Data Analysis Plan: Main and subsidiary assessments of outcome in the MRC/BHF Heart Protection Study

(updated September 2001)

PRIMARY (MAIN) COMPARISONS

Reductase inhibitor therapy: the primary comparisons will involve "logrank" analyses of **total mortality** and of **cause-specific mortality** during the scheduled treatment period among all those allocated active-simvastatin versus all those allocated placebo-simvastatin (i.e. "intention-to-treat" analyses)[1,2]. The two main cause-specific analyses will be of (a) CHD mortality (ICD 410-414 in the 9th International Classification of Diseases), and (b) non-CHD mortality.

Antioxidant vitamin supplementation: the primary comparisons will involve "logrank" analyses of **total CHD** and of **fatal CHD** during the scheduled treatment period among all those allocated active-vitamins versus all those allocated placebo-vitamins. (N.B. Total CHD is defined as definite/probable* non-fatal MI or fatal CHD.)

All time-to-event analyses will be based on the first relevant event. No allowance will be made for multiple hypothesis testing in the primary comparisons of each of the study treatments. Conventionally, in the final analyses of primary comparisons, two-sided P-values (2P) <0.05 are often described as "significant". But, in interpreting such findings it is necessary to consider whether they are supported by evidence on relevant non-fatal events. Moreover, the larger the number of events on which a comparison is based and the more extreme the P-value (or, analogously, the further the lower limit of the confidence interval is from zero), the more reliable the comparison and, hence, the more definite any finding[1,2].

SECONDARY COMPARISONS

Separate analyses of the effects of simvastatin allocation on ten specific causes, or groups of causes, of death: (i) haemorrhagic stroke (including intracerebral and subarachnoid haemorrhage: ICD 430-432); (ii) other stroke (including ischaemic and uncertain aetiology: 433-438); (iii) other vascular (rest of 390-459); (iv) neoplastic (140-239); (v) respiratory (460-519); (vi) hepatic (570-576); (vii) renal (580-593); (viii) other medical causes (rest of 000-799: including definitely unknown causes); (ix) suicide (950-959); and (x) other non-medical causes. In interpreting these results, allowance will be made for the multiple hypothesis testing in these ten analyses, for the effects observed on relevant non-fatal events, and for evidence from other studies.

The effects of simvastatin allocation and of vitamin allocation on: (i) total CHD rates in the first two years and in the later years of scheduled treatment to see if any protective effect increases with time (i.e. comparison of effect during years 1-2 with that during years 3+); (ii) cause-specific mortality rates (i.e. deaths from CHD and deaths from non-CHD, as defined above) not only during the scheduled treatment period but in long-term follow-up thereafter, to see if any benefits or hazards persist; and (iii) total (i.e. fatal and non-fatal) stroke and, separately**, presumed ischaemic stroke (i.e. all strokes not confirmed to be haemorrhagic) during the scheduled treatment period.

The effects of simvastatin allocation and of vitamin allocation on total CHD, and on "major vascular events" (defined as total CHD, total stroke and coronary or non-coronary vascular procedures), in the following different circumstances:

(i) in different categories of prior disease: MI; other CHD; and no CHD (cerebrovascular; peripheral vascular; diabetes mellitus; treated hypertension: considered together and separately)*;

(ii) in various other categories determined at Screening:

(a) men and women;

(b) age (years): <65; ≥65<70; ≥70*

(c) diastolic blood pressure (mmHg): <80; ≥80<90; ≥90*

(d) systolic blood pressure (mmHg): <140; ≥140<160; ≥160*

(e) total cholesterol (mmol/l): <5.0; ≥5.0<6.0; ≥6.0*

(f) HDL-cholesterol (mmol/l): <0.9; ≥0.9<1.1; ≥1.1*

(g) LDL-cholesterol (mmol/l): <3.0; ≥3.0<3.5; ≥3.5* (and, as a tertiary comparison, <100; ≥100<130; ≥130 mg/dl will also be considered**)

(h) apolipoprotein A_1 (mg/dl): <110; ≥110<130; ≥130**

(i) apolipoprotein B (mg/dl): <100; ≥100<120; ≥120**

(j) triglycerides: <2.0; ≥2.0<4.0; ≥4.0**

(k) creatinine (µmol/l): "normal" (<130 men; <110 women); "elevated"

(l) smoking: never regular smoker; ex-cigarette smoker; current smoker*

(m) alcohol (drinks/week): none; 1-21; ≥22**

(n) body mass index (kg/m^2): "lean" (<25 male / <24 female); "overweight" (≥25<30 male / ≥24<28 female); "obese" (≥30 male / ≥28 female)**

(o) waist (cm): "normal" (<94 male / <80 female); "increased" (≥94<102 male / ≥80<88 female); "excessive" (≥102 male / ≥88 female)**

(p) non-diabetic patients with and without the "metabolic syndrome" (defined as "excessive" waist measurement, plus HDL ≤1.0 mmol/l for men or ≤1.3 mmol/l for women, plus SBP ≥135 mmHg or DBP ≥85 mmHg).

(q) HbA_{1C} (%) among patients with diabetes: <7.0; ≥7.0

(r) vitamin E (µmol/l): <24; ≥24<30; ≥30*+

(s) vitamin C (µmol/l): <40; ≥40<60; ≥60*+

(t) beta-carotene (µmol/l): <0.24; ≥0.24<0.40; ≥0.40*+

(iii) in the presence and the absence of the other study treatment; and

(iv) among patients subdivided into 3 similar-sized groups with respect to the size of the reduction in blood cholesterol and the size of the increase in vitamin levels+, respectively, during the pre-randomisation Run-in period.

The very large numbers of patients in this trial may allow reasonably reliable **direct** assessment of the effects of the treatments on common outcomes in some major subcategories of patient. But, when a number of different subgroups are considered, chance alone may lead to there being no apparent effect in several small subgroups in which treatment really is effective. In such circumstances, "lack of direct evidence of benefit" is not good "evidence of lack of benefit", and clearly significant overall results would provide strong indirect evidence of benefit in some small subgroups where the results, considered in isolation, are not conventionally significant (or even, perhaps, slightly adverse). Hence, unless the proportional effect of treatment in some specific subcategory is clearly different from that observed overall (including, for example, in the presence and absence of the other study treatment), the effect in that subcategory is likely to be best estimated **indirectly** by applying the proportional effect observed among all patients in the trial to the absolute risk of the event observed among control patients in that category[3]. Tests for heterogeneity of the proportional effect observed in subgroups will be used (with allowance for multiple comparisons) to determine whether the effects in specific subcategories are clearly different from the overall effect[1,2]. If, however, patient categories can be arranged in some meaningful order (e.g. baseline total cholesterol: <5.0; ≥5.0<6.0; ≥6.0*) then assessment of any trend in the proportional effects would be made. Moreover, based on the differences in LDL-cholesterol observed during follow-up between all those allocated active-simvastatin and all those allocated placebo-simvastatin (i.e. irrespective of compliance), LDL-weighted analyses will be used to estimate the effects of actual compliance with simvastatin on total CHD in different circumstances (as well as the overall effects on fatal CHD, on total stroke and on other relevant outcomes)[4].

TERTIARY COMPARISONS

The effects of simvastatin allocation and of vitamin allocation on fatal CHD and on total stroke will be assessed separately during years 1-2 and years 3+ of follow-up, and in the different circumstances described under paragraphs (i) to (iv) of the Secondary Comparisons section**. These results will be interpreted in the context of the results of the parallel analyses of total CHD, with allowance made for multiple hypothesis testing. The effects of simvastatin allocation on total non-CHD mortality will also be assessed separately in the three pre-defined groups of baseline total cholesterol*.

In addition, the tertiary comparisons will include assessment of the effects of simvastatin allocation and of vitamin allocation on:

(i) site-specific cancers;

(ii) confirmed cerebral haemorrhage (excluding subarachnoid haemorrhage); and, separately**, subarachnoid haemorrhage;

(iii) coronary vascular procedures (i.e. CABG, PTCA); and non-coronary vascular procedures (i.e. carotid endarterectomy or angioplasty, other arterial grafts or angioplasty and amputation)*;

(iv) hospitalisations for angina; hospitalisations for respiratory disease; and hospitalisations for gallbladder disease (e.g. gallstones, cholecystectomy, biliary surgery) other than cancer*;

(v) days spent in hospital for: (a) any CHD event; (b) other vascular events; and (c) the aggregate of all other reasons**;

(vi) fractures of any kind; and fractures of hip, wrist or spine combined (excluding, in both cases, those due to road traffic accidents)**;

(vii) cognitive function: based on difference at final follow-up in TICS-m score, with cognitive impairment defined as <22 out of 39, among (a) all patients; and (b) those who have never had a stroke**;

(viii) respiratory function: based on difference at final follow-up in (a) forced expiratory volume in 1 second (FEV_1), and (b) forced vital capacity (FVC)**;

(ix) among diabetics at study entry, peripheral macrovascular complications (defined as lower limb amputation plus peripheral arterial revascularisation procedure plus leg ulcers).

(x) development of diabetes: based on reported diabetes and/or use of insulin or oral hypoglycaemic drugs by final follow-up among patients not known to be diabetic at baseline**;

(xi) angina severity: based on the change in angina score between baseline and final follow-up**.

Among a sample of the diabetics, the effects of simvastatin on changes from baseline of HbA_{1C} and of creatinine will be assessed. Many other analyses will be performed and presented (e.g. hospitalisations for various different causes), with due allowance for their exploratory (and, perhaps, data-dependent) nature.

1 Peto R, Pike MC, Armitage P et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part I: Introduction and design. Br J Cancer 1976; 34: 585-612

2 Peto R, Pike MC, Armitage P et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part II: Analysis and examples. Br J Cancer 1977; 35: 1-39

3 Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. Lancet 2001; 357: 373-80

4 Cuzick J, Edwards R, Segnan N. Adjusting for non-compliance and contamination in randomized clinical trials. Stat Med 1997; 16: 1017-29

Modifications/clarifications* or additions** to previously pre-specified analyses agreed, blind to treatment-related results, following discussions at the March 2001 Steering Committee meeting. Pre-specified analyses within categories determined by baseline vitamin levels+ are intended for assessment of the effects of vitamin allocation (and not for those of simvastatin allocation).