Appendix D
Health economic extractions and excluded studies

Included studies

No included references were found for any other questions (see also Excluded references below).

Question 3

What is effectiveness of the following strategies for identifying people with FH: cascade screening; GP note searching; secondary care registers; pathology registers or family history?

No 427 **Study Quality:** Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost effectiveness analysis
Author: Marks D; Wonderling D; Thorogood M; Lambert H; Humphries SE; Neil HA; 2000
Relevance
Intervention: Universal population screening, opportunistic (GP), opportunistic (people suffering from MI), case finding through FH probands
Comparison: The above methods head to head. The second model compared genetic diagnosis with clinical diagnosis
Population: People suspected of FH
Perspective: NHS
Study type: CEA
Methods:
Health valuations: NOT APPLICABLE
Cost components: Screening costs including invitation letters, lipid profiles and treatment costs (statin therapy), CHD events costs, genetic testing
Currency: £
Cost year: 1998/99
Time horizon: lifetime
Discount rate: 6% for costs and 1% for benefits
Results-cost: COST PER PATIENT FOR GENETIC DIAGNOSIS
Universal age 16yrs £9,610
Universal age 16-54yrs £61,661
Opportunistic (GP) £55,283
Opportunistic (MI) £17,116
Case finding age 16-54 exc cost of testing proband £2,580
Case finding age 16-54 inc cost of testing proband £3,856 3.5 £4,914

COST PER PATIENT FOR CLINICAL DIAGNOSIS
Universal age 16yrs £1,798
Universal age 16-54yrs £10,269
Opportunistic (GP) £8,909
Opportunistic (MI) £7,513
Case finding age 16-54 yrs £2,420
Results-effectiveness: DISCOUNTED LYG FOR GENETIC DIAGNOSIS
Universal age 16yrs 5.2
Universal age 16-54yrs 3.5
Opportunistic (GP) 3.7

Opportunistic (MI) 0.8
Case finding age 16-54 exc cost of testing proband 3.5
Case finding age 16-54 inc cost of testing proband 3.5

DISCOUNTED LYG FOR CLINICAL DIAGNOSIS
Universal age 16yrs 5.2
Universal age 16-54yrs 3.5
Opportunistic (GP) 3.7
Opportunistic (MI) 0.8
Case finding age 16-54 yrs 3.5

Results-ICER: COST/LYG FOR GENETIC DIAGNOSIS
Universal age 16yrs £14,842
Universal age 16-54yrs £78,060
Opportunistic (GP) £70,009
Opportunistic (MI) £21,106
Case finding age 16-54 exc cost of testing proband £3,300
Case finding age 16-54 inc cost of testing proband £4,914

COST/LYG FOR CLINICAL DIAGNOSIS
Universal age 16yrs £2,777
Universal age 16-54yrs £13,029
Opportunistic (GP) £11,310
Opportunistic (MI) £9,281
Case finding age 16-54 yrs £3,097

Result-Uncertainty: A number of sensitivity analysis was done. The opportunistic GP and universal 16-54 age were sensitive to discount rate when 5% was used for both cost sand effects. Universal was also affected by the number of mutations found for diagnostic testing.
Costs of drugs have since fallen by over 60% for simvastatin

Source Funding: Public

Comments: This is a well written HTA, the methods and assumptions are clearly written. There was no incremental analysis done to compare these strategies against each other and clinical versus diagnostic testing. Inclusion of QALY was going to be a useful too

No 430 **Study Quality:** Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia.[see comment]

Author: Marks D; Wonderling D; Thorogood M; Lambert H; Humphries SE; Neil HA; 2002

Relevance

Intervention: See Population section below

Comparison: no screening.

Population: Simulated heterozygous population aged 16-54, England and Wales

Perspective: 5 screening strategies are assessed. These are universal screening at 16, universal screening, opportunistic screening of patients NHS and Personal Social Services consulting for unrelated reasons in primary care, opportunistic screening of patients admitted to hospital with premature myocardial infarction, and systematic screening of first degree relatives of people with diagnosed familial hypercholesterolemia.
In the first four of these options, a non-fasting total cholesterol concentration above the population 95th centile are invited for a fasting blood test. If fasting total cholesterol concentration exceeds 7.5mmol/l and LDL cholesterol exceeds 4.9mmol/l, referral either to a lipid clinic consultant for diagnosis confirmation by clinical examination, or by genetic testing on blood or buccal cells.
Under the family screening approach, a lipid clinic nurse collects family history and approaches relatives.

Study type: Cost-effectiveness analysis, Cost per life year gained

Methods: RCT, other economic analysis and observational studies, references given

Health valuations: NOT APPLICABLE

Cost components: Costs of letters nurse appointments, lipid profiles, genetic tests, statin therapy (70% receiving simvastatin 40mg daily, 30% receiving atorvastatin 20mg daily), cost of CHD events.
Currency: £
Cost year: 1998
Time horizon: Lifetime
Discount rate: Costs were discounted at 6% per annum. Outcomes were discounted at 1% per annum.
Results-cost: The annual cost of statins was £411.
The cost per case detected ranges from £133 for the family tracing strategy to £9645 for the population wide strategy
Results-effectiveness:
Results-ICER: The base case results for cost per life year gained are as follows

Universal (16 year olds) –	Universal	Opportunistic (GP)	Opportunistic (MI)	Family tracing
Clinical	2 777	13 029	11 310	9 281	3097
Genetic	14 842	78 060	70 009	21 106	4 914

Prior to the section on sensitivity analysis, they present the results if costs and benefits are discounted at equal rates (3%). It should be noted that the results differ under this assumption which is more in line with NICE methodology.

Universal (16 year olds) -	Universal	Opportunistic (GP)	Opportunistic (MI)	Family tracing
Clinical	7 244	21 289	18 578	15 738	6 084
Genetic	33 882	120 841	108 578	32 833	8 865

Result-Uncertainty: Using the initial base case results, the authors undertake univariate sensitivity analysis. This alters the number of relatives per proband, the drug costs, attendance rates, CHD events costs and life years gained. Under the ranges of values the authors felt to be reasonable, the ranking of cost-effectiveness was not affected.
Source Funding: Public
Comments: The authors conclude that the screening of family members of existing cases is the most cost-effective option of those considered. This is a paper derived from the HTA report on the topic. It is of a high standard. It should be noted that they exclude morbidity effects from the calculation.

No 429 **Study Quality:** Comparing costs and benefits over a 10 year period of strategies for familial hypercholesterolaemia screening
Author: Marks D; Thorogood M; Neil HA; Wonderling D; Humphries SE; 2003
Relevance
Intervention: family tracing strategy in which a clinic nurse collects family histories from index cases.
Comparison: universal screening of 16 year olds
Population: Persons aged 16-54 with FH in England and Wales
Perspective: Healthcare provider (NHS)
Study type: CEA
Methods: The Simon Broome Register cohort data
Health valuations: NOT APPLICABLE
Cost components: Drug costs, healthcare professional time costs (healthcare professional use in screening outlined above, plus an annual GP appointment while under statin therapy), statin costs (based on 70% receiving 40mg Simvastatin and 30% receiving 20mg Atorvastatin)
Currency: £
Cost year: Not stated
Time horizon: 10 years
Discount rate: Discounting is not undertaken
Results-cost: The cost of universal screening (and its consequences) of 16 year olds in England and Wales was estimated to be £6.177 Million over 10 years. The cost of family tracing was estimated to be £46.431 Million over ten years. Thus, the family screening method incurs significant extra cost over the first 10 years.
Results-effectiveness: Under universal screening at 16, 470 new diagnoses can be expected, leading to a reduction in mortality of 11.7. Under family screening, the respective figures are 13 248

and 560. Thus, the family screening method provides significant extra benefits over the first 10 years
Results-ICER: No incremental analysis was done since the study was only comparing the costs and consequences of each strategy.

Relative to no screening, the universal screening at 16 option has a cost per case identified and treated of £13141 and a cost per death averted of £527 919. For the family tracing option, the cost per case identified and treated is £3 505 and the cost per death averted is £3187.
Result-Uncertainty: The paper itself does not contain any sensitivity analysis. However, it does report work within the HTA programme (see Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE. Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: systematic review and cost effectiveness analysis. Health Technol Assess 2000;4(29))
Within that work, the areas considered most important to the overall result were the cost of drugs and screening.
Source Funding: Charitable
Comments: A good paper covering the population relevant to NICE guidance. However, the choice of a 10 year cut-off in this paper means that significant mortality effects are ignored in the universal screening option. An incremental analysis comparing the two options would have been a potentially valuable addition to the study.

No 428 **Study Quality:** Cost-effectiveness analysis of the genetic screening program for familial hypercholesterolemia in The Netherlands
Author: Wonderling D; Umans-Eckenhausen MA; Marks D; Defesche JC; Kastelein JJ; Thorogood M; 2004
Relevance
Intervention: The intervention is the national genetic testing program for FH in the Netherlands, running since 1994. Those positive would

were given statin therapy
Comparison: The comparison is no screening.
Population: 0-60 year olds asymptomatic individuals with family members with a known genetic defect, Netherlands,
Perspective: THIRD PAYER
Study type: Cost-effectiveness analysis, Cost per life-year gained, Cost per new case identified
Methods: The Simon Broome registry and Data from the Dutch screening programme in 2000
Health valuations: NOT APPLICABLE
Cost components: Costs of screening and testing, lifetime treatment costs and costs of cardiovascular events.
Currency: US$
Cost year: 2001
Time horizon: Lifetime
Discount rate: Both costs and benefits were discounted at 4% per annum.
Results-cost: The cost per patient is not clearly stated. However, the author does show unit costs of screening (US$1 768 per new untreated case diagnosed) and the cost of drugs per annum (US$570) and the cost of a myocardial infarction (US$9 018)
Results-effectiveness: New cases identified by the screening programme gained an average of 3.3 years of life (undiscounted) and 0.9 years (discounted at 4% per annum).

The model estimated that 26 MIs would be avoided per 100 persons treated with statin between 18 and 60.
Results-ICER: The cost per new case identified was US$7 500. The cost per life-year gained was US$8 800.
Result-Uncertainty: The authors varied model parameters within confidence intervals considered reasonable. The parameter, and the confidence

intervals suggested are presented below.

Parameter	Range
Life years gained	0.4 - 1.5

Persons screened per year	506 – 959
Cost of complex DNA test	308.50 - 1 635
Case rate amongst relatives	35% - 39%
Relatives per index case	11 - 34
Proportion of patients already on medication	50% - 57%
Drug uptake rate	78% - 85%
Drug cost	$40.78 - $78.49
Cost of a coronary event	$2 490 - $16 757

The result was sensitive to the price of statin treatment and the number of life-years gained. If all of these parameters were set to the value within their respective range most unconducive to cost-effectiveness of the programme relative to no programme, the cost per life-year gained rises to $38 300.

The second component of the sensitivity analysis is to look at the effect of the discount rates chosen. The authors list a range of different strategies for discounting. The approach most supportive of the intervention was to discount costs at 6% and benefits at 0%, leading to a cost per life-year gained of $1 800. The approach more unsupportive of the intervention was to discount both costs and benefits at 5%, leading to a cost per life-year gained of $10 400.

It should be noted that the approach suggested within NICE is to discount costs and benefits uniformly at 3.5%. The base case is unlikely to diverge far from this value.

Source Funding: Not stated

Comments: A good paper with excellent internal validity. Unlike the other Netherlands-based paper, it relies on an FH population for the effect of statins on mortality. The use of discount rates is correct and it includes a compliance rate.

The generalisability of the result to England and Wales is not assured due to different cost bases between countries. However, it should be noted that the conclusion of the paper is relatively strong in favour of the intervention relative to the control.

Question 9

What is the effectiveness of the following adjunctive pharmacotherapy with statins in individuals with FH: statins with any of resins, fibrates, niacin, fish oils, nicotinic acid and ezetimibe (alone or in combination)?

No 257 **Study Quality:** Costs and benefits of Simvastatin 40mg Vs fluvastatin 80 mg in patients with Familial hyperlipidaemia: Technology Assessment Report No 2
Author: Metcalfe S; 1997
Relevance
Intervention: simvastatin 40mg/day
Comparison: fluvastatin 80mg/day.
Population: This paper examines the incremental benefits and costs of treating patients with FH with simvastatin 40mg/day, over and above the net costs and benefits of
Perspective: treatment with fluvastatin 80mg/day aged between 35-39 years
THIRD PAYER
Study type: CUA
Methods: DECISION ANALYSIS using data from 4S, Simon Broome
Health valuations: TTO
Cost components: Direct medical costs
Currency: New Zealand dollar (NZ$)
Cost year: 1996
Time horizon: 5 years
No discounting was undertaken
Discount rate: 7.8%
No discounting was undertaken
Results-cost: Cost difference $771/patient /year
Results-effectiveness: Fluvastatin80mg 0.89 QALYS
Simvastatin 40mg 1.03 QALYs
Results-ICER: Base case (35-59 years)
$32,947/QALY
55-59 years
$28,112/QALY
Children
$77,000/QALY
Result-Uncertainty: Not done
Source Funding: Public
Comments: The authors did not undertake a sensitivity analysis which weakens their study. In their base case model they assumed fluvastatin will cause a disutility of 0.01 (compared to a disutility of 0.00 for simvastatin), while in their discussion they acknowledge that published studies did not find any difference in utility between the two statins. The implications, which the authors acknowledge, are to exaggerate the QALY gains by simvastatin; hence making the ICERs favourable. It would have been more helpful if they had fully explored this in sensitivity analysis or assumed no difference in the base model.
In conclusion, simvastatin 40mg compared with fluvastatin 80mg used in patients with FH appears to have value for money; this finding is weakened by a lack of sensitivity analysis and, especially, the assumptions about utility loss between the two statins. Their finding seem to contradict our finding that in FH patients, cost effectiveness is favourable for those aged less than 60 years compared to those aged over 60 years.

Excluded studies

RM ID	Title	Authors	Year	Journal	Question	Reason for exclusion
2116	Documented need for more effective diagnosis and treatment of familial hypercholesterolemia according to data from 502 heterozygotes in Utah	Williams RR; Schumacher MC; Barlow GK; Hunt SC; Ware JL; Pratt M; Latham BD;	1993	American Journal of Cardiology	3	Not RCT