	£117,500
Total cost	£201,630	£319,130	£319,130	£319,130
Cost per patient	£202	£319	£319	£319

Table 6: The cost of diagnosis per relative using the different cascading methods per 1000 screened index cases when up to third degree relatives are screened

Relatives	Strategy 1	Strategy 2	Strategy 3	Strategy 4
Clinical confirmation	£520,980	£351,508	£384,871	£590,776
Genetic confirmation	–	£227,818	£227,818	£227,818
Total costs	£520,980	£579,326	£612,689	£818,594
Cost per patient	£116	£191	£184	£160

assumes the effect of high dose statins compared with no treatment, since if no cascading takes place we assume the relatives will not be identified and will not benefit from treatment. We also assumed that up to third degree relatives will be followed. In the main report we present results assuming that up to second degree relatives are followed and the assumption of sub-optimal treatment. For ease of interpretation of results we assumed that the level of implementation is the same as the effectiveness of implementation, e.g. 15 per cent increase in cascade screening is the same as the

15 per cent increase in effectiveness of cascade screening.

It is evident from **table 7** below that cascading using the recommended Strategy 4 will result in 1,772 positive cases being identified and offered treatment per 1,000 index cases when third degree relatives are followed, while the cholesterol only testing method will identify 808. As mentioned earlier, at least some cascading is better than not cascading at all; however, it has been established that by not using the recommended screening strategy

Table 7: Number of FH cases tested and positive cases identified per 1000 index cases screened up to third degree relatives

Relatives	Strategy 1	Strategy 2	Strategy 3	Strategy 4
True positives – FH	808	1671	1723	1772
False positives – not FH cascaded	454	0	30	57
False negatives – FH not detected	518	0	33	305
True negatives – no FH, not cascaded	2722	1367	1540	2971
Total numbers tested	4502	3038	3326	5105





Table 8: QALYs and LYG per 1,000 index cases cascaded up to second and third degree relatives using different methods

	Strategy 1	Strategy 2	Strategy 3	Strategy 4
Relatives tested up to second degree				
True positives – FH	730	1323	1371	1415
QALY	8696	15770	16336	16857
LYG	11854	21497	22269	22979
Relatives tested up to third degree				
True positives FH	808	1671	1723	1772
QALY	9623	19908	20535	21116
LYF	13117	27138	27992	28784

society as a whole will lose in terms of QALYs, which is an inefficient use of NHS resources.

Table 8 above shows the QALYs and LYG gained if relatives are followed from the age of 30 to 85 years for each screening strategy when optimal treatment is compared to no treatment.

Modelling “reality” of FH screening and events avoided

So far, the above analysis has assumed a best case scenario where all the FH people are identified and offered treatment. However, in reality only a small proportion of people with FH are identified and are being offered treatment. The current estimates suggest that only about 15 per cent of eligible patients are being offered treatment.³⁹ Crucial to realising the benefits of treatment mentioned above is identifying

those FH patients and offering them treatment. It is widely recognised that cascading may only identify 50 per cent of these predicted cases; hence there is strong case for investigating new methods for identifying new FH probands.

Below we will illustrate the potential savings that can accrue to the NHS by implementing cascade screening and the number of CV events that can be avoided. The analysis is done assuming that cascading is done using the recommended Strategy 4 of DNA based method and cascading from both definite and probable FH using additional LDL-cholesterol testing in order to maximise the benefits. Any other cascading method will yield substantial benefits, but it will be a comparatively inefficient use of resources as more cases could be identified cost-effectively using the recommended Strategy 4.

Table 9: Lifetime CV events avoided per 1,000 relatives assuming different proportions of people are found by cascade screening method when FH people are optimally treated by offering high intensity statins

Events	Proportions of people found by cascading and offered treatment									
	15%	20%	30%	40%	50%	60%	70%	80%	90%	100%
MI	21	28	42	56	70	84	99	113	127	141
Stroke	39	52	78	105	131	157	183	209	235	262
Heart failure	21	28	43	57	71	85	99	113	128	142
Re-vascularisation	5	7	10	13	17	20	24	27	30	34
Unstable angina	6	8	12	16	21	25	29	33	37	41
CV death	15	20	30	40	50	60	70	81	91	101
Other death	-5	-6	-9	-13	-16	-19	-22	-25	-28	-31
Total alive	10	14	21	28	35	42	48	55	62	69





The numbers of events in each column have been estimated by multiplying the number of events that that will be observed in an ideal situation by the actual percentages of FH people being screened by cascade screening. For instance, if all FH patients are identified and treated optimally (100 per cent), then 141 MIs will be avoided per 1,000 treated cases, but if say only 15 per cent are seen then only 21 MIs will be avoided per 1,000 treated cases (15 per cent*141). The column with 50 per cent identification rate represents what the current cascading methods should realise if the NICE FH guideline is followed, according to current estimates. The first column

shows the events avoided using the current estimated rate of identification, which suggests that only 15 per cent of FH cases are being treated. It is clear that by increasing cascading screening from its current levels to the realistically achievable rate of 50 per cent will save lives and save resources for the NHS. The avoided CV events will translate into QALYs and LYG as shown below.

The analysis shows that currently by identifying 15 per cent of FH patients, the NHS would be saving £591,647 and gaining 3,167 discounted QALYs per 1000 screened index cases when cascade testing and offering optimal treatment

Table 10: Estimated QALY and LYG by different cascading methods when different proportions of FH people are identified due to implementing cascading per 1,000 relatives, optimal treatment compared to no treatment up to third degree relatives

Strategy	Proportions of people found by cascading and offered treatment									
	15%	20%	30%	40%	50%	60%	70%	80%	90%	100%
QALY gains										
Strategy 1	1443	1925	2887	3849	4811	5774	6736	7698	8660	9623
Strategy 2	2986	3982	5972	7963	9954	11945	13936	15927	17917	19908
Strategy 3	3080	4107	6160	8214	10267	12321	14374	16428	18481	20535
Strategy 4	3167	4223	6335	8446	10558	12669	14781	16893	19004	21116
LYG gained										
Strategy 1	1968	2623	3935	5247	6558	7870	9182	10494	11805	13117
Strategy 2	4071	5428	8141	10855	13569	16283	18997	21710	24424	27138
Strategy 3	4199	5598	8398	11197	13996	16795	19594	22393	25193	27992
Strategy 4	4318	5757	8635	11514	14392	17270	20149	23027	25906	28784

Table 11: Lifetime savings for relatives due to CV events avoided assuming different proportions of FH people are found by cascade screening method when FH people are treated optimally

Event	Savings from proportions of people found by cascading & offered treatment									
MI	£35,991	£47,987	£71,981	£95,975	£119,969	£143,962	£167,956	£191,950	£215,943	£239,937
Stroke	£424,284	£565,712	£848,568	£1,131,424	£1,414,280	£1,697,136	£1,979,991	£2,262,847	£2,545,703	£2,828,559
Heart failure	£38,262	£51,017	£76,525	£102,033	£127,542	£153,050	£178,558	£204,067	£229,575	£255,083
Revascularisation	£55,340	£73,787	£110,680	£147,573	£184,466	£221,360	£258,253	£295,146	£332,040	£368,933
Unstable angina	£7,036	£9,382	£14,073	£18,764	£23,455	£28,146	£32,837	£37,528	£42,219	£46,910
CV death	£71,288	£95,051	£142,577	£190,102	£237,628	£285,153	£332,679	£380,204	£427,730	£475,255
Other death	-£1,179	-£1,572	-£2,358	-£3,144	-£3,931	-£4,717	-£5,503	-£6,289	-£7,075	-£7,861
Total savings	£591,647	£788,862	£1,183,293	£1,577,725	£1,972,156	£2,366,587	£2,761,018	£3,155,449	£3,549,880	£3,944,312





(Strategy 4). This will translate to a £8.5 million saving to the NHS over a 55 year period, or about £155,000 per year.

If the recommended strategy is fully implemented i.e. identifying 50 per cent of the affected relatives, potentially 10,558 QALYs will be gained and £1,972,156 will be saved per 1,000 screened index cases.

This will translate to £94.7 million savings nationally over a 55 year period, or £1.7m per year. By not fully identifying eligible patients (15 per cent currently being identified rather than the potential 50 per cent) 7,391 QALYs and the NHS is losing approximately £86.1 million over 55 years (£94.7m - £8.5m), or about £1.4 million per year (£1.6m-£155K).

However, ideally if screening methods could be improved to identify all the relevant FH cases, 21,116 QALYs could be gained and £3,944,312 will be saved per 1,000 index cases screened. Nationally, this will translate to 2,027,136 QALYs and savings of £378.6 million. This is based on cascading up to third degree relatives.

The case for a national FH database

An electronic register or database will be required to facilitate and performance manage the complexities of cascade testing over a large geographical area. A specific database application for FH which includes registry, advanced pedigree drawing, workflow management and reporting functions has been developed by PASS Software and has been successfully implemented in the national FH cascade screening program in Holland.

The English language translation has now been piloted for two years by NHS Wales, where it has been adapted specifically for the NHS. Below we have calculated the costs that are needed to run the national database using figures obtained

from PASS Software. The estimated total costs per patient are very small, given the efficiency gains such a database will bring.

PASS Clinical charges per named user. This is a healthcare professional that is registered in PASS Clinical and has a role in the system and the screening workflow (so s/he is a member of a group/each group has user rights). There are two models for having the database, the ALL IN ONE MODEL and the Conventional Model.⁴⁰

The most relevant model for a national programme is the ALL IN ONE, which requires a minimum of 20 named users. It costs € 1,200 (£1,043.88) per user for the first 20 named users, € 700 (£608.93) for 30-50 users, falling to € 400 (£347.96) if 301-400 users are named.

The total NHS costs calculated for 152 PCTs assuming two named users per primary care trust (PCT) are €171,600 (£149,274.84) per year $[(20 \times 1200) + (50 - 20) \times 700 + (100 - 50) \times 600 + (200 - 100) \times 500 + (300 - 200) \times 450 + (4 \times 400)]$.

This works out to be to €1.79 (£1.55) per patient, assuming all 96,000 relatives of FH index cases are in the database (632 patients per PCT). However, using current estimates, which suggest only 15 per cent of the FH cases are known, it will cost €11.92 (£10.37) per patient per year. Thus, as more and more patients are identified, the cost will eventually fall to the estimated £3.11 per patient per year if 50 per cent of patients are identified.⁴¹

If we assume there will be one named user per PCT, the annual cost will be £87,860 for the NHS. The cost per patient using current estimates suggesting 15 per cent of FH cases are known, this will cost £6.10 per patient per year falling to £1.83 if 50 per cent of patients are identified.





Conclusions and discussion

Lifetime treatment costs have been estimated to be £18,008, £17,664 and £17,959 and the lifetime QALY gains from treatment was estimated to be 10.96, 11.16 and 11.92 for relatives of index cases who are followed from the age of 30 to 85 years, who are not offered statin treatment, offered sub-optimal and high intensity, optimal statin treatment respectively. This finding shows that statin treatment results in more health benefits at a lower cost overall when compared to no treatment since no treatment has the highest lifetime costs £18,008 and least health benefits 10.96 QALY.

We thus say statin treatment dominates no treatment. Furthermore the results show that optimal statin treatment with high intensity statins is more beneficial than sub-optimal treatment. It results in both more cost and more health benefits. This results in an estimated incremental cost-effectiveness ratio of about £400/QALY, which is deemed cost-effective according to NICE FH guidance.

Our analysis demonstrates how the benefits in QALY and LYG translate into CV events avoided. For instance we have demonstrated that by offering the relatives optimal statin treatment to achieve an LDL-C reduction of more than 50 per cent, 101 CV deaths will be avoided per 1,000 FH patients compared to no treatment. Furthermore, 69 additional CV deaths will be avoided per 1,000 FH patients if people were offered optimal treatment rather than sub-optimal treatment. Our analysis also demonstrates that the cost of diagnosis per patient using cholesterol method is £202 for the index cases and £116 for relatives, which is almost half that of index cases. The same can be said for genetic testing, as the cost of DNA for the index case is £125 and £75 for relatives.

Greater benefits and savings for the NHS will accrue if all eligible FH patients are

identified and treated. We have shown that cascade screening at different levels of implementation will bring savings in the form of avoided CV events, which translate to QALYs and LYG gained. This analysis has demonstrated that when we breakdown the savings by CV events avoided, even at today's estimates which shows that 15 per cent of eligible FH patients are being identified, families cascade tested and affected members optimally treated, there are still some savings of £591,647 per 1,000 screened index cases who are offered optimal treatment.

This translates to £8.5million for the NHS over a 55 year period or £155,000 per year over the same period. If 50 per cent of patients were being identified according to the potential of current screening methods, then £1,972,156 would be saved. This will translate to national cost savings of approximately £94.7 million over 55 years, or £1.6 million per year. Thus, by ensuring that the screening methods are fully implemented at their current best, the NHS would save an additional £1.4 million (£1.6m - £155K) annually. This can translate to £86.1 million over the 55 year period.

To achieve maximum benefit from current screening methods, a national FH register will be required. This analysis has shown that the costs of implementing a national FH register are very small when compared to the improvements in efficiency of identifying relatives of affected index cases. We have estimated that the FH register and cascade testing support software will cost the whole of NHS £149,274 per year if they choose to fund two staff members per PCT to operate the database, or £87,860 per year if one person is funded per PCT. At current estimates where 15per cent FH cases are known, this works out to be about £10.37 or £6.10 per person in the database.



CHAPTER 4:

A national FH programme for England

This report has demonstrated the value of implementing cascade screening for FH in England. It shows the importance of QALYs gained and cardiovascular events avoided, all of which impact on individuals, their families and society as a whole. It also demonstrates that the more cascade screening takes place, the greater the financial benefits.

Yet the commissioning system in England has not accommodated a rollout of the NICE guideline for FH. The very nature of FH, with family members living in more than one area, requires national action and local implementation.

The commissioning system is presently undergoing a process of change. While the National Commissioning Board (NCB) is yet to commence its work, the latest information indicates that the NCB will have overall responsibility for a budget of £80bn, of which it will allocate £60bn directly to Clinical Commissioning Groups (CCGs, formerly called GP consortia). The NCB will directly commission a range of services, including primary care and specialised services and have a key role in improving broader public health outcomes. One of its key roles will also be to promote equality and reducing inequalities in access to healthcare, in co-operation with Public Health England.⁴²

The remit of the NCB should accommodate people with FH for the following reasons:

- The localised commissioning structure has not served people with FH well. International experience has shown the necessity of ring-fenced national programmes to tackle FH
- The NCB is keen to reduce inequalities in access to healthcare. People with undiagnosed but suspected FH continue to suffer a host of access issues with respect to DNA testing and follow up for their family members. An NCB programme would reduce the inequalities facing this patient group
- If CCGs are tasked directly with commissioning FH services, the NCB could still set standards for delivering a programme locally (as in Northern Ireland).

Recommendation

HEART UK recommends that the NCB creates a national programme for FH in England. This is the best means of ensuring that FH services are available beyond the limited boundaries of a PCT or CCG.





Considering the better position of other countries in the UK, this national programme should include the following key elements:

- A new national register of FH patients. The register should serve as patient database and accommodate cascade screening and clinical management tools and ideally should be able to link to similar systems in Wales, Scotland and Northern Ireland.
- A dedicated network of involved professionals, including lipid clinics, primary care and genetic services. This is critical in the multidisciplinary management of FH patients
- Clear referral pathways at the local level
- The employment of FH nurses to rollout the cascade screening process

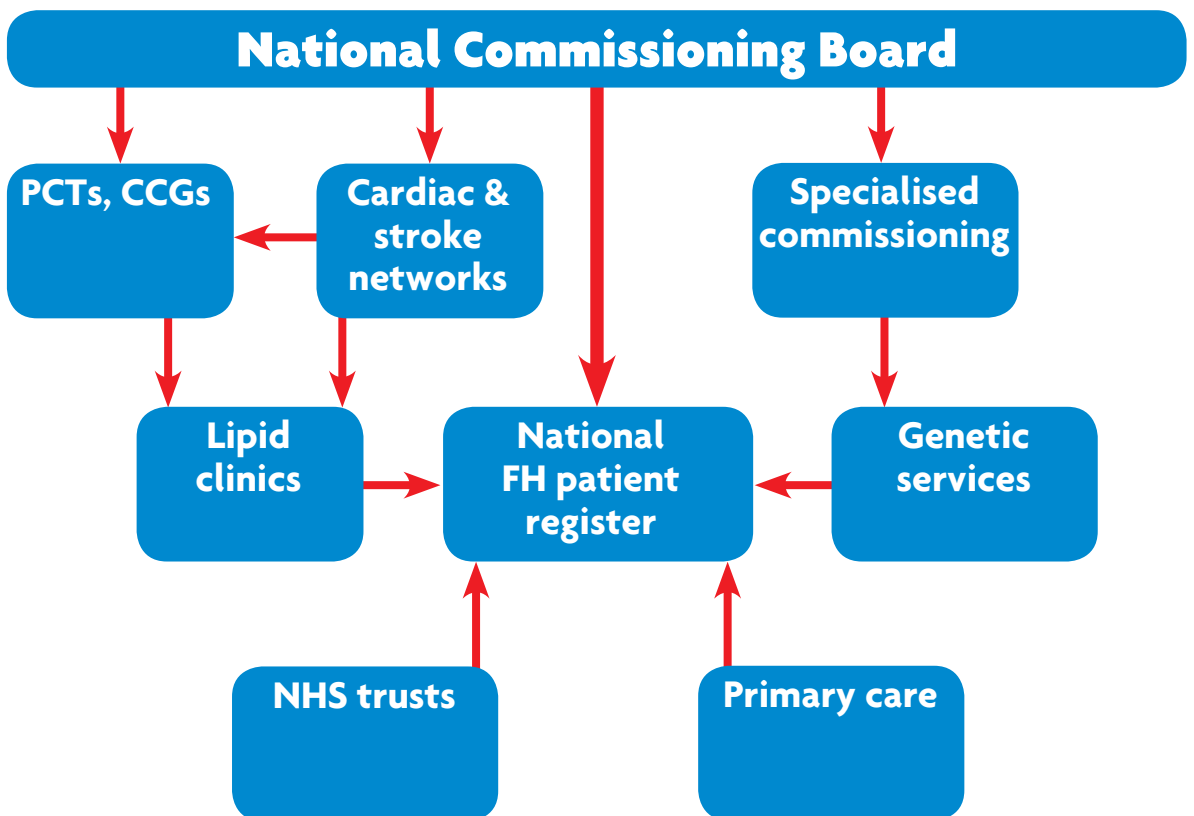
Such a programme could commence as a pilot in an area equivalent to an SHA and involve cardiac and stroke networks to help deliver the programme locally. Given the importance of genetic services and

the role of CCGs/PCTs in local delivery, these organisations should also be involved.

Maintaining the NHS Health Checks prevention programme is an important element of a national FH programme in England. The Health Checks document, Putting Prevention First, advises that it is important to consider FH if cholesterol levels exceed 7.5mmol/L.⁴³ Health Checks may therefore prove a critical primary care referral point for patients with suspected FH.

The NCB or similar national body could have direct oversight of an FH programme, with ringfenced money dedicated to rolling out the recommendations of the NICE guideline. The NCB could also include a performance measure for diagnosing and treating cases of FH as part of the operating framework for CCGs.

A chart of a national programme for FH in England is demonstrated below.





Useful resources

The NICE guideline on the Identification and Management of Familial Hypercholesterolaemia (CG71):

<http://www.nice.org.uk/CG71>

NHS Primary Care Service Framework on FH, aimed at assisting commissioning of FH services:

http://www.pcc.nhs.uk/uploads/commissioning/2010/02/primary_care_service_framework_familial_hypercholesterolaemia.pdf

HEART UK FH Toolkit, intended to assist with the development of local FH services:

<http://www.heartuk.org.uk/FHToolkit/>

Royal College of Physicians National Audit of FH:

<http://www.rcplondon.ac.uk/resources/audits/FH>

HEART UK Parliamentary Yearbook editorial (HEART UK Freedom of Information requests on FH):

<http://www.parliamentaryyearbook.co.uk/heart-uk-editorial.html>

Inherited heart conditions: Familial hypercholesterolaemia – patient booklet produced by the British Heart Foundation and HEART UK:

<http://www.heartuk.org.uk/images/uploads/beendiagnosedpdfs/fhbooklet.pdf>

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