Appendix E
Health Economic modelling

1 Use of high intensity statin compared to low intensity statin in the management of FH patients

1.1 Introduction

Familial hypercholesterolemia (FH) is a genetic disorder characterized by hypercholesterolemia, xanthomas, and premature coronary heart disease (CHD) Austin[1] and Humphries[2]. The estimated frequency of FH in western countries is 1 in 500 persons. Heterozygotes typically have values for total serum cholesterol in the range of 7–10mmol/l. Efficient lipid-lowering drug therapy by the statin class of drugs is effective in FH patients and is known to reduce CHD mortality[3]. Currently in the UK less than 15% of the predicted 110,000 patients are diagnosed Marks et al[4] and less than 10% are being adequately treated LIPID Study Group 1998[5],[3]. FH is caused by mutations in three different genes, namely those coding for the receptor for low density lipoprotein (LDL) particles (*LDLR*) for the major apolipoprotein of the LDL particle apolipoprotein B (*APOB*) and for an enzyme involved in the degradation of the receptor as it recycles, *PCSK9* Humphries 2006[2]. We searched for cost effectiveness evidence in this population and no studies were found. Consequently, the GDG requested the development of a de novo economic model to help inform the guideline recommendations.

1.2 Model structure and analytical methods

1.2.1 Population

There is little evidence of the effectiveness of statin use in children thus this model considered adults with heterozygous FH aged 18 years and beyond. The cost-effectiveness of high intensity statins versus low intensity statins is likely to vary between by age since the baseline risk of having cardiovascular disease varies by age and sex. However it was acknowledged that the guideline was unlikely to make separate recommendations based on sex thus the model was run separately for different age groups and not by sex.

1.2.2 The choice of comparators

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.

1.2.3 Outcomes

The outcomes of interest were death from other causes, and cardiovascular mortality, MI, angina, revascularisation, PAD and stroke. The model did not explicitly include cost impacts of withdrawals, non-concordance or transfers between treatments. The impact of such changes on effectiveness is implicitly included through the use of intention-to-treat trial data. Health outcomes for the cost-effectiveness analysis are summarised in the form of Quality Adjusted Life Years (QALYs), where one QALY represents one year of healthy life.

1.2.4 Model structure and assumptions

In a Markov model there are a finite number of health states. It is assumed that at any point in time, all patients must be in one and only one of the states. The model then replicates how a hypothetical cohort of people moves between the states.

Figure 1 in section 3.2 shows a schematic representation of the patients' pathways. All patients start in the FH state. During each annual cycle of the model, a proportion of patients enter one of the qualifying event health states (MI, angina, stroke, revascularisation or death) while the remainder stay in the FH state. Patients can experience more than one non-fatal event in subsequent periods of the model.

The rate at which people move through the model is regulated by transition probabilities, which describe the likelihood of moving between states over each model cycle (twelve months). These transition probabilities are adjusted for age. The model was run simultaneously for the cohort assuming they were receiving a low intensity statin and then a high intensity statin. For

patients on high intensity statins the transition probabilities were adjusted to reflect the expected reduction in cardiovascular events from the observational and clinical trial data. Health care costs and QALYs were then estimated for each option by multiplying the time spent in the various states by mean costs and 'utilities' (health-related quality of life) of the health states. The cost and utility data used in the model was sought from literature. The time horizon modelled is lifetime, with an assumed upper age of 100, by which time all of the cohort have died.

1.2.5 Baseline risks

Baseline risks were taken from the Statins TA 94[6] which shows the prevalence of CHD in the general population. This is obviously different from the population with FH. We applied the age-adjusted risk of cardiovascular disease reported in the updated Simon Broome paper (Neil 2008)[7]. Thus for ages groups 20-39 we increased the risk of developing cardiovascular disease by 84.3, for those aged 40-59 a risk of 5.76 was used and those over 60 a risk of 1.2. Stroke and PAD were assumed to be the same as seen in the general population. Death from other causes was assumed to be the same as that the general population and was taken from the life tables of England and Wales[8]. See Figure 2 in section 3.2 for baseline data used in the model.

1.2.6 Treatment effects

There was no trial evidence considering high intensity statins with low intensity statins in FH patients. The only available evidence was observational data from the Simon Broom register which showed benefit from treatment before and after the use of statins. We used data from the Simon Broome[7] to estimate treatment from being on statins. We also assumed that FH patients do not benefit differently from statin treatment from patients with after myocardial infarction with stable coronary disease (CAD). This enabled us to use reduction in cardiovascular events reported by the TNT (LaRosa (2005)[9] and IDEAL (Pedersen 2005)[10] trials which we meta-analysed and used in sensitivity analysis

1.2.7 Cost data

The NICE reference case specifies that costs should be measured from an NHS and personal social services perspective. These should include the direct cost of drug treatment and also potential savings from avoided treatments due to reduced incidence of cardiovascular disease. Costs were calculated using cost for each of the health states of the model, multiplied by the time spent in each state. Costs were at 2007 prices. As per current NICE guidance[11], an annual discount rate of 3.5% was used for both costs and health benefits.

Estimates of costs were taken from the literature or NHS reference cost[12]. Drug costs were taken from the prices quoted by the drug tariff, Prescription Pricing Authority (PPA)[13]

1.2.8 Health related quality of life (health state utility)

In the NICE reference case, the value of health outcomes – including beneficial and harmful impacts of treatment on mortality and morbidity – is estimated using the Quality Adjusted Life Year (QALY) approach. This requires estimates of survival and quality of life associated with each health state included in the model. Utility data was obtained from published literature.

Utilities were adjusted to reflect the fact that health-related quality of life in the general population decreases with age (i.e. multiply the disease utility weight by age utility weight). Age utility weights were taken from the Department of Health, Health Survey for England (1996)[14].

Statin therapy may be expected to have two opposing effects on quality of life: i) improvements through the reduced incidence of cardiovascular events and ii) reductions in quality of life through the impact of treatment-related adverse effects. Differences in adverse effects between high and low intensity statins can have an influence on their relative cost-effectiveness. However there are no published studies that have quantified the difference in quality of life due to treatment side effects. Published studies suggest that there is no difference

in quality of life between high intensity when compared with low intensity statins. We thus assumed that high intensity statins will not result in loss of quality of life for the base model.

1.2.9 Cost effectiveness

The results of cost-effectiveness analysis are presented as Incremental Cost-Effectiveness Ratios (ICERs), which determine the additional cost of using high intensity statins per additional QALY gained compared with low intensity statin

ICERs = (cost of high intensity statins – cost of low intensity statins)/ (QALY of high intensity statins – QALY of low intensity statins of statins)

1.2.10 Sensitivity analysis

The model includes a base case analysis supplemented with univariate deterministic sensitivity analyses to test the impact of uncertainty over various model parameters and assumptions.

1.3 Results

The base case results are presented below, and cost-effectiveness is assessed against a threshold of £20,000/QALY. We have separately modelled high intensity stains assuming the price of atorvastatin 80mg and simvastatin 80mg.

1.3.1 Results using effectiveness data from Simon Broome

Table 1 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 with 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 1 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 Neil et al 2008)
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

1.3.1.1 Cost effectiveness results using the price of atorvastatin 80mg

Our model results demonstrate that 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.

1.3.1.2 Cost effectiveness results using the price of simvastatin 80mg

Our base model estimated that 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 statin statins since they result in fewer costs (savings) and more QALYs. The model results are stable in sensitivity analysis.

1.3.2 Results using effectiveness data from post MI patients with stable coronary artery disease (CAD) as seen TNT and IDEAL trials

Table 2 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 with 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 2 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

Health state	Low intensity	High intensity (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

1.3.2.1 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. For instance 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.

*1.3.2.2 **Cost effectiveness results using the price of simvastatin 80mg***

Our base model estimated that for people on simvastatin 80mg, there are 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 (savings) and more QALYs. The model results are stable in sensitivity analysis.

1.3.3 Sensitivity analysis

A range of univariate sensitivity analyses were conducted to assess the impact of different input parameters on the base case results. In these analyses we change one parameter at a time holding other parameters constant at their base case values. The results are interpreted using a cost-effectiveness threshold of £20 000 per QALY. The model was stable in sensitive analysis using data from the Simon Broome updated register[7] if prices of either atorvastatin or simvastatin were used for all outcomes tested. Results using effectiveness data from post MI patients and prices of atorvastatin are reported unless stated otherwise.

*1.3.3.1 **Efficacy of treatment (using lower and upper confidence intervals)***

The efficacy of high intensity compared to low intensity was assessed using the upper and lower 95% confidence intervals from the meta-analysis. The model became more cost effective when the treatment effects were improved (set to their lower confidence interval) and worsened (upper confidence interval) for all outcomes. The ICERs when stroke is the treatment effect

examined and the effect on stroke is set at its upper 95% CI (RR=0.96) are about £24,000/QALY and when the upper confidence interval of CVD deaths is used, the high intensity results in more CVD deaths than the low intensity treatment and the high intensity becomes dominated by low intensity. This result implies the high intensity resulted in higher costs and less benefits than the low intensity at this level for all ages. The model is thus sensitive to assumptions about treatment effect on mortality and slightly to effects of treatment on stroke.

Table 3 Efficacy of treatment (using lower and upper confidence intervals)

	Mean (95% CI)	**ICER (£/QALY) (stable CAD)**	
	CAD	Lower limit	Upper limit
Non-fatal MI	0.81 (0.72-0.91)	£17,000	£22,199
Non-fatal stroke	0.82(0.70-0.96)	£16,000	£23,781
Heart failure	0.77(0.65-0.92)	£18,500	£19,600
Revascularisation	0.78(0.71-0.86)	£18,700	£19,300
Unstable angina	0.84(0.69-0.1.01)	£16,600	£22,500
CVD mortality	0.92(0.72-1.171)	£10,443	D

*1.3.3.2 **Results by age***

The model results suggest that higher intensity statins are cost effective for ages below 60 years when compared to low intensity statins when using atorvastatin 80mg. Beyond 60 years, high intensity statins are not cost effective when using the treatment effect from the Simon Broome data or from post MI patients with stable coronary artery disease as those in the TNT[9] and IDEAL[10].

Table 4a Effect of age on cost effectiveness using the price of atorvastatin 80mg

Cost per QALY using the cost of ATORVA 80mg (treatment effects from MI patients with stable CAD)					
Age	Costs Low dose	QALY Low dose	Costs High dose	QALY High dose	ICER (Cost/QALY)
20-39	£13,444	9.95	£16,631	10.12	£18,687
40-59	£5,253	11.36	£9,617	11.59	£19,006
60-74	£2,413	7.96	£5,807	8.03	£49,648
Over 75	£1,222	4.98	£3,490	5.00	£80,296
Cost per QALY using the cost of ATORVA 80mg (using treatment effects from Simon Broome					
Age	Costs Low dose	QALY Low dose	Costs High dose	QALY High dose	ICER (Cost/QALY)
20-39	£13,444	9.95	£14,318	14.75	£182
40-59	£5,253	11.36	£9,263	12.08	£5,568
60-74	£2,413	7.96	£5,851	8.05	£37,286
Over 75	£1,222	4.98	£3,508	5.01	£60,420

However when using the cost of simvastatin 80mg, the model results are not sensitive to age since high dose will be recommended to all age groups. These results suggests that simvastatin 80mg can be prescribed to anyone above 30 years but atorvastatin 80mg may need to be targeted to those patients with FH aged below 60 years.

Table 4b Effect of age on cost effectiveness using the price of simvastatin 80mg

Cost per QALY using the cost of SIMVA 80mg (treatment effects from MI patients with stable CAD)					
Age	Costs Low dose	QALY Low dose	Costs High dose	QALY High dose	ICER (Cost/QALY)
20-39	£13,444	9.95	£13,002	10.12	High intensity dominates low intensity
40-59	£5,253	11.36	£5,200	11.59	High intensity dominates low intensity
60-74	£2,413	7.96	£2,610	8.03	£2,881
Over 75	£1,222	4.98	£1,410	5.00	£6,667
Cost per QALY using the cost of SIMVA 80mg (treatment effects from Simon Broome)					
Age	Costs Low dose	QALY Low dose	Costs High dose	QALY High dose	ICER (Cost/QALY)
20-39	£13,444	9.95	£9,010	14.75	High intensity dominates low intensity
40-59	£5,253	11.36	£4,654	12.08	High intensity dominates low intensity
60-74	£2,413	7.96	£2,644	8.05	£2,504
Over 75	£1,222	4.98	£1,425	5.01	£5,357

1.3.3.3 Results for males/females of all age groups, relative risk of CHD mortality

In the base model we assumed that people with cardiovascular disease have a two-fold increase in risk of dying from other causes compared with the general population. This was a conservative assumption. Packham et al[15], and Robinson et al[16], demonstrated that this could be more than four fold. In sensitivity analysis we assumed that there was no difference and that there was a four fold risk of dying from other causes for people with coronary heart diseases. The model results are slightly sensitive to changes in this assumption especially when the risk is assumed to be four fold. The ICERs increase to about £23,000/QALY when the risk is assumed to be four.

*1.3.3.4 **Discounting***

Discounting is a technique which allows the calculation of present values of costs and benefits which accrue in the future. Discounting is based on a time preference which assumes that individuals prefer to benefits now rather than latter, and by the same reasoning, individuals prefer to delay costs rather than incur them in the present. The strength of this preference is expressed by the discount rate which is inserted in economic evaluations. NICE recommends we discount both cost and benefits at 3.5%.

We tested two different scenarios i.e. no discounting and a 5% discount rate. The model was not sensitive to assumptions about discounting. When there is no discounting performed, the ICERs fall and when the discount rate increases the ICERs increase as shown in the table below but the ICERs were still borderline cost effective.

Table 5 Results for males of all age groups, impact of discounting

No discounting		**5% discount rate**	
ICER (£/QALY) (Simon Broome)	ICER (£/QALY) (post MI stable CAD)	ICER (£/QALY) (Simon Broome)	ICER (£/QALY) (post MI stable CAD)
£4,708	£14,654	£5,991	£21,146

*1.3.3.5 **Health state utilities and costs of cardiovascular events***

The health state utilities used in the model were obtained from the literature. We tested the assumption that the mean health state utilities were 0.2 less or more than those obtained from the literature. The costs of cardiovascular events were increased by 100% and reduced by 50% (GDG assumption). In all cases the model results were not sensitive to changing assumptions about quality of life estimates and costs of cardiovascular events and ICERs ranged between £17,000 and £20,000/QALY.

1.4 Discussion and limitations

Our model results demonstrate that 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. However our base model estimated that if people are 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 statin statins since they result in fewer costs (savings) and more QALYs. The results are stable in sensitivity analysis when the price of simvastatin 80mg is used. When the price of atorvastatin is used the results are sensitive to age and treatment effect.

The effect of age is not unexpected since younger patients have a much bigger risk if left untreated. For instance, if untreated the risk of cardiovascular disease is about 84 times more than the general population[7] for those aged less than 40 years compared to an increased risk of 20% for those aged over 60 years. Also the younger patient benefits more from treatment, with a relative risk reduction in events from treatment of about 87%[7] compared to a reduction of 18% for those aged over 60 years. Thus if patients are on atorvastatin 80mg, the ICERs for those aged over 60 years is about £37,000/QALY using treatment effect from the Simon Broome[7] and about £50,000 if treatment effect from post MI patients is used.

One of the main limitations of our model is the lack of long term outcome trials in the use of statins in the treatment of patients with FH. We assumed that FH patients will not benefit differently from statins when compared with patients post MI. Thus trial data from MI patients was meta-analysed to derive treatment effect of statins. There is also lack of long-term safety and utility data for high intensity statins in trials. The trials reported that there was no significance difference between high and low intensity with regards to major side effects. However the GDG is aware of issues with the recruitment of the post MI trials TNT[9] and IDEAL[10] which only include people who could tolerate the statins hence the finding of no difference may be confounded by this. Our model assumed that there would be no loss in utility due to treatment side effects which may not be the case. In this respect our model may overestimate the cost effectiveness of high intensity statins (make them look more favorable)

Another limitation of the model arises because of the nature of Markov models. These assume that the probability of an individual moving to any given health state in one time period depends only their current health state (there is no longer 'memory' in the model). Thus the probability of heart failure for a patient whose last CVD event was an MI is assumed to be the same irrespective of how many CVD events they have previously had. Similarly, a patient's health outcome and health care costs incurred are assumed to depend only on their current health state. These assumptions are unlikely to be strictly true, and will tend to underestimate overall costs and overestimate health outcomes for the cohort. Thus, interventions that prevent more CVD events will tend to appear rather less cost-effective than they may be in reality. So the model is conservative in this respect.

The model did not directly address the issue of treatment of withdrawals and non-concordance with treatment. Since the treatment effects are based on 'intention-to-treat' analyses, the impact of withdrawals and non-concordance from the trials is already included in the model. However, the model continues to attribute drug costs for all patients throughout their lifetime. This is a conservative assumption that will tend to underestimate the cost-effectiveness of treatment. On the other hand, concordance and continuation of treatment may well differ between the trial context and routine practice.

1.5 Conclusions

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 high intensity statins are cost effective for those aged below 60 years.

2 Cascade testing for FH using DNA testing and low density lipoprotein (LDL) cholesterol methods

2.1 Introduction

Familial hypercholesterolemia (FH) is a genetic disorder characterized by hypercholesterolemia, xanthomas, and premature coronary heart disease (CHD)[1] and[2]. The estimated frequency of FH in western countries is 1 in 500 persons. Heterozygotes typically have values for total serum cholesterol in the range of 7–10mmol/l. Efficient lipid-lowering drug therapy by the statin class of drugs is effective in FH patients and is known to reduce CHD mortality[3]. Currently in the UK less than 15% of the predicted 110,000 patients are diagnosed, Marks et al[4] and less than 10% are being adequately treated LIPID Study Group 1998[5],[3]. FH is caused by mutations in three different genes, namely those coding for the receptor for low density lipoprotein (LDL) particles (*LDLR*) for the major apolipoprotein of the LDL particle apolipoprotein B (*APOB*) and for an enzyme involved in the degradation of the receptor as it recycles, *PCSK9*[2].. The availability of DNA diagnosis at an asymptomatic stage and availability of effective lipid lowering therapy support the utility of cascade testing for FH[17] In 1994 an FH testing programme was started in The Netherlands; this programme actively approaches first and second degree relatives of index patients with a known mutation for testing, after informing them about their possible risk[18]

In the UK, FH is diagnosed by clinical criteria based on lipid levels, family history, and presence of xanthomas[19]. Individuals fulfilling these criteria are given the diagnosis of definite FH (DFH), while those showing elevated lipid levels and family history only are given the diagnosis of possible FH (PFH). Depending on the sensitivity of the methods used for mutation screening, a mutation causing FH can be identified in 60-80% of DFH patients[2;20] but only 20-30% of PFH patients[21] suggesting that many of the latter do not have monogenetic FH. Once the underlying mutation has been identified in an

index patient, molecular genetic screening of first degree relatives has a sensitivity and specificity close to 1.0, and this makes misclassification a rarity. In contrast, when based on lipid levels, where typically the ninety-fifth percentile of total serum cholesterol or LDL-cholesterol (LDL-C) is used as a cut-off value, misclassifications will occur in 15–30% of the patients[22-24]. Because of within-individual fluctuations and because of change over time, some individuals will move from below to above the cut-off value on repeat measurements, while a DNA test is unambiguous and is only required once. Thus, if the diagnosis is made solely by lipid levels classification errors will occur, and as well as some FH patients being given a false negative diagnosis, this will reduce the efficiency of secondary cascade testing, and erroneous screening results will occur. As described below, several different models were examined.

2.2 Model structure and analytical methods

For the cost effectiveness analysis, the standard method of clinical diagnosis and identification of affected relatives using elevation of LDL-C levels is the base line comparator, and is referred to in this model as the “Cholesterol” method. The UK FH Cascade Audit Project (FHCAP) has shown that, based on the Simon Broom criteria, 30% of the patients currently being treated in lipid clinics have DFH and 60% have PFH and 10% fail to meet either criterion Hadfield et al[25]. 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 will be included for cascade testing, and the relatives tested for the family mutation. This is the model used in the Netherlands[18]. All individuals with elevated LDL-C levels are offered appropriate treatment (irrespective of whether or not they carry the family mutation), but further cascade testing is only carried out from mutation-positive patients. Two variants of the DNA method were also modeled. In the first, following DNA testing of the probands, cascade testing of relatives is undertaken in all mutation-positive probands as above (i.e. using the DNA information to offer appropriate lipid-

lowering treatment and to select those from whom secondary cascading will be undertaken), and additionally, in the relatives of DFH probands, cascade testing is undertaken using measures of LDL-C levels to identify “affected” relatives for treatments and for secondary cascading (DNA+DFH method). In the second, cascade testing is undertaken in all mutation-positive probands and additionally from both DFH and PFH probands (DNA+DFH+PFH method). In all methods, all individuals identified as having 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 case is one who is not selected for cascade testing but who actually does have a monogenic cause of FH, and a true-negative case 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 levels 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 levels above the diagnostic cut-off for age and gender but the cause is due to polygenic plus environmental causes). A false-negative case 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 levels below the diagnostic cut-off for age and gender due to “protective” polygenic plus environmental causes), and a true-negative case 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 levels below the diagnostic cut-off for age and gender or who does not carry the family mutation).

The model estimates the incremental cost effectiveness of cascading using these different approaches, using data on the cost of identification of probands and relatives from the recently completed DH UK FH cascade audit project (UKFHCAP), and up-to date figures for the costs and effectiveness in reducing CHD mortality and morbidity of statins[7]. In the base model it is assumed that 65% of the first degree relatives and 60% of the second degree relatives will agree to testing. In the FHCAP, these values were 85% and 80% respectively, and the impact of this on cost effectiveness of second and subsequent relatives was tested in sensitivity analysis. Figure 4 in section 3.2 shows the model structure.

A decision tree was constructed in Excel where a hypothetical 1000 patients referred from general practice with a suspicion of heterozygous FH entered the model. The structure and the proportions of patients in the different arms of the decision tree was agreed by the GDG and is shown in Figure 4 in section 3.2, with four strategies being compared as described above. A decision node (square) is placed directly following the diagnostic dilemma being resolved. Chance nodes (circles) represent uncertain outcomes of each of these decisions. Probabilities of branches coming off the chance node add up to one. A terminal node (triangle) is reached when all outcomes for a particular pathway have been accounted for. It was assumed that every proband has five first degree relatives that are tested, and each of these five has two first degree relatives (i.e. second degree relatives of the index case), and each of these has two first degree relatives (i.e. third degree relatives of the index case). Sensitivity analysis was carried out comparing cascading to third degree relatives and only to second degree relatives

Assumptions for the relative proportions in all branches were reached from the available published data and from assumptions agreed by the GDG. For the cholesterol method, it was assumed that 90% of the DFH and 35% of the PFH are true FH (i.e. 270 + 210), and 10% and 65% respectively are false positive (30 + 390 respectively). We are unaware of any published data to address this directly, and this is an extrapolation from the relative number of mutations identified in DFH and PFH patients (see below). The relative

proportion of “FH” and non-FH relatives from the true FH index cases was estimated from the FHCAP data and analysis of the Netherlands relative data set[24]. This showed that using as a diagnostic cut-off the intersection between the distribution of LDL-C levels in mutation-carriers and non-carriers results in a false positive identification rate of 14.9% in 15-24 year olds and of 16.3% in 45-55 year olds, and a false negative rate of 28.9% and 42.4% respectively (cut-offs for Males and Females 3.01/4.31mmol/l and 3.32/4.05 respectively). From false- negative index cases cascade testing will identify no true-positive relatives, but a proportion will be identified as “affected” (i.e. false-positives) because they have LDL-C levels above the diagnostic cutoffs (estimated to be A% at 18 years and B% at 50 years Similar proportions were used for the second and third degree relatives.

For the DNA method, the mutation detection rate in DFH was taken to be 80 %[20.2,23]. Cascade testing only takes place from mutation-positive index cases and results in a 50% detection rate (since FH is a monogenic autosomal dominant disorder). Since current mutation detection methods are not 100% sensitive, a proportion of the mutation-negative index cases are false negatives, assumed to be 50% of the mutation-negative DFH and 7% of the PFH mutation-negative index cases.

For the DNA+DFH method, cascade testing is undertaken using LDL-C diagnostic cut-offs in all 60 no-mutation DFH patients (of whom 50% (i.e. 30) are true-positive and 50% (i.e. 30) are false-positive. The proportions of “affected” and “non-affected” FH relatives (and the proportion of true- and false-positive diagnoses) from these two groups were estimated as in the cholesterol method. Similarly, for the DNA+DFH+PFH method, cascade is undertaken using LDL-C diagnostic cut-offs in the additional group of 420 non-mutation PFH index cases, of whom 7% (i.e. 29) are true positive and 93% (i.e. 391) are false positive.

2.2.1 Estimation of treatment benefit from statins

A Markov model was developed using Microsoft™ Excel to estimate the treatment benefit from statins. The structure of the model was agreed by the

GDG. This enabled the calculation of long-term outcomes of lifetime treatment statin for the management of FH from a UK NHS perspective. Eight health states were modeled; Well (no event), unstable angina, myocardial infarction (MI), stroke, heart failure, revascularisation, cardiovascular death and death from other causes. All patients start in the well state, with the risk of developing any of the other health states. Baseline probabilities were taken from the Statins TA 94[6] and are shown in the Table 20 in section 3.1, by age. The risk of developing a cardiovascular event varies with age for FH patients. Data from the Simon Broome has shown that for patients aged below 40 years the risk can be as high as 125 for females[3]. For those aged 40-59 years the risk falls to about 6 fold and for those aged over 60 years the risk is about 1.2 compared to the general population. In the model we have increased the risk of having a CVD event by 84.3, 5.67 and 1.2 for ages <40 years, 40-59 years and over 60 years respectively[7] for definite FH patients. For people who have elevated lipids but no FH (false positives) their risk was assumed to be 20% more than the general population and the same across all age groups (GDG assumption).

2.2.2 Cost data

Drug costs were taken from the prices quoted by the Prescription Pricing Division[13] (see Table 26 in section 3.1). Consultant costs, nurse, clerk, phlebotomist costs were taken from Neaten at al 2007[26] (see Table 27 in section 3.1). Estimates of time taken by each health care professional were provided by the GDG members (personal communication). Costs of full fasting and non-fasting cholesterol measurements were taken from the updated HTA (personal communication Dr Marks) and from the experience of GDG members. Costs of CVD events were taken from the statin TA 94[6] and adjusted for inflation. All costs were at 2007 prices. As per current NICE guidance, an annual discount rate of 3.5% was used for both costs and health benefits.

2.2.3 Outcomes and quality of life (utility)

Clinical outcomes modeled were MI, stroke, stable and unstable angina, cardiovascular and total mortality. Age-adjusted utilities were then assigned to these events. The value of health outcomes – including beneficial and harmful impacts of treatment was estimated using the Quality Adjusted Life Year (QALY) (see Table 20 and Table 31 in section 3.1)

2.2.4 Cost effectiveness:

The results of cost-effectiveness analysis are presented for a 50 year old index case and 30 year old relative. This 30 year estimate is the rough average age of the five first degree relatives of the index case, based on the model family used with on average two siblings of similar age, and two children of 18 year age (plus one living parent. The results are presented as discounted Incremental Cost-Effectiveness Ratios (ICERs), which determine the additional cost of using one strategy (for instance DNA method) per additional QALY gained compared with the baseline strategy (cholesterol method).

Where more than two interventions are being compared, the ICERs are calculated using the following process:

1) The interventions are ranked in terms of cost (from the cheapest to the most expensive);

2) If an intervention is more expensive and less effective than the previous one, then it is said to be ‘dominated’ and is excluded from further analysis;

3) ICERs are calculated for each intervention compared with the next most expensive non-dominated option. If the ICER for an intervention is higher than that of the next more effective strategy, then it is ruled out by ‘extended dominance’. This means that there is some mixture of two other strategies that is more effective and less expensive;

4) ICERs are recalculated excluding any options subject to extended dominance.[27]

2.2.5 Sensitivity analysis

The model included a base case analysis and was supplemented with univariate deterministic sensitivity analyses to test the impact of uncertainty for various model parameters and assumptions.

2.3 Results

Table 5 shows the numbers of true- and false-positive and negative FH identified by each strategy. For each method, starting with a hypothetical 1000 suspected FH patients, and based on the FHCAP data, 30% will be DFH and 60% will be PFH. 100 will not meet the diagnostic criteria of DFH or PFH and no cascade testing is carried out from them. Based on assumptions agreed by the GDG, these are all classified as true-negatives. It is possible that 1-2 of these individuals may actually have FH and would therefore be incorrectly classified as such, but this would be the same for each strategy and so would not impact on the relative cost effectiveness comparisons. Of the 300 DFH 90% (i.e. 270) are true-positives while 35% of the PFH (i.e. 210) are true-positives.

For the Cholesterol method, based on the false-positive and false-negative rate of LDL-C cut-offs (using the "gold-standard" of mutation carrier status in the Netherlands relative data set[28], the three rounds of cascade screening would entail the testing of 4058 relatives, of whom 14.8% will be true-positives, 10.2% false positives, 62.4% true-negatives and 12.6% false-negatives. The low overall proportion of relatives designated as positives is due to several reasons. Firstly, while a small proportion of DFH index cases are false-positives (10%), a large proportion of PFH are false-positives (65%), and no true FH relatives can be identified by cascading from false-positive index cases. Secondly, because of the overlap between LDL-C levels in mutation-positive and non-mutation relatives[28], many false-positive and false-negative diagnoses based on LDL-C cut-offs will occur, with a false-negative

rate of >45% in 45-55 year-olds (i.e. in the siblings of the index case). Finally, the consequence of this is that while many affected people will thus be missed (and not cascaded from and their at-risk relatives not identified), many non-FH relatives will incorrectly be selected for further cascade testing and no true-positive relatives will be detectable from such cascading. A further consequence for the 513 false-negative individuals is that they may not be offered the appropriate level of care required for adequate management of their FH.

For the DNA method, cascading takes place from all 420 mutation-positive index cases (240 from DFH and 180 from PFH, based on the predicted mutation detection rate in these groups). Each of these has five first degree relatives of whom 50% are mutation-carriers, each of whom has two first degree relatives of whom 50% are carriers and similarly for the third round. This result in testing 2675 relatives of whom 50% is mutation-positive. A proportion of the relatives are identified as having elevated LDL-C by the lipid measurement and are offered appropriate lipid-lowering therapy. Costs for this are included in the modeling, but because they do not have FH they are likely to need only a low dose of statin to achieve adequate response. Since they do not carry the family mutation no cascade testing from them is carried out and their relatives are not tested. However, 30 of the DFH and 29 of the PFH index cases are false-negative cases because mutation detection methods are not 100% sensitive, and thus the opportunity to cascade test from these cases is missed (6.6% of the 900 sent for DNA testing).

For the DNA+DFH method, cascading takes place from all 420 mutation-positive index cases (with affected relatives identified based on DNA results) plus from all the 60 remaining non-mutation DFH index cases. 50% of these are false-negative and 50% are false positive FH cases, and identification of their “affected” and “unaffected” relatives occurs using LDL-C cut-offs. This results in the proportions of false-positive and negative relatives as for the cholesterol method, and overall the number of tested relatives increases by 10%, with the number of true-positives increasing by 2.7%, and with 28 relatives receiving a false-positive diagnosis (1% of the total tested). For the

DNA+DFH+PFH method the approach is the same, with cascading taking place from an additional 391 mutation-negative PFH index cases. 7% of these are false-negative and 93% are true-negative FH cases. Overall the number of tested relatives increases by 72% compared with the DNA method, and by 13.6% compared with the cholesterol method, because of the higher number of true-positives identified by the DNA method who are subsequently included in secondary and the tertiary cascading. Compared to the DNA+DFH method, the number of true-positive relatives identified increases by 2.6%, and the number of false-positive relatives identified increases by nine fold, although this still represents only 5.5% of the total number of tested relatives and is less than the 10% figure for the cholesterol method.

Table 5 Total numbers of index cases cascaded from, number of relatives tested in each strategy and numbers predicted to be "affected" and "non-affected" with FH

	Cholesterol	DNA	DNA + DFH	DNA+DFH+PFH
INDEX CASES				
Total tested	**1000**	**1000**	**1000**	**1000**
True positives - FH, cascaded	480	420	420+30	420+30+29
False positives - not FH, cascaded	420	0	30	30+391
False negatives - FH, not cascaded	0	30+29	29	0
True negatives - FH, not cascaded	100	100+421	100+391	100
RELATIVES*				
True positives - FH	602	1338	1375	1412
False positives - not FH cascaded	412	0	28	252
False negatives – FH not detected	513	0	32	64
True negatives - not FH not cascaded	2531	1338	1508	2884
Total tested	**4058**	**2675**	**2944**	**4611**

2.3.1 Total costs of diagnosis for each strategy

Total costs of diagnosis included the total cost of clinical conformation for index cases, the cost of DNA testing for the index cases and the costs of contacting relatives and taking LDL-C measures (and DNA testing) for the diagnosis of relatives. The 100 referred patients classified as not having FH were not cascaded from in any strategy, and would not be sent for DNA testing so costs for DNA includes only 900 patients. The total cost of clinical confirmation was estimated to be £147 per index case and £87 per relative. DNA testing was estimated to cost £400 per index case and £100 per relative. These costs were multiplied by the numbers of people tested under each strategy. Cholesterol method is the cheapest strategy in making a diagnosis, with a cost of £499 per 1000 index cases entering the pathway, compared to DNA methods which ranged between £1,006 to £1,174.

Table 6 Costs of diagnosis for the four strategies

	Cholesterol	**DNA**	**DNA+DFH**	**DNA+DFH+PFH**
INDEX CASES				
LDL-C measures	£147,300	£147,300	£147,300	£147,300
DNA testing	-	£360,000	£360,000	£360,000
Subtotal	**£147,300**	**£507,300**	**£507,300**	**£507,300**
RELATIVES				
LDL-C measures	£351,263	£231,609	£254,825	£399,215
DNA testing	-	£267,540	£267,540	£267,540
Subtotal	**£351,263**	**£499,149**	**£522,365**	**£666,755**
Total	**£498,563**	**£1,006,449**	**£1,029,665**	**£1,174,055**

2.3.2 Cost of treatment and QALY gain per patient estimated from the Markov model for both index cases and relatives

To estimate treatment costs and QALY gain from treatment for the different populations, for instance the true FH index case or relative compared to the false-positive index case or relative, we modeled the discounted lifetime costs and benefits expected if people were given “high intensity” statin therapy compared to being on low intensity statins. True FH cases were given high intensity statins which in our model were either high doses of simvastatin, atorvastatin alone or in combination with ezetimibe or low dose simvastatin

with ezetimibe. The low intensity statin was assumed to be simvastatin 40mg in our model. Table 7 shows that true FH index patients will benefit by 0.72 QALYs when on high intensity statins compared to being on low intensity statins for an additional cost of about £4,332 over a lifetime period, while non-FH index cases gain 0.17 QALYs at an additional cost of £5,386. The difference in QALY gain between the true FH and non FH (false positives) is explained by their baseline risk which in turn will determine absolute benefit from treatment. For instance for a true FH aged below 40 years they have a relative risk of having a cardiovascular event of 84 while for a non FH case its 1.2 compared to the general population if untreated[3]. The table also shows that relatives have more gains in QALYs compared to index cases. True-FH relatives gain about 4.80 QALYs and non-FH relatives gain about 0.31 QALYs. Overall relatives gain more QALYs compared to index cases because relatives tend to be younger and it is the younger FH patients who tend to benefit more from treatment because of their increased risk[3].

Table 7 Cost of treatment and QLY gain per patient

	Index cases	
True FH (Index case)	**Cost**	**QALYs**
Low intensity treatment	£5,247	11.36
High intensity treatment	£9,579	12.08
Difference	**£4,332**	**0.72**
Non FH (Index case)	**Cost**	**QALYs**
Low intensity treatment	£3,948	12.28
High intensity treatment	£9,333	12.45
Difference	**£5,386**	**0.17**
	Relatives	
True FH (Relatives)	**Cost**	**QALYs**
Low intensity treatment	£13,444	9.95
High intensity treatment	£14,680	14.75
Difference	**£1,236**	**4.80**
Non FH (Relatives)	**Cost**	**QALYs**
Low intensity treatment	£5,035	17.31
High intensity treatment	£12,175	17.62
Difference	**£7,140**	**0.31**

The cost and QALY difference per person from treatment were used to estimate the total cost and QALY gain for each strategy under consideration,

by multiplying the number of index cases and relatives diagnosed by the cost and QALY difference. The total cost of each strategy was the sum of the diagnosis and treatment costs for each strategy. Table 8 and Table 9 below summarises the total cost of treatment and QALY gained by each strategy. Treatment costs accounted for the bulk of the costs. For instance, for the cholesterol method diagnosis costs are about £500 per patient while the lifetime treatment costs are about £27,300 per patient. For the DNA method treatment costs are lower at £16,000, because while more FH relatives are identified fewer non-FH relatives are identified and given (inappropriate) high intensity statin therapy. For DNA+DFH, there is a modest increase in overall treatment costs because of the larger numbers of identified individuals.

Table 8 Total cost of treatment for index cases and identified "affected" FH patients

TOTAL COST OF TREATMENT	Cholesterol	DNA	DNA + Chol M-ve DF	DNA + Chol M-ve DF +PFH
INDEX CASES				
True positives	£2,079,185	£1,819,287	£1, 949,236	£2, 076,586
False positives	£2,261,926	£2,267,312	£2, 261,926	£2, 265,158
False negatives - FH, low intensity statin	£0	£255,566	£129,949	£0
True negatives - not FH, low intensity statin	£538,554	£538,554	£538,554	£538,554
Subtotal	**£4,879,665**	**£4,880,719**	**£4, 879,665**	**£4, 880,297**
RELATIVES				
True positives	£744,042	£1,653,648	£1, 700,151	£1, 746,002
False positives	£2,941,697	£0	£198,429	£1, 796,952
False negatives (FH, treated for lipids)	£633,814	£0	£39,613	£78,672
True negatives (no FH, treated for lipids)	£18,070,423	£9,550,903	£10, 769,822	£20, 589,322
Subtotal	**£22,389,976**	**£11,204,551**	**£12, 708,015**	**£24, 210,948**
Total	**£27,269,641**	**£16,085,270**	**£17,**	**£29,**

			587,680	**091,246**

Table 9 Total QALYs gained in each strategy

TOTAL QALYS GAINED FROM TREATMENT	Cholesterol	DNA	DNA + Chol M-ve DF	DNA + Chol M-ve DF +PFH
INDEX CASES				
True positives	346	302	324	345
False positives	72	72	72	72
False negatives - FH, treated for lipids	0	42	22	0
True negatives -not FH, treated for lipids	17	17	17	17
Subtotal	**435**	**435**	**435**	**435**
RELATIVES				
True positives	2,891	6,425	6,606	6,784
False positives	128	0	9	78
False negatives - FH, treated for lipids	159	0	10	20
True negatives -not FH, treated for lipids	786	415	469	896
Subtotal	**3,964**	**6,841**	**7,093**	**7,778**
TOTAL QALY GAIN	**4,399**	**7,275**	**7,528**	**8,212**

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. Cholesterol method is ruled out by simple dominance. For example compared to DNA method, cholesterol results in more costs and less 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 the DNA and cascading from mutation negative definite FH individuals alone. The least efficient strategy is the use of cholesterol method alone. The model is sensitive to treatment effect on cardiovascular outcomes and age. For instance the model suggests that cascade screening will yield more QALYs if relatives of the index cases are found when they are still young (aged under 45 years). The model indicates that if the relatives of the index case are aged over 45 years, strategy 4 will no longer be cost effective at £20,000/QALY threshold since the estimated ICER is about £41,300/QALY when compared to strategy 3.

Table 10 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**

2.3.3 Sensitivity analysis

A number of univariate sensitivity analyses were done changing the base case assumptions. Assumptions about age of index cases and relatives, treatment effect on cardiovascular outcomes affected the model results. Assumptions about drug prices and combinations also had a marginal effect on model results. Other univariate sensitivity analysis that did not change the model results are shown in Table 14 below.

*2.3.3.1 **Effect of age of index case and relatives on Incremental cost effectiveness of the four strategies***

In the base model, the staring age for the index case was 50 years, while for the relatives it was 30 years (representing the average of the five first degree relatives of siblings and children). As shown in the table below, assuming that index cases are diagnosed at 65 year of age and the relatives when they are over an average of 45 years, the cost effectiveness was reduced and thus becomes less favorable. Using a NICE threshold of 20,000/QALY, compared to DNA+DFH, the DNA+DFH+PFH estimated ICER was £41,332/QALY which is well above the level considered affordable by the NHS. DNA+DFH compared to DNA alone resulted in an estimated ICER of about £25,984/QALY, suggesting that DNA alone would be the preferred strategy. This result is not unexpected since when patients are diagnosed early, they will benefit more from early treatment and they will have the benefit of more potential QALYs to be gained, which more than of-sets the higher cost of the longer period of statin treatment required by their earlier diagnosis. This is especially true for FH patients where the absolute benefit from treatment for people aged less than 40 and 60 is more since they have a heightened risk of developing cardiovascular disease than when they are over 60 years.

Table 11 Effect of age of index case and relatives on Incremental cost effectiveness of the four strategies

Strategy	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (QALY)	ICER (£/QALY)
DNA (strategy 2)	£18,065	1.22			
DNA + Chol M-ve DF (strategy 3)	£19,517	1.28	£1,453	0.06	**£25,984**
Cholesterol (strategy 1)	£25,709	0.96	-	-	**-**
DNA + Chol M-ve DF +PFH (strategy 4)	£29,043	1.51	£9,526	0.23	**£41,332**

2.3.3.2 Effect of treatment effect (using lower and upper 95%CI) on incremental cost effectiveness of the four strategies

In base model the reduction in cardiovascular events was dependent on age. Statin effect was estimated to reduce cardiovascular events by 87% for those aged below 40 years, 48% and 18% for those aged below 60 and over 60% respectively. When upper limits of the 95% confidence interval were used thus events were reduced by 82%, 40% and 10% for the three age groups respectively[7], the ICER increased from about £17,000 to about £28,000/QALY when strategy 4 was compared with strategy 3 while strategy 3 compared with strategy 2, had an estimated ICER of about £8,000/QALY. Using a threshold of £20,000/QALY, strategy 3 will be the preferred strategy suggesting the model is sensitive to this assumption.

Table 12 Effect of treatment effect (using lower and upper 95%CI) on incremental cost effectiveness of the four strategies

Strategy	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (QALY)	ICER (£/QALY)
DNA (strategy 2)	£18,355	6.00			
DNA + Chol M-ve DF (strategy 3)	£19,959	6.19	£1,604	0.19	**£8,291**
Cholesterol (strategy 1)	£29,168	3.37	-	-	**-**
DNA + Chol M-ve DF +PFH (strategy 4)	£31,925	6.62	£11,966	0.43	**£27,636**

2.3.3.3 Effect of different drug combinations and proportions of people on the different drugs on Incremental cost effectiveness of the four strategies

As shown in Table 13, the model was also slightly sensitive to the combination of the drugs used. The combination of drugs and proportions of people on the different drugs affects the overall price. The price of drugs was a weighted average of different combinations of drugs and the proportions of patients taking each drug. For the base model we used a combination that a

GDG co-opted expert provided (Dr Antony Wiezbecki, personal communication and reference provided). The drug costs were thus £389/year. In sensitivity analysis we used a combination used by the team updating the HTA FH. The annual drug costs were £484 (Dr Dayla Marks, personal communication). The ICERs increased to about £21,744/QALY which is borderline cost effective at £20,000/QALY threshold.

Table 13 Effect of different drug combinations and proportions of people on the different drugs on Incremental cost effectiveness of the four strategies

Strategy	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (QALY)	ICER (£/QALY)
DNA (strategy 2)	£23,373	7.28			
DNA + Chol M-ve DF (strategy 3)	£25,401	7.53	£2,028	0.25	**£8,021**
Cholesterol (strategy 1)	£36,811	4.40	-	-	**-**
DNA + Chol M-ve DF +PFH (strategy 4)	£40,281	8.21	£14,880	0.68	**£21,744**

*2.3.3.4 **Other sensitivity analysis***

Variables shown in Table 14 were changed by doubling or halving costs or time taken by health care professionals. In all cases changing the base assumptions had minimal impact on the cost effectiveness of the strategies. The table shows two ICERs, one for DNA+DFH vs. DNA+DFH+PFH vs. DNA+DFH and the second is for DNA+DFH vs. DNA alone.

For instance Table 14 shows that if assumptions about the number of relatives per proband was reduced from 5 to 3 for first degree and from 2 to 1 for second degree relatives, or was increased to 6 and 3 respectively, there is very little change in the cost per QALY. With fewer relatives per probands, there is a slight increase in ICERs from £17,021 to £17,423/QALY and when there are more relatives per proband the ICERs fall to about £16,611/QALY. The cost of DNA testing was varied within the range suggested by the GDG between £200 and £600. Increasing the cost or halving them did not alter the order of cost-effectiveness between the strategies since the comparison was

between DNA based strategies. Percentage of probands consenting to cascade testing in the base model were 65% and 60% for index and relatives respectively. In sensitivity analysis we used 85% & 80% for index and relatives which were that achieved by the FH audit team and further tested 100% consent for both index cases and relatives. The ICERs fell slightly in both cases.

We also assumed a fall in price of statins. A reduction in the statin price of atorvastatin should follow the end of the patent period (after 2011), and we have estimated a 30% of all statins included in the model. This reduction resulted in a large effect on the ICERs which all become more favorable. If the statin price were to fall by 30%, then the estimated ICERs will fall to £11,200 /QALY. We also changed the time taken by nurses, consultant, cost of sending letters, and percentage of probands consenting to cascade testing, in all cases this did not alter our cost effectiveness conclusions. In the base model cascading was done to third degree relatives. We also assumed the cascading was stopped at second degree relatives and the ICERs slightly increased to £17,200/QALY.

Table 14 Other sensitivity analyses (which did not alter the base case conclusions)

	Cost/QALY Relevant comparison	
Parameter	**DNA+DFH+PFH vs. DNA+DFH**	**DNA+DFH DNA alone**
BASE CASE RESULTS	**£17,021**	**£6,034**
Percentage of probands consenting to cascade testing 85% & 80%	£16,757	£5,791
Percentage of relatives consenting to cascade testing 100%	£16,534	£5,911
Halve nurses time	£16,984	£6,018
Double nurses time	£17,094	£6,066
Double consultant time	£17,096	£6,066
Halve consultant time	£16,983	£6,018
Costs of Cholesterol testing double	£17,057	£6,050
Costs of Cholesterol testing halve	£17,003	£6,026
Cost of letters double	£17,023	£6,035
Cost of letters halve	£17,020	£6,033
DNA 600 & 200	£17,021	£6,034
DNA halve	£17,021	£6,034
Cost of statins fall by 30%	£11,198	£3,585
Limit cascading to second degree relatives	£17,262	£6,094
3 first degree rel and 1 second	£17,423	£6,126
6 first degree rel and 3 second	£16,611	£5,939
Relative risk of non CVD death (RR=1)	£15,594	£5,880
No discounting	£12,062	£5,446

2.4 Discussion and conclusions

These analyses show that cascade testing using DNA information alone followed by combinations of DNA testing and LDL-C measurements from patients with either definite FH (DFH), or DFH and possible FH (PFH) are more cost-effective than that a strategy based on LDL-C measurements alone. The estimated ICER is about £17,000/QALY. The Cholesterol method is the least efficient and has been ruled out by simple dominance, and the second most efficient method is DNA + cascading from DFH mutation-negative index cases

It should be noted that in all the strategies modeled here it was assumed that any individual identified with elevated LDL cholesterol levels will be treated whether or not they carried the family mutation. Individuals who do not carry

the mutation are likely to be adequately treated with a lower dose of statin and the costs and benefits for this have been included in the model. We have assumed people over the age of 60 will benefit in the same as the general population from statins. This is because the effectiveness data from the Simon Broome Register cohort show no significant reduction in mortality in FH patients over 60 years old[3]. We do not advocate ceasing drug treatment at the age of 60 years, but the cost-effectiveness of treating this patient group aggressively is less favorable. Our model did not include children, and due to a lack of effectiveness data, the consequences of screening and treating children have been omitted. If children were included in the case-finding approach, this strategy might become even more cost-effective (as the number of relatives per proband increases).

Our model conclusions that DNA based methods are more cost effective are consistent with other published studies. Marks (2002)[29] did a cost effectiveness analysis from the NHS perspective which considered the different approaches to screening for FH patients aged between 16 and 54. They concluded that tracing of family members was the most cost effective strategy with an estimated ICER of about £3097/LYG and universal population screening was the least cost effective strategy with an estimated ICER of £13,029/LYG. Marks (2003)[30] did a cost comparison study over a 10 year period of the strategies for FH screening. The authors again concluded that family tracing was most efficient strategy and the cost per death averted was £3187. However in both studies they did not do an incremental analysis between the methods being compared. Wonderling (2004)[31] did a cost effectiveness study of genetic screening programme in Netherlands FH patients compared no screening. 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.

The modeling supports cascade testing using a combination of both DNA information and LDL-C levels where a mutation has not been identified as being cost- effective, based on an initial population of index patients with a strong clinical suspicion of FH. Although a number of assumptions were

necessary, sensitivity analysis indicates that changes in the response rate, costs of nurses and consultant time, or costs of lipid or of DNA testing have a negligible impact on the overall conclusions.

The majority of the costs involved are for treatment, and therefore cost effectiveness is particularly sensitive to the cost of statins. Due to the genetic nature of the defect in patients with FH, patients will frequently require either a high dose of one of the more efficacious statins or a combination of several different lipid lowering drugs to achieve adequate LDL-C lowering. Because FH patients have very high LDL cholesterol levels from birth, this warrants the use of high intensity lipid lowering therapy sufficient to reduce LDL-cholesterol to recommended levels, and longitudinal cohort studies have shown that statin treatment is associated with reduced mortality[3]. As the more efficacious statins are more expensive and are still patent protected, it is anticipated that in the future, when these statins become available in generic form, the cost of recommended treatment of FH patients will reduce and overall the cost effectiveness will become more favorable. In sensitivity analysis assuming a 30% fall in prices after 2011 of patented statins, the ICERs fell to about 12,000/QALY.

The modeling was also sensitive to assumptions about the age of index cases, with older index cases having older brothers and sisters who will have fewer life years to be gained by their identification and treatment. DNA + cascading from both mutation negative DFH and PFH index cases will not be cost effective at the £20,000/QALY threshold, if the age of the index cases was increased to 65 and the average age of their relatives was thus increased to 50 years, as the ICER will rise to more than £40,000/QALY. The consequence of this is that identification of FH patients at an early age is of greatest clinical benefit, and has the potential of preventing more deaths and extending life expectancy in a greater number of relatives who can be identified. The model is also sensitive to assumptions about treatment effect. When upper limits of the 95% CI are used (the worsening the treatment effect), the ICERs will be about £28,000/QALY.

One of the most important consequences of cascade testing where DNA information is not available is the high false-positive and false-negative rate for the identification of affected and non-affected relatives based on LDL-C measurements. An overlap between LDL-C levels in FH and non FH children is well established[32],[33] and false-positive and false-negative rates of between 8-15% for families followed up through DNA testing and subsequent lipid measurements have been observed in a number of different studies (Ref). The data used here for the false-positive and negative rates for LDL-C measures was obtained from an analysis of the Dutch relative dataset of more than 2000 mutation carriers and 4000 non-mutation carrying relatives, which represents the largest data set available[24]. However when this is analyzed by age cut-offs, some of the groups have small numbers which reduces accuracy, and there is also uncertainty as to the direct applicability of cut-offs based on patients in the Netherlands to patients in the UK. This data do however represent the best information available.

While a false-negative diagnosis may deny a 'true FH' patient and possibly their offspring (who are at 50% risk of inheriting the mutation) the benefit of more intensive lipid-lowering therapy for their specific condition, another significant issue is that cascade testing from false-negative cases (i.e. relatives who have elevated LDL-C levels who do not carry the family mutation) will not result in any true FH patients being identified. UK data characterising LDL-C levels in mutation-carrying and non-carrying relatives are needed so that the most appropriate cut-offs can be obtained so that cascade testing from non-mutation FH index cases can be carried out with optimal efficiency.

It is anticipated that the proportion of definite FH patients in whom a mutation can be identified is likely to increase over the next few years. This will both be because of improvements in the current techniques for mutation identification, and also the identification of new genes where mutations cause FH. Such improvements will increase the cost-effectiveness.

In conclusion, using a threshold of £20,000/QALY, the most cost effective method for cascade screening is strategy using DNA testing plus cascading from both DFH and PFH mutation negative index cases compared with DNA + cascading from DFH mutation negative index cases. All methods involving DNA testing are cost effective when compared to cholesterol testing alone. The model suggests that cascade screening will yield more benefits if relatives of the index cases are found when they are still young. Once the relatives of index cases are over 45 years it appears that only cascading from mutation-positive index cases is cost effective. . The model results are sensitive to treatment effect on cardiovascular outcomes and the costs of statin treatment and all strategies will become more cost effective when the more efficacious statins required for adequate lipid-lowering in these people come off-patent.

3 Data tables and figures

3.1 Data tables

Table 15 Costs of health states used in the model

	2006 UK £ pa					
	Value in model	Lower	Mean	Upper	SE	Source
No event	£171	£86	£171	£342	£17	Ward et al 2005
MI (first year)	£4,448	£2,224	£4,448	£8,896	£445	Hartwell 2005
MI (subsequent)	£500	£250	£500	£1,000	£50	NICE 2004
Stroke (first year)	£8,046	£4,023	£8,046	£16,092	£805	Ward et al 2005
Stroke (subsequent)	£2,163	£1,082	£2,163	£4,326	£216	Ward et al 2005
PAD (first year)	£1,064	£532	£1,064	£2,128		Assumption
PAD (subsequent)	£264	£132	£264	£528		Assumption
Heart failure	£2,350	£1,175	£2,350	£4,700	£235	NHS ref cost 2006
Heart failure (subsequent)	£500	£250	£500	£1,000	£50	Assumption
Revasc	£3,021	£1,511	£3,021	£6,042		Palmer 2005
Revasc (subsequent)	£500	£250	£500	£1,000		Assumption
Unstable angina (first year)	£2,107	£1,054	£2,107	£4,214	£211	Palmer 2004
Unstable angina (subsequent)	£880	£220	£440	£880	£88	Ward et al 2005
CVD	£0	£0	£0	£0	£0	Ward et al 2005
Death other	£0	£0	£0	£0	£0	Ward et al 2005

Table 16 Cost of drugs used in the model

Drug costs	Unit cost/month	Annual costs	Source
Simvastatin 40mg	4.23	£55.14	Drug Tariff Dec 2006
Simvastatin 80mg	24.07	£313.77	
Atorvastatin 80mg	28.21	£367.74	

Table 17 Additional costs if on high intensity regime

Drug costs	Unit cost/month	Annual costs	Source
GP visit	24 (assumed two extra visits)	£48	PSSRU
Biochemical tests	1.59 (assumed 2 extra tests)	£3.18	NHS reference costs
Neurological tests	8.01	£8.01	NHS reference costs

Table 18 Health state utility weights used in the model

Health state	Utility weight	Source
MI (first 6 months)	0.76	Statins
Post MI	0.88	Harvard CE Registry
Unstable angina (first 6 months)	0.77	Statins
Post UA	0.80	Assumption
Stroke	0.63	Statins
Diabetes	0.90	Harvard C.E Registry
Heart failure	0.71	Harvard C.E Registry
Death	0.00	Statins

Table 19 Utility weight by age

Age group	Age utility weight	Source
20-40	0.85	Health Survey of England 1996
40-60	0.79	
61-75	0.78	
75+	0.73	

Table 20 CVD event rates per person per annum for true-positive FH cases (annual transition probabilities)

Age	UA	REV	MI	HF	Stroke	CVD death
30	14.16%	9.48%	23.71%	0.01%	0.26%	12.14%
50	0.98%	0.59%	1.70%	0.01%	0.40%	1.15%
65	0.17%	0.21%	0.37%	0.01%	0.88%	0.41%
75	0.16%	0.08%	0.36%	0.02%	0.91%	0.40%
85	0.17%	0.01%	0.39%	0.03%	0.96%	0.39%

Table 21 CVD event rates per person per annum for false-positive FH cases (non FH but elevated cholesterol) (annual transition probabilities)

Age	UA	REV	MI	HF	Stroke	CVD death
30	0.20%	0.14%	0.34%	0.00%	0.255%	0.17%
50	0.21%	0.12%	0.36%	0.00%	0.320%	0.24%
65	0.17%	0.21%	0.37%	0.01%	0.639%	0.41%
75	0.16%	0.08%	0.36%	0.02%	0.605%	0.40%
85	0.17%	0.01%	0.39%	0.03%	0.639%	0.39%

For unstable angina, MI, stroke, and CVD death: Ward et al 2005[6] ScHARR statins model, ttp://www.nice.org.uk/pdf/statins_assessment_report.pdf.

For heart failure Cowie MR,[34] For PAD: Murabito JM[35] For revascularisation: Johansen H[36].

Table 22 Baseline input parameters from other health states following MI annual transition probabilities

From stroke to					
Stroke	0.0769	0.1667	0.2069	0.2632	[37]
MI	0.0016	0.0031	0.0055	0.0080	[6]
Heart failure	0.0058	0.0060	0.0072	0.0106	Assumed to be 1/2 of MI to HF
Revascularisation	0.0000	0.0000	0.0000	0.0000	Assumed no transition
Unstable angina	0.0016	0.0031	0.0055	0.0080	Same as stroke to MI
Cardiovascular death	0.0046	0.0111	0.0260	0.0586	[6]
From heart failure to					
Heart failure	0.0416	0.0416	0.0416	0.0416	[38]
MI	0.0081	0.0081	0.0081	0.0081	[38]
Stroke	0.0019	0.0019	0.0019	0.0019	[38]
Revascularisation	0.0000	0.0000	0.0000	0.0000	Assumed No Transition
Unstable angina	0.0081	0.0081	0.0081	0.0081	Assumed to be 1/2 of MI To HF
Cardiovascular death	0.0455	0.0455	0.0455	0.0455	[38]
From revascularization to					
Revascularisation	0.0300	0.0300	0.0300	0.0300	[39]
MI	0.0300	0.0300	0.0300	0.0300	[40]
Stroke	0.0100	0.0100	0.0100	0.0100	Hartwell 2005
Heart failure	0.0150	0.0150	0.0150	0.0150	Assumed to be 1/2 of revascularisation to MI
Cardiovascular death	0.0079	0.0079	0.0079	0.0079	[39]
From unstable angina to					
Revascularisation	0.1420	0.1420	0.1420	0.1420	[41]
MI	0.0495	0.0497	0.0488	0.0466	Statins
Stroke	0.0053	0.0062	0.0112	0.0186	Assumed to be same as MI to stroke
Heart failure	0.0440	0.0440	0.0440	0.0440	[42]

Cardiovascular death	0.0016	0.0027	0.0046	0.0074	[6]

Table 23 Treatment effect of statins, results from the updated Simon Broome Register[7] for patients with FH

AGE	Mean	Lower limit 95% CI	Upper limit 95% CI
<40 YRS	0.13	0.1	0.18
40-59YRS	0.52	0.45	0.6
>60YRS	0.82	0.75	0.9

Table 24 Treatment effect of statins, results of meta-analysis of IDEAL[10] & TNT[9] for patients with stable coronary artery disease

Outcome	Mean (RR)	Lower CL	Upper CL
MI	0.81	0.72	0.91
Stroke	0.82	0.70	0.96
Heart failure	0.77	0.65	0.92
Revascularisation	0.78	0.71	0.86
Unstable angina	0.84	0.69	1.01
Cardiovascular death	0.92	0.72	1.17
Death from other causes	1.00	1.00	1.00

Table 25 Costs of CVD events

Costs of Health States

	2006 Uk £ Pa				
	Value In Model	Lower	Mean	Upper	Source
MI (First Year)	£4,448	£2,224	£4,448	£8,896	[40]
MI (Subsequent)	£500	£250	£500	£1,000	[43]
Stroke (First Year)	£8,046	£4,023	£8,046	£16,092	[6]
Stroke (Subsequent)	£2,163	£1,082	£2,163	£4,326	[6]
Heart failure	£2,350	£1,175	£2,350	£4,700	[12]
Heart failure (Subsequent)	£500	£250	£500	£1,000	Assumption
Revascularizations	£3,021	£1,511	£3,021	£6,042	[27]
Revascularizations (Subsequent)	£500	£250	£500	£1,000	Assumption
Unstable angina (First Year)	£2,107	£1,054	£2,107	£4,214	[27]
Unstable angina (Subsequent)	£440	£220	£440	£880	[6]
CVD	£0	£0	£0	£0	[6]

Table 26 Annual drug costs taken from the Prescription Pricing Division Dec 2007

Drug	Number of tablets	Cost/packet	Cost/year
Simvastatin 40mg	28	£1.31	£17.08
Simvastatin 40mg	28	£4.91	£64.01
Atorvastatin 80mg	28	£28.21	£367.74
Simvastatin 40mg + ezetimibe	28	£33.42	£435.65
Simvastatin 80mg + ezetimibe	28	£41.21	£537.20
Ezetimibe	28	£26.21	£341.67

Source: Drug Tariff December 2007[13]

Table 27 Unit costs of health care professionals and estimated times taken in hours to attend to patients

HCP	Unit cost/hr	Time Hrs(IC)	Time Hrs(Rel)	Cost Index	Cost Relatives	Source
Nurse	£30.00	2	1	£60.00	£30.00	[26]
Clerk	£15.00	1	0.5	£15.00	£7.50	ibid
Phlebotomy	£15.00	0.17	0.17	£2.55	£2.55	ibid
Consultant	£73.00	0.75	0.42	£54.75	£30.66	ibid
Non-fasting TC	£7.00			£7.00	£7.00	Dr Dayla Marks (personal communication)
Full, fasting TC	£8.00			£8.00	£8.00	ibid
£ letter for relatives	£0.86			£0.00	£0.86	ibid
Cost of GP visit	£2.20/min		11 minutes			[26]

Table 28 Proportions of patients on different Lipid-lowering drugs estimated from Wald et al used for the base model, data provided by Dr Anthony Wierzbicki, personal communication

Drug	% (proportions on the drug)*
Simvastatin 40mg	2%
Simvastatin 80mg	9%
Atorvastatin 80mg	64%
Simvastatin 40mg + ezetimibe	4%
Simvastatin 80mg + ezetimibe	11%
Atorvastatin 40mg + ezetimibe	10%

Table 29 Proportions of patients on different Lipid-lowering drugs data provided by Dr Dayla Marks (personal communication)

Drug	% (proportions on the drug)*
Atorvastatin 40mg	30%
Atorvastatin 40mg + ezetimibe	30%
Atorvastatin 80mg	10%
Atorvastatin 80mg + ezetimibe	10%
Simvastatin 40mg	5%
Simvastatin 40mg+ ezetimibe	5%
Simvastatin 80mg	5%
Simvastatin 80mg+ ezetimibe	5%

Table 30 Health state utilities

Health State	Mean	Lower Limit	Upper Limit	Source
MI	0.76	0.56	0.96	[6]
Post MI	0.88	0.68	1.00	[44]
Stroke	0.63	0.43	0.83	[6]
Post Stroke	0.63	0.43	0.83	[6]
Heart failure	0.71	0.51	0.91	[44]
Post heart failure	0.71	0.51	0.91	Assumption
Revascularisation	0.80	0.60	1.00	[27]
Post revascularisation	0.88	0.68	1.00	Assumption
Unstable angina	0.77	0.57	0.97	[6]
Post Unstable angina	0.80	0.60	1.00	Assumption
CVD death	0.00	-	-	

Table 31 Age-related utility from Health Survey for England 1996

Age specific quality of life

Age group	Mean	SE
45-54	0.85	0.004
55-64	0.79	0.006
65-74	0.78	0.006
75+	0.73	0.007

Source: Health survey of England 1996[14]

Table 32 Decision tree probabilities for the cascade model

	Probability	Source
Prevalence of DFH using Simon Broome	0.3	Simon Broome
Prevalence of PFH using Simon Broome	0.6	Simon Broome
Prevalence of no FH using Simon Broome	0.1	Simon Broome
Probability of true FH for a DFH using cholesterol method	0.9	The UK FH Cascade Audit Project (FHCAP) Personal communication from Dr G Hadfield
Probability of true FH for a PFH using cholesterol method	0.35	Ibid
Probability of mutation positive for a DFH using DNA method	0.8	Ibid
Probability of mutation positive for a PFH using DNA method	0.3	Ibid
		Ibid
Probability of true FH for a DFH mutation negative using cholesterol method	0.5	Ibid
Probability of true FH for a PFH mutation negative using cholesterol method	0.07	Ibid
Cascading probabilities		**Ibid**
From index cases true positives		**Ibid**
Probability of true positives using cholesterol method	0.27	Ibid
Probability of false positives using cholesterol method	0.07	Ibid
Probability of true negatives using cholesterol method	0.43	Ibid
Probability of false negatives using cholesterol method	0.23	Ibid
From index cases false positives		**Ibid**
Probability of true positives using cholesterol method	0	Ibid
Probability of false positives using cholesterol method	0.14	Ibid
Probability of true negatives	0.86	Ibid

using cholesterol method		
Probability of false negatives using cholesterol method	0	Ibid

3.2 Figures

Figure 1 Model structure for cost effectiveness of lower intensity statins versus higher intensity statins in secondary prevention

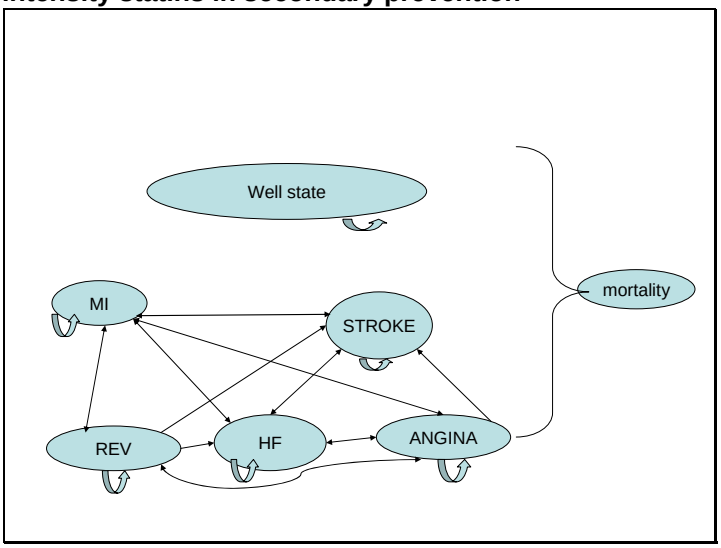
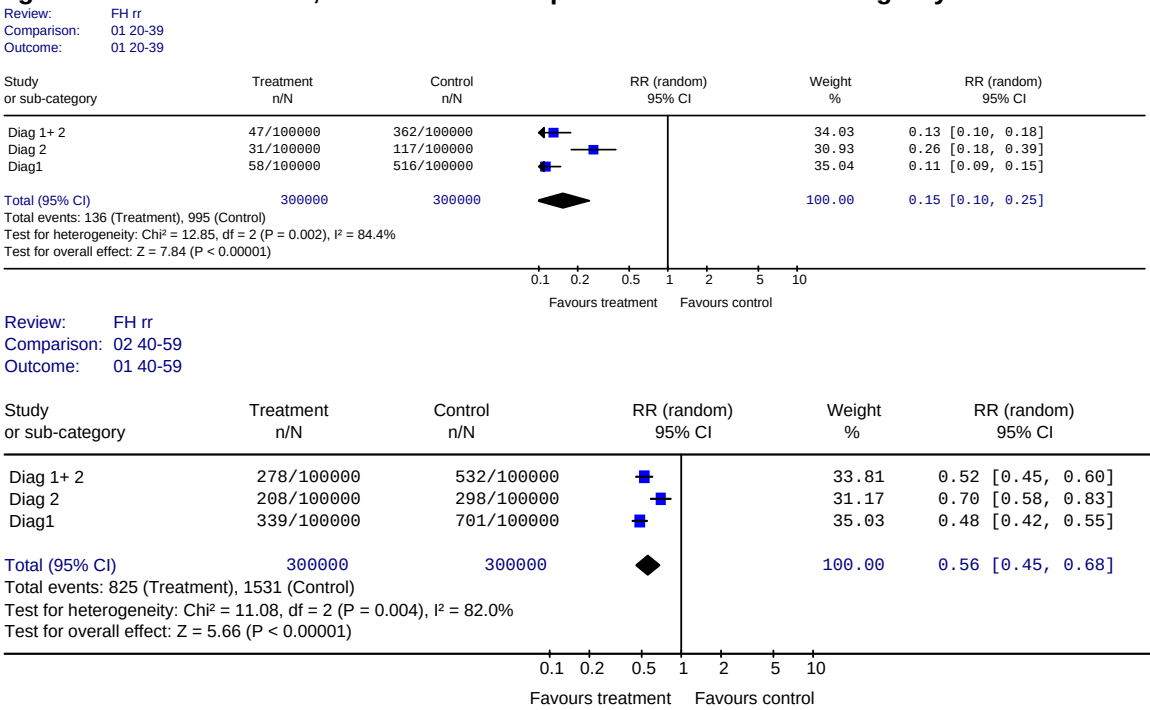


Figure 2 Treatment effect, data taken from updated Simon Broome Registry Neil et al[7]



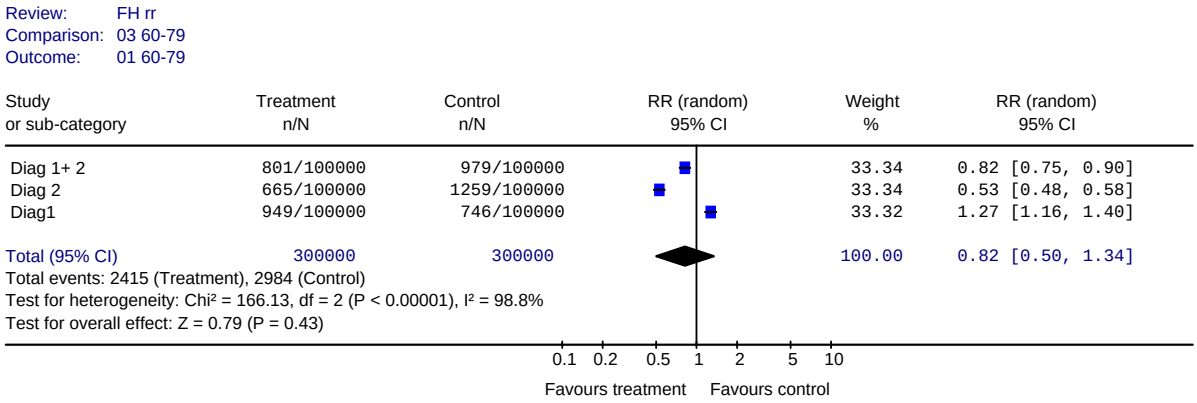
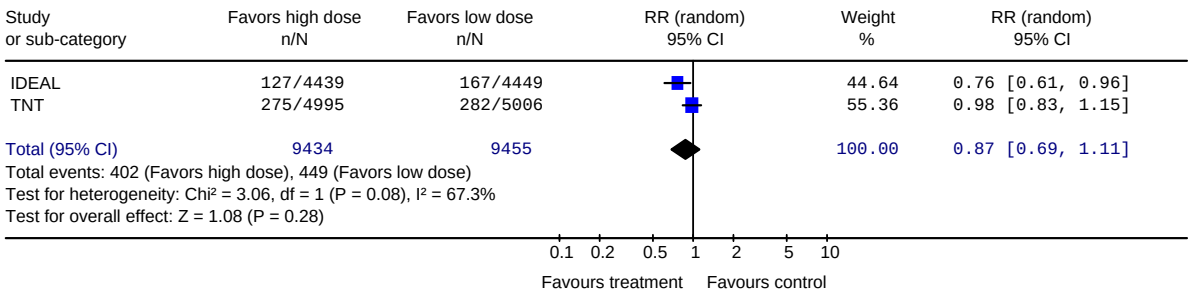
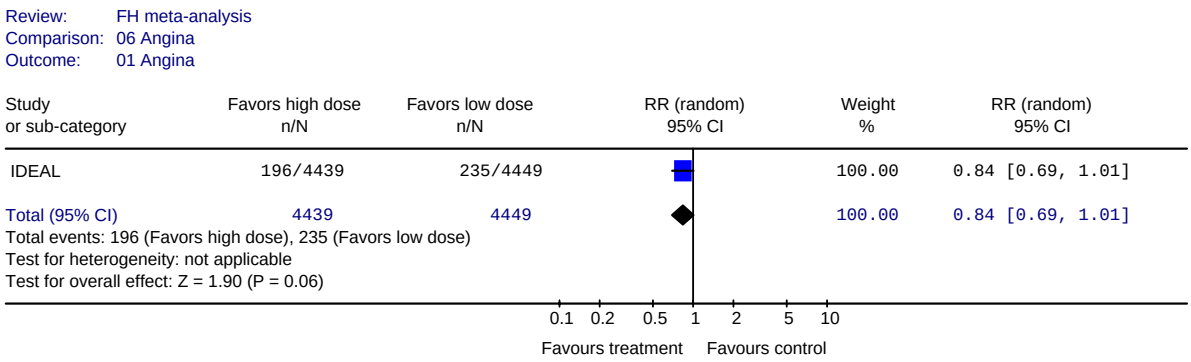
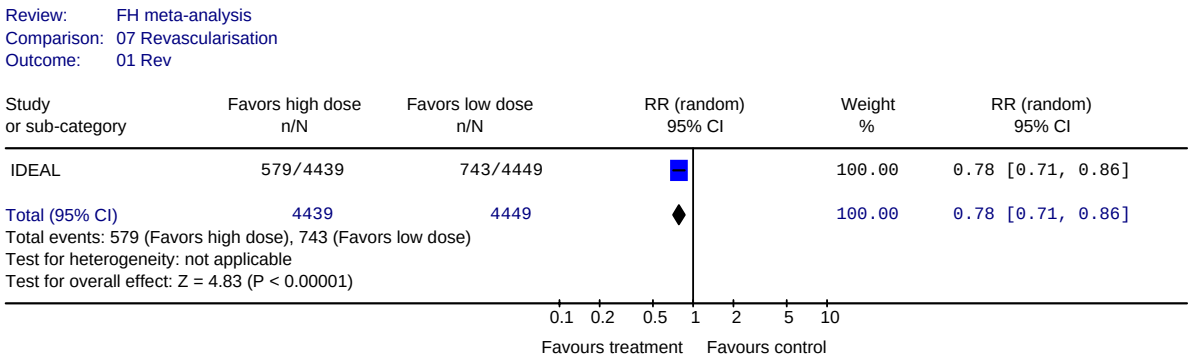


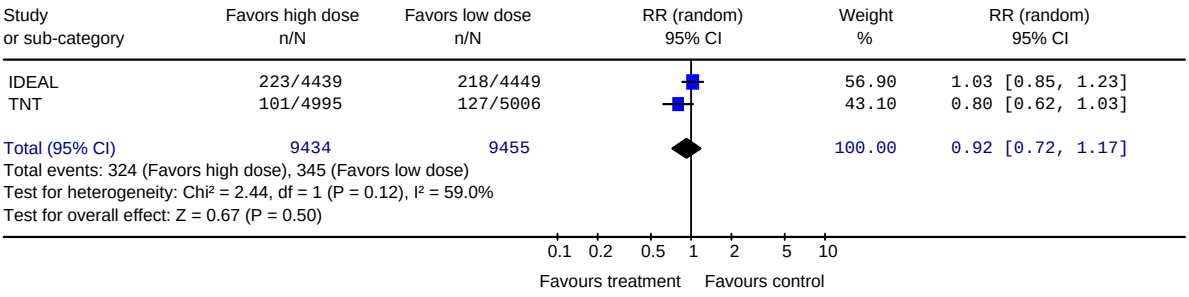
Figure 3 Treatment effect used in the model, meta-analysis of IDEAL[10] and TNT[9]







Review: FH meta-analysis
Comparison: 08 CVD mortality
Outcome: 01 CV mortality



Review: FH meta-analysis
Comparison: 09 Total mortality
Outcome: 01 Total

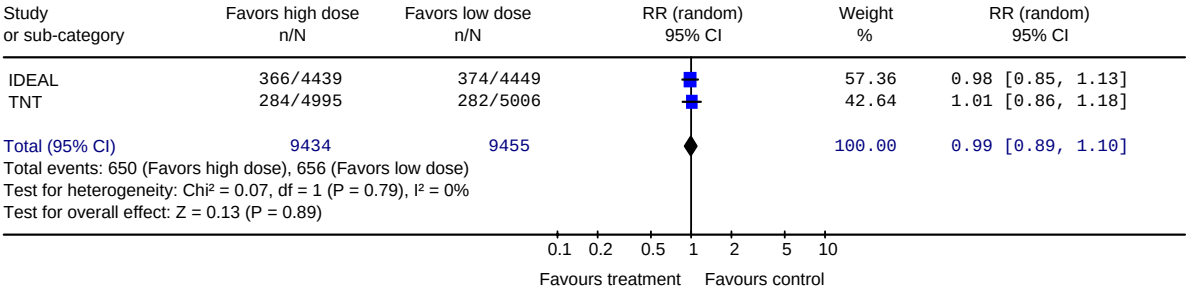
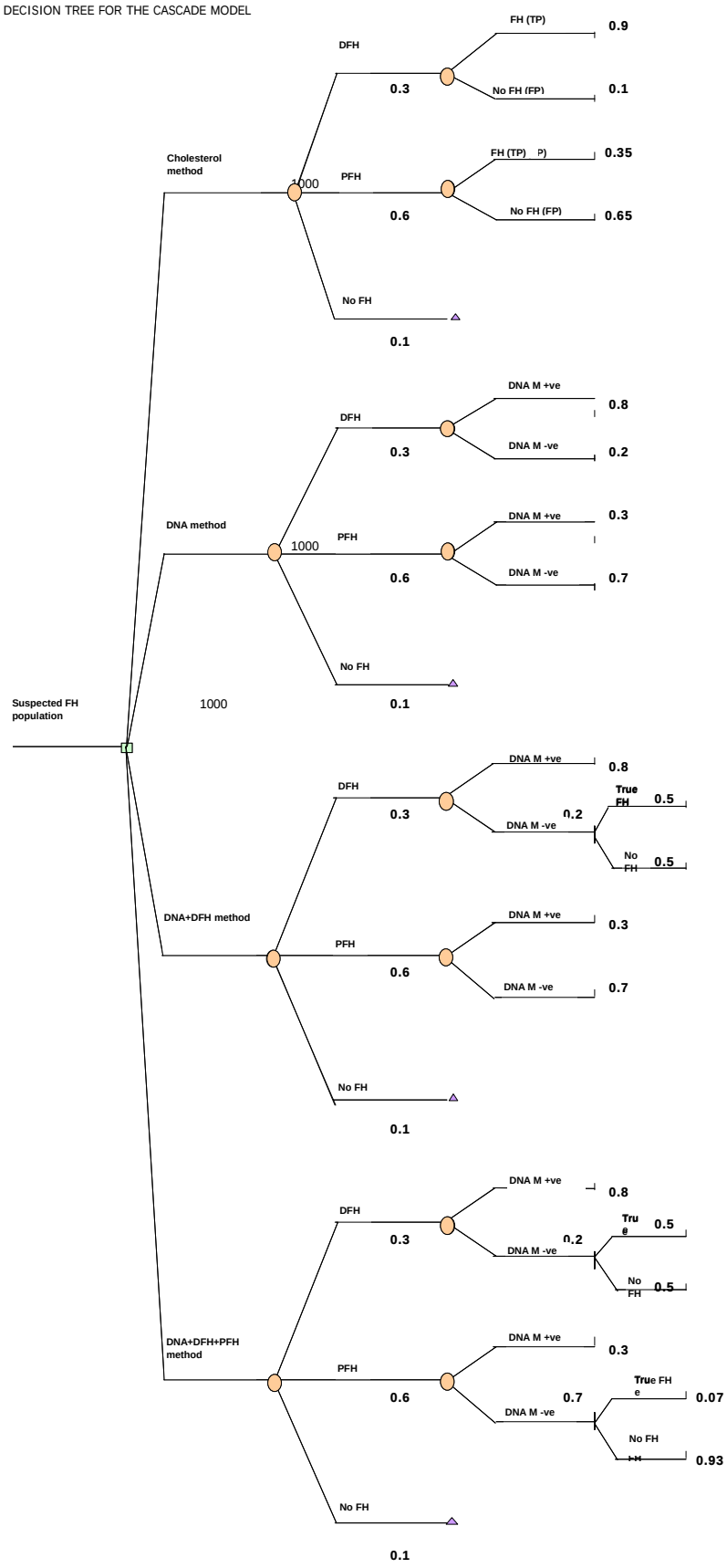


Figure 4 Decision model for cascade screening



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