NCCHTA

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1. Title of the project:

Early high dose lipid-lowering therapy to prevent cardiac events

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3. Plain English Summary

Cardiovascular disease (CVD) is a disorder of the heart and blood vessels, which can lead to cardiovascular events such as heart attack (myocardial infarction, MI) and stroke. The most common form of CVD is coronary heart disease (CHD), also known as coronary artery disease and ischaemic heart disease. CHD is caused by the narrowing of the arteries that supply the heart and is due to a gradual build-up of fatty material called atheroma. The narrowing can cause MI, angina (pain or discomfort in the chest or neighbouring parts of the body due to insufficient oxygen reaching the heart) and other forms of chronic heart disease. Angina is usually classified as stable or unstable disease. Other forms of CVD are stroke, transient ischaemic attack (TIA) and peripheral vascular disease (PVD). CVD is the most common cause of death in the UK, accounting for over 208,000 deaths in 2005.[1] Approximately 49% of these deaths were from CHD and 28% from stroke. CVD is also a significant cause of morbidity and can have a major impact on quality of life.[2]

Cholesterol is a key component in the development of atherosclerosis (the accumulation of fatty deposits (atheroma) on the inner lining of the arteries). Mainly as a result of this, cholesterol increases the risk of CVD.[3,4] The lowering of cholesterol whether by diet, drugs or other means, decreases CVD risk.[5] Statin therapy, associated principally with lowering concentrations of total cholesterol (Total-c) and LDL-c, with smaller effects in raising high-density lipoprotein cholesterol (HDL-c) and decreasing triglyceride levels, can reduce the risk of cardiovascular events, morbidity and mortality.[6]

Although blood cholesterol is an important risk factor for CVD, cholesterol lowering with drug therapy is only one of a number of methods of reducing the risk.[7] Dietary and lifestyle modifications (e.g. weight loss, smoking cessation, aerobic exercise) are an integral part of risk management. If these are unsuccessful and the patient is at high risk, more effective therapy, including lipid regulating drug therapy, is initiated.[8] The decision to initiate therapy with a lipid-regulating drug is generally based on an assessment of overall CVD risk. Statins are the current cholesterol-lowering drugs of choice for the long-term management and secondary prevention of CVD.[9] While long-term statin therapy reduces CVD events, the early period following an acute coronary syndrome (i.e. MI or unstable angina) or coronary revascularisation (coronary artery bypass grafting, CABG or percutaneous transluminal coronary angioplasty, PTCA) represents a stage where the individual is at highest risk of recurrent cardiovascular events and mortality.[10] Meta-analyses of randomised controlled trials (RCTs) have shown that early, intensive (high) dose statin therapy is of benefit in reducing death and cardiovascular events when prescribed immediately after an acute coronary syndrome compared to standard (moderate) statin therapy.[11,12] However, in the UK, there is great

variation in the prescribing practices (particularly current standard dose) and management of patients with ACS. Some Primary Care Trusts (PCTs) recommend simvastatin 40g as the current standard dose whereas others recommend atorvastatin 80mg/d. Initiation of standard dose would be on the first day of the event and duration is in theory for life.

The aim of this review is to systematically evaluate and appraise the potential clinical and cost effectiveness of switching from the current standard dose statin (i.e. simvastatin 40mg/d) to a high dose statin (i.e. simvastatin 80mg/d, atorvastatin 80mg/d or rosuvastatin 40mg/d) in patients who have recently had a myocardial infarction or unstable angina, or who have recently undergone revascularisation and who are currently prescribed simvastatin 40mg/d.

4. Decision problem

4.1 Purpose of the assessment

The assessment will address the question: "Should patients in the UK who have recently had a MI, unstable angina or revascularisation procedure, who are currently using simvastatin 40mg/d switch to higher doses such as simvastatin 80mg/d, atorvastatin 80mg/d or rosuvastatin 40mg/d".

4.2 Clear definition of the intervention

Statins are a group of drugs that are widely used to reduce the level of cholesterol in the blood. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis. Inhibition of HMG CoA reductase lowers low density lipoprotein cholesterol (LDL-c) levels by slowing down the production of cholesterol in the liver and increasing the liver's ability to remove the LDL-c already in the blood.[9]

At present, five statins have a marketing authorisation in the UK: atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin. These statins are generally indicated for the treatment of lipid disorders (e.g. primary hypercholesterolaemia or mixed dyslipidaemia) and prevention of cardiovascular disease.[13] Of these, fluvastatin and pravastatin are the least effective in reducing serum LDL-c, [14] thus are not commonly prescribed at standard or high dose in the UK.[4,5]

The intervention of interest for this research is simvastatin 80mg/d, atorvastatin 80mg/d or rosuvastatin 40mg/d. In the absence of data on atorvastatin 80mg/d or rosuvastatin 40mg/d evidence will be included from studies using treatment doses of atorvastatin 40mg/d or rosuvastatin 20mg/d.

4.3 Place of intervention in the treatment pathway

The review will focus on the use of high dose statin therapy in patients who have recently had a MI, unstable angina or a revascularisation procedure in the UK.

For symptomatic people with CVD, the traditional approach has been to start with dietary advice and then consider lipid lowering therapy some months after the acute event.[5] The National Service Framework for CHD[15,16] recommends that patients with clinical evidence of CHD or those with a 10 year risk greater than 30% should be prescribed lipid lowering therapy (combined with advice on diet and lifestyle) with the aim of reducing serum total cholesterol (TC) to less than 5 mmol/L (or a reduction of 20-25% if that produces a lower concentration) and LDL-c to below 3 mmol/L (or a reduction of about 30% if that produces a lower concentration). However, more recent advise from six joint British Societies[5] advocate lower treatment thresholds (e.g. TC less than 4.0 mmol/L *and* LDL-C below 2.0 mmol/L in all people with CVD or at high risk of CVD). Current guidelines from the National Institute for Health and Clinical Excellence (NICE)[9] recommend the initiation of low acquisition cost statin therapy for the long-term management in all people with a history of CVD and as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD.

Although specific guidance is limited on the use of early, high dose statin therapy after an acute coronary event or coronary revascularisation, the joint British Societies[5] recommend that all people with acute atherosclerotic (coronary, cerebral and peripheral) disease, but not cerebral haemorrhage, be prescribed early in-hospital statin treatment, regardless of the initial cholesterol value. Thereafter (approximately 8 to 12 weeks after the acute event) fasting lipids should be measured and drug therapy appropriately modified to ensure lipid targets are achieved.

4.4 Relevant comparators

The comparator will be simvastatin 40mg/d.

4.5 Populations and relevant subgroups

The population will include adults (defined as ≥ 18 years of age) who have recently had a MI, unstable angina, or a revascularisation procedure such as a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA).

4.6 Key factors to be addressed

The review will aim to evaluate the following objectives:

1. evaluate the clinical effectiveness of switching to higher dose statins in terms of mortality and cardiovascular morbidity

2. evaluate the adverse effect profile and toxicity associated with switching to higher dose statins

3. estimate the incremental cost effectiveness of switching to higher dose statins, in comparison to simvastatin 40mg/d

4. identify key areas for primary research

5. estimate the possible overall cost in England and Wales

5. Report methods for synthesis of evidence of clinical effectiveness

A review of the evidence for clinical effectiveness will be undertaken systematically following the general principles recommended in the QUOROM statement.[17]

5.1 Population

5.1.1 Inclusion criteria

Adults (defined as $\geq$ 18 years of age) with recent (defined as less than 28 days) MI, unstable angina or who have undergone revascularisation (CABG or PTCA). In the absence of RCT evidence in the aforementioned population, the time since event will be relaxed to "less than six months" with time since event included in the Bayesian model.

5.2 Interventions

High dose statins defined as simvastatin 80mg/d, atorvastatin 80mg/d or rosuvastatin 40mg/d.

5.3 Comparators

Simvastatin 40mg/d

5.4 Setting

Any

5.5 Outcomes

As there is currently no published evidence from rosuvastatin, RCTs reporting effectiveness results in terms of reductions in either cardiovascular events or mortality, the primary outcome measure will include the following:

- effectiveness in reducing LDL-c

Secondary outcome measures will include the following:

- any adverse events
- health-related quality of life (HRQoL)

5.6 Search strategy

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

5.6.1. Electronic searches

A comprehensive search will be undertaken to systematically identify clinical and cost-effectiveness literature pertaining to early high dose statin therapy for the prevention of cardiac events. Search strategies will be used to identify relevant trials (as specified under the inclusion criteria, below) and systematic reviews/meta-analyses (for identification of additional trials). Searches will not be restricted by language or publication date. An example of the Medline search strategy is shown in Appendix 1.

5.6.2. Databases

The following electronic databases will be searched from inception: MEDLINE (Ovid); CINAHL; EMBASE; The Cochrane Library including the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register (CENTRAL), DARE, NHS EED and HTA databases; Science Citation Index (SCI); National Research Register (NRR); Current Controlled Trials.

5.7 Inclusion criteria

The following studies will be included:

- Head to head RCTs comparing simvastatin 80mg/d, atorvastatin 80mg/d, rosuvastatin 40mg/d with simvastatin 40mg/d

- RCTs comparing simvastatin 40mg/d, simvastatin 80mg/d, atorvastatin 80mg/d, rosuvastatin 40mg/d with placebo

- RCTs comparing any of the following treatments: simvastatin 40mg/d, simvastatin 80mg/d, atorvastatin 80mg/d, rosuvastatin 40mg/d.

For the review of clinical effectiveness, only RCTs of at least 12 weeks duration will be included. In the absence of sufficient evidence from trials of at least 12 weeks duration the use of data from trials of less than 12 weeks duration will be considered. This criterion will be relaxed for consideration of adverse events, for which observational studies may be included. Titles and abstracts will be examined for inclusion by one reviewer.

5.8 Exclusion criteria

Reviews of primary studies will not be included in the analysis, but will be retained for discussion and identification of additional trials. Moreover, the following publication types will be excluded from the review: non-randomised studies (except for adverse events); animal models; preclinical and biological studies; narrative reviews, editorials, opinions; non-English language papers and reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality.

5.9 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction form (see Appendix 2). Where multiple publications of the same clinical study are identified, data will be extracted and reported as a single study.

5.10 Quality assessment strategy

The methodological quality of selected studies will be assessed (by a single reviewer) based on Section 6 of The Cochrane Reviewers' Handbook[18] and will consist of the following factors: generation of allocation sequence, allocation concealment, blinding and loss to follow-up. Based on these criteria, studies will be categorised as low, moderate or high risk of bias. Further details are provided in Appendix 3. The purpose of such quality assessment is to provide a narrative account of trial quality for the reader and, where meta-analysis is appropriate, inform potential exclusions from any sensitivity analysis.

5.11 Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. A synthesis of the available evidence will be performed using Bayesian hierarchical modelling. The analysis will incorporate both direct and indirect evidence to enable comparisons to be made between treatments. The analysis will be done by the Centre for Bayesian

Statistics in Health Economics (CHEBS), based at the University of Sheffield, using the freely available software WinBUGS.[19]

5.12 Methods for estimating quality of life

Ideally, evidence on the impact of statins on HRQoL will be available directly from the trials included in the review. In the absence of such evidence, evidence used in an existing cost-effectiveness model will be retained.[20]

6. Report methods for synthesising evidence of cost-effectiveness

The time horizon of our analysis will be a patient's lifetime in order to reflect the chronic nature of the disease. The perspective will be that of the National Health Services and Personal Social Services. Both costs and QALYs will be discounted at 3.5%.

6.1 Identifying and systematically reviewing published cost-effectiveness studies

The sources detailed in section 5 will be used to identify studies which examine the potential economic evaluations exploring the cost-effectiveness of high dose versus standard dose statin therapy. The quality of economic literature will be assessed using a combination of key components of the British Medical Journal checklist for economic evaluations together with the Eddy checklist on mathematical models[21,22] (see Appendix 4).

6.2 Economic model

An economic evaluation will be carried out from the perspective of the UK NHS using a Markovian modelling approach. An existing CVD model[20] will be adapted to explore the cost and benefits associated with high dose statin therapy compared with standard dose statin therapy. The health states will be expanded to include one for individuals who have recently undergone a revascularisation procedure. A published relationship linking changes in LDL-c with cardiovascular events will be utilised to model the effectiveness of the interventions.[6] Costs will include the direct cost of statins, costs of adverse events (if appropriate) and costs associated with CHD events. Results will be reported in terms of cost per quality adjusted life year gained.

7.0 Expertise in this TAR team

- **TAR Centre**

The ScHARR Technology Assessment Group (ScHARR-TAG) undertakes reviews of the effectiveness and cost effectiveness of health care interventions for the NHS R&D Health Technology Assessment Programme on behalf of a range of policy makers in a short timescale,

including the National Institute for Health and Clinical Excellence. A list of our publications including a completed NICE technology appraisal assessment of 'statins for the prevention of coronary events' and 'ezetimibe for the treatment of hypercholesterolaemia' can be found at: http://www.sheffield.ac.uk/scharr/sections/heds/collaborations/scharr-tag/reports. Much of this work, together with our reviews for the international Cochrane Collaboration, underpins excellence in health care worldwide.

- **Team members' contributions**

Roberta Ara, Research Fellow: has extensive experience in health economic research including involvement in the recent NICE HTAs: Statin for the prevention of cardiovascular events - Technology appraisal; Ezetimibe for treatment of primary hypercholesterolaemia – Technology appraisal, and a HTA review on Aspirin for the primary prevention of cardiovascular disease. RA will co-ordinate the review process, protocol development, abstract assessment for eligibility, quality assessment of trials, data extraction, data entry, data analysis and review and development of cost effectiveness.

Abdullah Pandor, Research Fellow: has extensive experience in systematic reviews of health technologies including involvement in the recent NICE HTAs: Statin for the prevention of cardiovascular events - Technology appraisal; Ezetimibe for treatment of primary hypercholesterolaemia – Technology appraisal, and a HTA review on Aspirin for the primary prevention of cardiovascular disease. AP will be involved in the protocol development, abstract assessment for eligibility, quality assessment of trials, data extraction, data entry, data analysis and review development of background information and clinical effectiveness.

Sue Ward, Senior Operational Research Analyst: has extensive experience in health economic research including involvement in the recent NICE HTA: Statin for the prevention of cardiovascular events - Technology appraisal and various other NICE HTA cancer related appraisals. SW will be involved in the protocol development, the review and development of both the clinical and cost effectiveness.

John Stevens, Lecturer in Bayesian statistics and Deputy Director, Centre for Bayesian Statistics in Health Economics (CHEBS): JS has experience in the design, analysis and reporting of clinical trials and Bayesian methods in cost-effectiveness. JS will be involved in the protocol development and data analysis/synthesis of clinical evidence.

Angie Rees, Systematic Reviews Information Officer:
Protocol development, develop search strategy and undertake the electronic literature searches.

Gill Rooney, Project Administrator:
Retrieval of papers and help in preparing and formatting the report.

Prof. Paul Durrington, Professor of Medicine, Department of Medicine, University of Manchester, Manchester Royal Infirmary, Oxford Road, Manchester. M13 9WL
Protocol development (advisor), help interpret data, provide a methodological, policy and clinical perspective on data and review development of background information and clinical effectiveness.

Prof. Tim Reynolds, Consultant Chemical Pathologist, Queen's Hospital, Belvedere Rd, Burton-on-Trent, Staffordshire, DE13 0RB:
Protocol development (advisor), help interpret data, provide a methodological, policy and clinical perspective on data and review development of background information and clinical effectiveness.

Dr Anthony S. Wierzbicki, Consultant in Specialist Laboratory Medicine, Department of Chemical Pathology, St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH:
Protocol development (advisor), help interpret data, provide a methodological, policy and clinical perspective on data and review development of background information and clinical effectiveness.

8.0 **Competing interests of authors**

None of the authors (except John Stevens, see below) have financial interest in the companies who manufacture the drugs included in this review.

The School of Health and Related Research (ScHARR)
The School of Health and Related Research (ScHARR) including Abdullah Pandor helped prepare the industry submission for Sanofi-Synthelabo Ltd/Bristol-Myers Squib on clopidogrel for the prevention of atherothrombotic events to the National Institute for Clinical Excellence (NICE) between June 2002 and April 2003. A full appraisal determination (FAD) was produced by NICE in April 2004 and a resulting publication from the work in July 2005.

John Stevens
Holds personal shares in AstraZeneca

Prof. Paul Durrington

Until 2005 acted as an International Advisory Board member to Merck Sharp & Dohme/Schering Plough and advised the same companies nationally until the beginning of 2006. Received remuneration for advice. Resigned advisory roles to these and other companies when joined an advisory group to the Commission on Human Medicines earlier this year (2006). Thus had already done so when approached by ScHARR to assist in the current HTA project.

Dr Anthony Wierzbicki

Merck Sharp & Dohme	Advisory boards (national & international); speaker fees 2001-2
Pfizer	Advisory boards (national & international); speaker fees 2001-4
MSD/Schering-Plough	Advisory boards (national & international); speaker fees 2001-5
AstraZeneca	Advisory boards (national & international); speaker fees 2001-4

Prof. Tim Reynolds

Has received payment for lecturing from several pharmaceutical companies selling lipid lowering and other agents. These include (past 5 years): AstraZeneca, Bristol Myers Squibb, Merck,Merck Sharpe & Dohme, Novartis, Roche, Sanofi-Aventis. Also been funded for attendance at medical conferences by a variety of pharmaceutical and diagnostics companies, including Abbott Diagnostics, AstraZeneca, DPC, Roche. He does not hold any personal identifiable shares in pharmaceutical or diagnostics companies but there may be shares in such companies held in unit or investment Trusts or in endowment / unit-linked mortgage saving over which he has no direct control. In December 2007 he will be participating in an advisory board for MSD, and another for Solvay. He has also been involved in some advisory boards for AstraZeneca.

9.0 Timetable/milestones

Milestone	
Draft protocol	**24th December 2007**
Final protocol	**25th January 2008**
Draft assessment report	**26th May, 2008**
Assessment report	**30th June, 2008**

10. Appendices

Appendix 1: Draft Medline search strategy for RCTs

1	Coronary Disease/
2	Myocardial Infarction/
3	myocardial infarc$.tw.
4	Angina, Unstable/
5	unstable angina.tw.
6	angina unstable.tw.
7	acute coronary syndrome.tw.
8	Angioplasty, Transluminal, Percutaneous Coronary/
9	ptca.tw.
10	percutaneous transluminal coronary angioplasty.tw.
11	Coronary Artery Bypass/
12	cabg.tw.
13	coronary artery bypass graft.tw.
14	revascularisation.tw
15	revascularization.tw
16	or/1-15
17	Hydroxymethylglutaryl-CoA Reductase Inhibitors/
18	Anticholesteremic Agents/
19	statin$.tw.
20	Simvastatin/
21	simvastatin.tw.
22	atorvastatin.tw.
23	rosuvastatin.tw.
24	hmg$.tw.
25	co-a reductase inhibitor$.tw.
26	lipid lowering.tw.
27	randomized controlled trial.pt.
28	controlled clinical trial.pt.
29	randomized controlled trials/
30	random allocation/
31	double blind method/
32	single blind method/
33	clinical trial.pt.
34	exp clinical trials/
35	(clin$ adj25 trial$).ti,ab.
36	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
37	placebos/
38	placebos.ti,ab.
39	random.ti,ab.
40	research design/
41	or/27-40
42	or/17-26
43	16 and 42
44	43 and 41

Appendix 2: Example data extraction form

Study	Design	Duration	Numbers randomised	Population characteristics Disease status and time since event and type of event	Mean age, yrs (range) Gender (male/female)	Body mass index, Smoking, Socioeconomic status and Ethnicity	Intervention characteristics (statin/dose)	Outcomes Baseline LDL-c (sample number, mean, SD (or SE) 95% CI)	Mean % change in LDL-c from baseline (sample number, mean, SD (or SE), 95% CI) at time points reported	Adverse events As reported in studies and including any results on compliance
			T1: T2:		T1: T2:	T1: T2:	T1: T2:	T1: T2:	T1: @ t=1 @ t=2….t=n T2: @ t=1 @ t=2….t=n	T1: T2:

Appendix 3: Draft quality assessment tool

Allocation sequence (randomisation)	Allocation concealment	Blinding	Intention to treat analysis and loss to follow up	Overall assessment
A- Adequate sequence generation is reported (such as computer generated random numbers and random number tables, whilst inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week). B - Did not specify one of the adequate reported methods in (A) but mentioned randomisation method. C - Other methods of allocation that appear to be biased.	A - Adequate measures to conceal allocations. Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. B - Unclearly concealed trials, in which the authors either did not report an allocation concealment approach at all, or reported an approach that did not fall into one of the categories in A. C - Inadequately concealed trials, in which method of allocation is not concealed. Inadequate approaches will	A- Participants and investigators were blinded B – Unclear (blinding methods are unclear, only the participant is blinded) C- no blinding at all	A - Studies where an intention to treat analysis is possible and minor exclusions (with adequate reporting of these exclusions). B - Studies which reported exclusions as reported in (A), but exclusions were less than 10 percent. C - No reporting of exclusions; exclusions of 10 percent or more or wide differences in exclusions between groups	A – All criteria met, low risk of bias B- one or more criteria partly met, moderate risk of bias C- one or more criteria not met, high risk of bias

	include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque			

Appendix 4: Critical appraisal checklist for economic evaluations using key components of the British Medical Journal checklist for economic evaluations[22] together with the Eddy checklist on mathematical models employed in technology assessments.[21]

Reference ID		
Title		
Authors		
Year		
Modelling assessments should include:		**Yes/No**
1	A statement of the problem;	
2	A discussion of the need for modelling vs. alternative methodologies	
3	A description of the relevant factors and outcomes;	
4	A description of the model including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting. *Note: n=number of health states within sub-model*	
5	A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence;	
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships, and distributions) and the data;	
7	A list of parameter values that will be used for a base case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis;	
8	The results derived from applying the model for the base case;	
9	The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold.	
10	A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect;	
11	A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity.	
12	A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results;	
13	A description of research in progress that could yield new data that could alter the results of the analysis	

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