Protocol for a Prospective Collaborative Overview of All Current and Planned Randomized Trials of Cholesterol Treatment Regimens

Prepared by the Cholesterol Treatment Trialists' (CTT) Collaboration

The Cholesterol Treatment Trialists' Collaboration aims to provide reliable information about the effects on mortality and morbidity of treatments that modify blood lipid levels for a wide range of patient populations and risk groups. This protocol prospectively defines study eligibility, the main questions to be addressed, and statistical methods to be used. Additionally, by establishing a register of ongoing and planned trials prior to any trial results being known, this systematic overview attempts to avoid the methodologic problems and potential data-dependency of a retrospective project. The collaboration expects to have individual patient data on >60,000 subjects by the year 2000, including 12,000 women and 20,000 elderly subjects, and should have good power to examine any effects on non-coronary artery disease events. Overall, there should be about 1,900 non-coronary artery disease deaths and >2,000 total cancer events.

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There is general agreement that elevated blood cholesterol levels are an important cause of coronary artery disease (CAD), and therefore various cholesterol-lowering treatments have been devised and tested over the past few decades.[1–4] Previous randomized studies of these older cholesterol-lowering drugs or diet, taken together, have demonstrated clearly that within just a few years of reducing blood cholesterol, there are reductions in nonfatal acute myocardial infarction and fatal CAD.[5] More prolonged treatment, and treatments that produced larger cholesterol reductions, produced greater reductions in CAD. Some of these older trials were large, but the cholesterol reductions were too small (only about 10% on average), and there were too few CAD deaths (because many of the patients randomized were at low risk for death from CAD) to provide reliable direct evidence of the effect of cholesterol lowering on total mortality. Moreover, overall, the reduction in fatal CAD was offset by a slight excess (perhaps by chance[6]) of non-CAD mortality among patients in the cholesterol-lowering treatment groups. Thus, there remains substantial uncertainty—both in the medical profession and in the general population—about the overall survival benefits of lowering cholesterol.[7–9]

More recently developed cholesterol-lowering drugs, such as the hydroxymethylglutaryl coenzyme A reductase inhibitors (e.g., simvastatin, pravastatin, lovastatin, and fluvastatin) and the more potent fibrates (e.g., bezafibrate, ciprofibrate, fenofibrate), produce much larger reductions in total and low-density lipoprotein (LDL) cholesterol[10–12] than were seen in previous cholesterol-lowering trials. These drugs now provide an opportunity to assess directly the effects of lowering blood cholesterol on total and cause-specific mortality, and to determine which particular types of patients can expect worthwhile benefit. Although the cholesterol reductions achievable with the new drug regimens are large, it is unlikely that any of the current trials of these agents are large enough, on their own, to resolve all of the current uncertainties reliably.[13] Hence, a systematic overview (or meta-analysis)[14] of all current and planned randomized trials of treatments that modify blood lipid levels is planned as a collaboration among the principal investigators of these studies.

By reducing random errors and avoiding biases, systematic overviews of randomized trials can provide much more reliable information about the effects of a particular treatment strategy than any individual study. In addition to providing unequivocal evidence about the net effects of several years of treatment on total mortality, the present collaborative overview will provide uniquely reliable assessments of the separate effects of cholesterol lowering on CAD mortality and on specific non-cardiac causes of death. The overview should be of sufficient statistical power to assess reliably the separate effects on fatal and total (i.e., fatal and nonfatal) CAD among a number of special interest groups (e.g., those with different levels of CAD risk, women, the elderly, those with below average cholesterol levels, diabetics, those with a history of hypertension [Tables I and II[15–17]]), and to assess the magnitude of the effect with increasing time from the start of the intervention. The overview will also be able to assess the effects on other major morbid events (such as total stroke and intracerebral hemorrhage, need for vascular surgery, site-specific cancer), which will be particularly important because of concerns that have been expressed about possible hazards of various previous cholesterol-lowering treatments.[7,9,15,18]

Recent reports of observational epidemiologic studies support an independent role for low blood levels of high-density lipoprotein (HDL) cholesterol, and possibly for high triglycerides, in the development of CAD.[19,20]

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Several trials included in the collaboration have been specifically designed by their investigators to evaluate therapies that principally act to modify favorably the levels of these lipid fractions. Hence, in addition to providing important evidence about the effects of lowering total and LDL cholesterol, the effects of changes in the levels of HDL cholesterol and triglycerides will also be explored in this overview.

Controversy has arisen over the conclusions of previous overviews of trials of cholesterol-lowering, at least in part due to the varying definitions of the research questions to be addressed and of the studies eligible for inclusion.[5,9,15,18,21] For example, although one recent overview reported a reduction in total mortality in secondary prevention,[5] it is not agreed whether this effect, if real, is confined to the subgroup of patients at extremely high risk for further CAD.[15] Methodologic problems have included the retrospective and, therefore, potentially data-dependent definition of the research questions, of the criteria for study selection and of the treatments and patient groups under evaluation, the possibility of publication bias, and the failure to obtain reliable data on all randomized patients (to allow intention-to-treat analyses) and on all relevant outcomes. These problems can best be avoided by prospectively planning an overview based on individual patient data from all relevant randomized trials.[22,23] A prospective description of the research questions to be addressed, the criteria for study selection, and the actual trials to be included (based on a comprehensive registry of trials) can allow an unbiased assessment of the effects of treatment using standard groupings of patients and outcomes. Overviews based on individual patient data can provide more information than the more usual overviews of grouped data because they allow more detailed analyses (such as the effects of cholesterol-lowering in various categories of patients and survival analysis of clinical events).[24]

This protocol describes the planned conduct of the Cholesterol Treatment Trialists' (CTT) prospective collaborative overview of current and planned randomized trials of treatments that modify blood lipid levels. A unique feature of this overview is that the trials to be included are those for which results had not been reported at the time of finalizing the protocol, and so a number of a priori hypotheses can be specified in ignorance of the results of any of the contributing studies. This should help to avoid potentially unreliable data-dependent emphasis on particular subgroups.

METHODS

Study eligibility: Eligible studies are properly randomized trials in which the principal effect of at least one of the interventions being studied is the modification of blood lipid levels, and whose final results were not known at the time this protocol was agreed upon by the collaborative group (see Appendix). Trials are to be included only if they are "unconfounded" (i.e., the relevant treatment arms differ only with respect to the lipid intervention); thus, multiple risk-factor intervention studies are not to be included. The principal analyses will include only trials of ≥2 years' scheduled treatment duration which aim to recruit ≥1,000 patients.

Identification and registration of all randomized trials of cholesterol treatment: The secretariat of the Cholesterol Treatment Trialists' Collaboration (which is jointly based at the Medical Research Council/Imperial Cancer Research Fund Clinical Trial Service Unit in Oxford, United Kingdom, and the National Health and Medical Research Council Clinical Trials Centre in Sydney, Australia) will coordinate the collaboration. Potentially eligible studies are to be identified prospectively by a range of methods, including computer-aided literature searches, manual searches of journals, scrutiny of the reference lists of trials and review articles, scrutiny of abstracts and meeting proceedings, collaboration with the trial register of the International Committee on Thrombosis and Haemostasis, and by inquiry among colleagues, collaborators, and manufacturers of lipid-modifying agents. All unconfounded randomized trials of therapy to modify lipid levels (irrespective of the scheduled treatment duration) that aim to involve ≥500 patients are to be registered. For trials that involve ≥2 years' scheduled duration and aim to include ≥1,000 patients (Table I), a copy of the protocol and summary information describing the study will be sought. Newly identified studies will be included in the overview process, provided that they are registered before their results are known.

Data collection: Data will be sought from each trial at prospectively specified intervals (1996 to 1997 for trials reporting by 1997 [4S, Post-CABG, WOSCOPS, CARE, LIPID; full titles for these studies are listed in the Appendix] and 1998 to 2000 for trials reporting by 2000, and so forth). The date by which it is expected that mortality and major morbidity results will emerge from the studies will guide the timetable for seeking data from collaborators (Table I). Trial data submitted to the Cholesterol Treatment Trialists' secretariat will be held in strict confidence and will not be used in any publication without the permission of the responsible trialists. Particular care will be taken to ensure that the overview cycles of data collection and analysis do not compromise any of the individual trials, and data will not be sought from any trial before the principal manuscript for that trial has been accepted for publication.

Both individual patient and summary data will be sought, as both are important in ensuring the accuracy of the overview analyses.

INDIVIDUAL PATIENT DATA: Certain baseline characteristics recorded before randomization, details of the randomly allocated treatments, and any of the prospectively agreed outcomes occurring during the scheduled treatment period (i.e., intention-to-treat) are to be sought for each and every randomized patient (Table III). The data provided for patients in each trial will be checked carefully for internal consistency and completeness of individual patient records, for balance of group sizes overall and according to certain prognostic categories (for compatibility with the summary tabulations provided for each trial: see next paragraph), and for other indicators of possible anomalies. For missing values of lipid levels, the baseline value will be assumed in the primary analyses. All queries regarding particular trials will be referred back, in confidence, to the principal investigators of the trial, and computer-generated outputs con-

TABLE I Register of Current and Planned Randomized Trials of Cholesterol Treatment With Scheduled Treatment Period of ≥2 Years and Recruitment of ≥1,000 Patients

Study*	Expected Date of Results	Dates of Recruitment	Post-AMI Patients	Approx. No. of Patients	Age (yr)	Women (%)	Entry Lipid Criteria	Intervention (mg/day)	Expected Difference (%) TC	HDL	TG	Primary Study End Point	Approx. Number of Events All CAD	CM	Non-CM
4S	Nov. 1994	5/88–8/89	±	4,444	35–70	19	TC 5.5–8 mM	S 20/40	–23	+8	–16	TM	1,000	360	80
Post-CABG	1995	3/88–8/90	±	1,351	21–70	8	LDL 130–175 mg/dl	L 10/80	–24	+5	–10	Graft occlusion	300	150	25
WOSCOPS	Mid-1995	2/89–8/91	–	6,445	45–64	0	LDL 4–6 mM	P 40	–18	+7	–15	CM + AMI	400	100	80
CARE	March 1996	11/89–12/91	+	4,159	21–75	14	TC <240 mg/dl LDL 115–174 mg/dl	P 40	–20	+5	–15	CM + AMI	780	260	80
LIPID	1997	6/90–12/92	+	9,014	31–75	17	TC 4–7 mM	P 40	–18	+7	–15	CM	1,400	700	180
GISSI Prevention	1997	7/93–7/95	+	6,000	No limits	20	TC 200–250 mg/dl	P 20	–16	+5	–10	TM + AMI + CVA	1,000	500	120
AFCAPS/TEXCAPS	Feb. 1998	5/90–2/93	–	6,605	45–73 (or 55–73 if female)	15	TC 180–264 mg/dl HDL ≤45, TG ≤400 mg/dl LDL 130–190 mg/dl	L 20–40	–18	+5	–10	CM + AMI + new unstable angina	320	100	150
BIP	Jan. 1998	5/90–1/93	+	3,122	45–74	8	TC 180–250 mg/dl HDL ≤45, TG ≤300 mg/dl LDL ≤180 (≤160 if age <50)	B 400	–8	+25	–40	CM + AMI	435	180	120
HIT	Dec. 1998	9/91–12/93	+	2,500	<74	0	HDL ≤40 mg/dl LDL ≤140, TG ≤300 mg/dl	G 1,200	–6	+10	–30	CM + AMI	670	250	55
HPS	2000	7/94–7/96	±	20,000	40–75	30	TC >3.5 mM	S 40	–25	+9	–19	TM	3,000	1,500	1,000
ALLHAT	2002	2/94–7/96	±	20,000	60+	45	LDL 120–190 mg/dl (or 100–160 if CAD) TG <350 mg/dl	Statin	–20	+5	–10	TM	1,900	1,100	1,600
WHI	2007	9/93–8/97	–	48,000	50–79	100	Nil	20% cal. as fat	–6	–5	+10	CM + AMI	2,100	1,400	2,000

*The full title of each study is listed in the Appendix.
All CAD = acute (fatal and nonfatal) coronary artery disease events (i.e., in most instances coronary artery disease mortality plus acute myocardial infarction, although definitions may vary and may also include other coronary artery disease events); AMI = acute myocardial infarction; Approx. = approximate; B = bezafibrate; cal. = calories; CM = coronary artery disease mortality; CVA = stroke; G = gemfibrozil; HDL = high-density lipoprotein; L = lovastatin; LDL = low-density lipoprotein; Non-CM = non–coronary artery disease mortality; P = pravastatin; S = simvastatin; TC = total cholesterol; TG = triglycerides; TM = total mortality; + (under Post-AMI Patients) = all, or almost all, are patients who have had myocardial infarction; ± (under Post-AMI Patients) = patients with and without a history of acute myocardial infarction; – (under Post-AMI Patients) = none or only a few have had myocardial infarction.

sisting of detailed summary tabulations, and consistency checks based on the data provided to the secretariat will be returned to each collaborator for review and confirmation. This process should help to ensure that the individual study results are incorporated correctly into the overview and, hence, that the overview analyses are reliable.

SUMMARY DATA: For each contributing trial, details will also be sought as to the number of patients allocated to each treatment group, the numbers who developed each of the prospectively defined outcomes, and the absolute differences in total, LDL, and HDL cholesterol, triglycerides, and apolipoprotein B between the treatment and control groups at, or just after, the end of each year of follow-up (or at such intervals as are conveniently available). These data will be checked for consistency with any published reports and with the individual patient data provided.

Main and subsidiary hypotheses to be addressed: Table II lists the expected numbers of patients and events in currently registered trials. All comparisons will be of outcome during the scheduled treatment period among all those allocated to the lipid treatment group versus all those allocated to the control group (i.e., intention-to-treat comparisons). The main questions to be addressed will be the effects of lowering cholesterol on: (1) total mortality, (2) CAD mortality (ICD 410-414 in the 9th revision of the *International Classification of Disease*), and (3) non-CAD mortality (all other causes).

In addition, there will be separate analyses of specific non-CAD causes of death: hemorrhagic stroke (ICD 430-432); other stroke (433-438); other vascular (rest of 390-459); neoplastic (140-239); respiratory (460-519); hepatic (570-576); renal (580-593); other medical causes; suicide (950-959); accidental death, homicide, and other non-medical causes. There will be an allowance for multiple hypothesis testing in the analyses of these non-CAD causes of death.

While it is regarded that the principal effect of many cholesterol treatments is likely to be through reduction in cholesterol levels (particularly LDL cholesterol), it is recognized that other changes in lipid fractions and drug-specific non-lipid effects may be relevant to changes in outcome. For this reason, the effects of: (1) different class-

TABLE II Approximate Total Numbers of Patients and Events Expected in Current and Planned Studies

	Expected by the Year 2000	For All Studies
Total no. of patients	64,400	132,400
Prior AMI	34,600	38,400
No prior AMI	29,800	94,000
Diabetic	12,000	12,000
Statins	58,800	78,800
Fibrates	5,600	5,600
Diet alone	0	48,000
Men	52,900	62,900
Women	11,500	69,500
≥65 years	20,200	56,000
<65 years	44,200	76,400
TC <5.2 mM (<200 mg/dl)	10,500	19,500
TC <6.5 mM (<250 mg/dl)	38,000	84,000
Low HDL cholesterol	12,200	12,200
Total no. of events		
All-cause mortality	6,600	12,650
CAD mortality	4,700	7,150
Non-CAD mortality	1,900	5,500
Fatal and nonfatal CAD	9,300	13,300
Fatal and nonfatal cancer	2,200	4,200

Abbreviations as in Table I.

TABLE III Information Sought for Each Randomized Patient

Data recorded before randomization
Sex; race; age; history of hypertension, diabetes mellitus, or arterial disease; smoking; alcohol; lipid profile (total, LDL, and HDL cholesterol, apolipoprotein B and triglyceride); blood pressure; height; weight

Follow-up information
Vital status; myocardial infarction; stroke; angina leading to hospitalization; vascular procedures; cancer; reasons for stopping study treatment; lipid profile at end of year 1 and end of trial

Abbreviations as in Table I.

es of treatments (statins, fibrates, dietary interventions) on the above-mentioned outcomes will be examined separately in order to estimate the effects within each group, and to examine consistency of effects across groups; and (2) changes in different lipid fractions (e.g., LDL cholesterol decrease, HDL cholesterol increase, and triglyceride decrease) on CAD will be explored in a subsidiary analysis (see later).

The principal subsidiary questions to be addressed will be the effects of lipid-treatment allocation on: (1) rates of total CAD (defined as nonfatal acute myocardial infarction or fatal CAD), for as many years as the available data are reasonably informative (using survival analysis methods); (2) fatal CAD and total CAD in each of the following groups of special interest (as defined by each study protocol): (a) separate categories of prior disease ("secondary prevention" [post–acute myocardial infarction]; other evidence of occlusive CAD [e.g., angina pectoris, percutaneous transluminal angioplasty, coronary artery bypass graft surgery]; peripheral vascular disease of non-coronary arteries [e.g., transient ischemic attack, stroke, peripheral vascular disease]; "primary prevention" [no evidence of occlusive disease]; hypertension; diabetes mellitus); (b) various categories of patients (men and women; aged >65 and ≤65 years at entry; diastolic blood pressure >90 and ≤90 mm Hg at entry; baseline total cholesterol ≤5.2, >5.2 but ≤6.5, and >6.5 mmol/L; LDL cholesterol ≤3.5, >3.5 but ≤4.5, and >4.5 mmol/L; tertiles of HDL and of triglycerides; and current smokers at baseline versus others); blood pressure and lipid level analyses will also be performed using these as continuous variables; and (c) separate categories of different treatments (statins, fibrates, and dietary intervention), with consideration of the relative contributions of changes in LDL and HDL cholesterol and triglyceride levels.

Subsidiary comparisons will also be made of the effects of cholesterol-lowering on the incidence of (1) site-specific cancers, (2) total strokes, (3) any hospital admission for angina, (4) vascular procedures, and (5) confirmed cerebral hemorrhages. In addition to any retrospective analyses carried out on other subsidiary questions, there will be an opportunity to define additional questions prospectively by examining them only in the subset of trials that are ongoing with blinded results. Such prospective questions would be formally added to an updated protocol at a recorded time.

Statistical analyses: The medical principles that underlie an overview of randomized trials and the statistical methods have been described previously,[25–27] and are therefore only briefly summarized here. The "assumption-free" Mantel-Haenszel method for combining data from different studies will be used,[27] with the "observed minus expected" values from each trial given weights that are proportional to the absolute LDL cholesterol difference (treatment vs control) at, or just after, the end of the first year of follow-up. (Subsidiary analyses, based on weighting of values by LDL and HDL cholesterol and triglyceride differences, will also be conducted [see later].) In most of the trials that are to be analyzed as part of the overview, results on particular outcomes of interest (e.g., death) are likely to be available separately for each year after randomization. For each trial this means that a separate value can be calculated for each year of follow-up, and the sum of these separate values can be used to yield the log-rank test statistic for a year of event analysis of that trial. Separate log-rank test statistics for each trial can then be combined to produce an overview analysis of all trials. The chief advantage of the availability of information from each separate year is not that log-rank analyses are more sensitive than crude analyses—since the improvement in sensitivity is only small in trials in which most patients do not have the outcome of interest (as is anticipated for trials of lipid treatment included in this overview). It is that log-rank analyses readily permit assessment of the effects of treatment in each separate year, which should help to determine the speed with which treatment has its effect on particular outcomes. Similarly, stratified analyses combining the results from separate trials within various patient subgroups will allow questions about whom to treat to be addressed directly. The relative contribution of changes in LDL cholesterol, HDL cholesterol, and triglycerides on CAD will be determined in a regression model based on study-specific lipid changes by size (absolute reduction) and duration. In interpreting subgroup results, emphasis will be placed on the overall

results, unless there is good evidence of heterogeneity.[24–27]

Publication policy: The preparation of this manuscript and its contents were agreed upon at the American Heart Association meeting in Dallas, Texas in November 1994 before presentation of the results of the Scandinavian Simvastatin Survival Study (4S). The 4S investigators were required to make final contributions before their unblinding to the 4S results. Any report of overview results will be published in the names of all collaborating trialists, and will be circulated to the collaborators for comments and approval before submission for publication. A complete protocol for the collaboration, in more detail than is possible to publish, is available from the secretariat.

Administration and funding: All data management for the overview will be jointly coordinated by a secretariat based at the Medical Research Council/Imperial Cancer Research Fund Clinical Trial Service Unit, Oxford, United Kingdom, and the National Health and Medical Research Council Clinical Trials Centre, Sydney, Australia. All collaborating trialists retain the right to withdraw their data from some or all of the overview analyses.

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APPENDIX

Current Membership of the Cholesterol Treatment Trialists' Collaboration:
STUDY INSTITUTES AND INVESTIGATORS: AFCAPS/TEXCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study): J.R. Downs, A. Gotto, M. Clearfield; ALLHAT (Antihypertensive Lipid Lowering Heart Attack Trial): D. Gordon, T. Manolio; BIP (Bezafibrate Infarction Prevention Study): U. Goldbourt, E. Kaplinsky; CARE (Cholesterol and Recurrent Events Study): L. Moyé, F. Sacks, M. Pfeffer, C.M. Hawkins, E. Braunwald; GISSI Prevention (Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto miocardico): M.G. Franzosi, A. Maggioni, G. Tognoni; HIT (Veterans Administration Low-HDL Intervention Trial): S. Robins, H. Rubins; LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease): J. Simes (secretariat), A Keech (secretariat), S. MacMahon, A. Tonkin; McMaster University, Canada: S. Yusuf, M. Flather; Medical Research Council/British Heart Foundation HPS (Heart Protection Study): R. Collins (secretariat), A. Keech, J. Armitage, C. Baigent (secretariat), R. Peto, P. Sleight; Post-CABG (Post-Coronary Artery Bypass Graft Study): G. Knatterud; 4S (Scandinavian Simvastatin Survival Study): J. Kjekshus, T. Pedersen, L. Wilhelmsen; WHI (Women's Health Initiative): J. Roussouw, J. Probstfield; WOSCOPS (West Of Scotland Coronary Prevention Study): S. Cobbe, P. Macfarlane, J. Shepherd.
OBSERVERS (AFFILIATION AND PERSONNEL): Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey, USA: M. Mellies, M. McGovern; Commonwealth Serum Laboratories, Melbourne, Australia: J. Varigos; Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey, USA: J. Tobert, J. Shaw.

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