Heart Protection Study Protocol Addendum

Date: 12 November 2025

Version: HPS/P/2/0894/ADD121125

Ethics Ref: 19/SC/0262 (South Central – Oxford B Research Ethics Committee)

IRAS number: 262231

Addendum, dated 12 November 2025, version HPS/P/2/0894/ADD121125, is to provide minor clarifications for the MRC/BHF Heart Protection Study Long-term Follow-up

Study title: Heart Protection Study. A randomised study of the effects on mortality and morbidity of HMG CoA reductase inhibitors and of antioxidant vitamins in a wide range of people at high risk of coronary heart disease.

Addendum applies to study protocol version: HPS/P/2/0894

Background: Between 1994 and 2001, 20,536 people at increased vascular risk were randomly allocated 40 mg simvastatin daily or placebo for around 5 years. During this 5 year "in-trial" period, allocation to statin therapy yielded an average reduction in LDL cholesterol of 1.0 mmol/L, which reduced the risk of major vascular events by around one quarter.

To assess the long-term effects of a substantial reduction in LDL-cholesterol sustained for 5-years, all surviving HPS participants were followed up for around 6-years after the end of the randomised phase of the trial. Non-fatal events and statin use were reported by participants (or their GPs) in annual questionnaires, supplemented with cause specific mortality and site-specific cancer incidence via central registries. Response rates to these annual questionnaires were high (~80%) with participants giving assent to receive another questionnaire in each following year.

Prolonged post-trial follow-up of participants in HPS showed that the substantial reductions in vascular mortality and morbidity associated with a 1.0 mmol/L reduction in LDL-cholesterol during the 5-year "in-trial" period persisted largely unchanged during the 6-year "post-trial" period, when statin use was similar in both groups. Reassuringly, there was no evidence that any adverse effect on particular causes of non-vascular mortality or major morbidity (including site-specific cancers) was emerging during this prolonged follow-up period. These findings support the prompt initiation and long-term continuation of statin therapy in people at increased vascular risk and were reported in a leading scientific journal (see Lancet paper: Appendix i) and the popular press and media.

Whilst direct contact with HPS participants and their GPs stopped in 2007, long-term follow-up of the study population continued via linkage to national registries (i.e., cause specific mortality and cancer) and using routinely collected electronic health records, and we aim to continue this indirect long-term follow-up until the last HPS participant dies**.**

Aims: Whilst the available randomised evidence shows that lipid-lowering therapy with statins is safe and effective, concerns persist amongst the public about their long-term safety, limiting compliance and exposing patients to potential harm. Continued remote follow-up of HPS participants via central registries and routine health records will provide uniquely reliable evidence about the long-term safety of lipid-lowering therapy, and is of importance to the many millions of patients in whom statins are indicated and their doctors who prescribe them. Considering efficacy, it is unlikely that extended follow-up will change the existing evidence of a substantial reduction in heart attacks and strokes associated with allocation to statin therapy. However, the effect of statin therapy on dementia is less clear. Allocation to lipid-lowering therapy had no apparent effect on cognitive impairment during the randomised phase of HPS, but dementia has an extremely insidious onset, and consequently, any beneficial effect may take several decades to emerge. However, if statin therapy were shown to reduce dementia risk, this finding would have a significant impact on population health worldwide.

Methods

The following outcomes will be measured in linked electronic health data: all major cardiovascular disorders (e.g., heart attacks, strokes, revascularisation procedures; heart failure and amputations); dementia; myopathies; renal impairment; incident site specific cancer and cause specific mortality. UK participants will be linked with the following datasets:

1. NHS England*: Hospital Episode Statistics (HES) Admitted Patient Care, Mental Health datasets, Cancer Registrations, Demographics, and Civil Registrations of Death
2. Digital Health and Care Wales (DHCW): Patient Episode Database Wales (PEDW) Admitted Patient Care.
3. Secure Anonymised Information Linkage Databank (SAIL): Welsh cancer datasets
4. Public Health Scotland (PHS): Scottish Morbidity Records (Inpatients, Cancers, Mental Health) and National Records of Scotland (NRS) deaths*.
5. Existing data within Heart Protection Study systems and records.

* Note that some historical Scottish deaths and cancers data were previously provided via NHS England's precursors, e.g. HSCIC. This data is now under the control of the NHS Central Register (NHSCR, National Records of Scotland).

Details of data management procedures and data flow shown in Appendix ii.

Statistical Analyses

The main comparisons involve logrank analyses of the first post-randomisation occurrence of particular events during the in-trial period (defined as events occurring up to 11 November 2001) and during the post-trial period (defined as events occurring after 11 November 2001) among all those originally allocated 40 mg simvastatin or antioxidant vitamin supplements daily versus all those allocated matching placebo tablets (i.e. “intention-to-treat” analyses).

The primary outcome for the analyses of long-term follow-up are pre-specified to be the first post-randomisation major vascular event (MVE: defined as non-fatal myocardial infarction or coronary death, fatal or non-fatal stroke, coronary or non-coronary revascularisation).

Secondary comparisons are to be of the effects of the randomly allocated treatment on major coronary events (MCE: non-fatal myocardial infarction or coronary death), strokes, and revascularisations separately; on deaths from vascular and non-vascular causes separately; on cancers at all sites (excluding non-melanoma skin cancer); and on MVEs during each separate year of follow-up and in various subcategories of patients (as pre-specified in the Data Analysis Plan for the in-trial period: Appendix iii).

Other objectives are to assess the effects of allocated study treatment on other major adverse outcomes (e.g. dementia; site-specific cancer; cerebral haemorrhage, hospitalisation for angina and for various other causes) during prolonged follow-up, both overall and during each separate year of follow-up. Allowance for multiple comparisons and for the post-hoc nature of such analyses will be made in the interpretation of the observed results.

Finally, given the size of the HPS population, their elevated vascular risk and duration of follow-up, these data will provide a unique opportunity to explore associations between various established and novel cardio-vascular risk factors and the risk of developing diseases (such as dementia and heart failure) that have an insidious time course.

Appendix i:

HPS Long-Term Follow-Up Lancet Paper

Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial.
Heart Protection Study Collaborative Group
2011 Lancet, 378(9808), 2013-2020
http://doi.org/10.1016/S0140-6736(11)61125-2

Appendix ii:

Data Management

All data will be transferred, handled and processed in agreement with the NHS England Data Sharing Framework Contract, (or other formal Data Sharing/Access Agreement for Scotland and Wales), and will be subject to Fair Processing requirements.

NHS Data Custodians undertake the linkage between the HPS trial participants and the datasets that they hold. Data will be received by Oxford in an encrypted format via an approved transfer method. Received data will then be linked with data already held (at NDPH) for HPS participants. See Appendix ii Data Flow Diagrams for details.

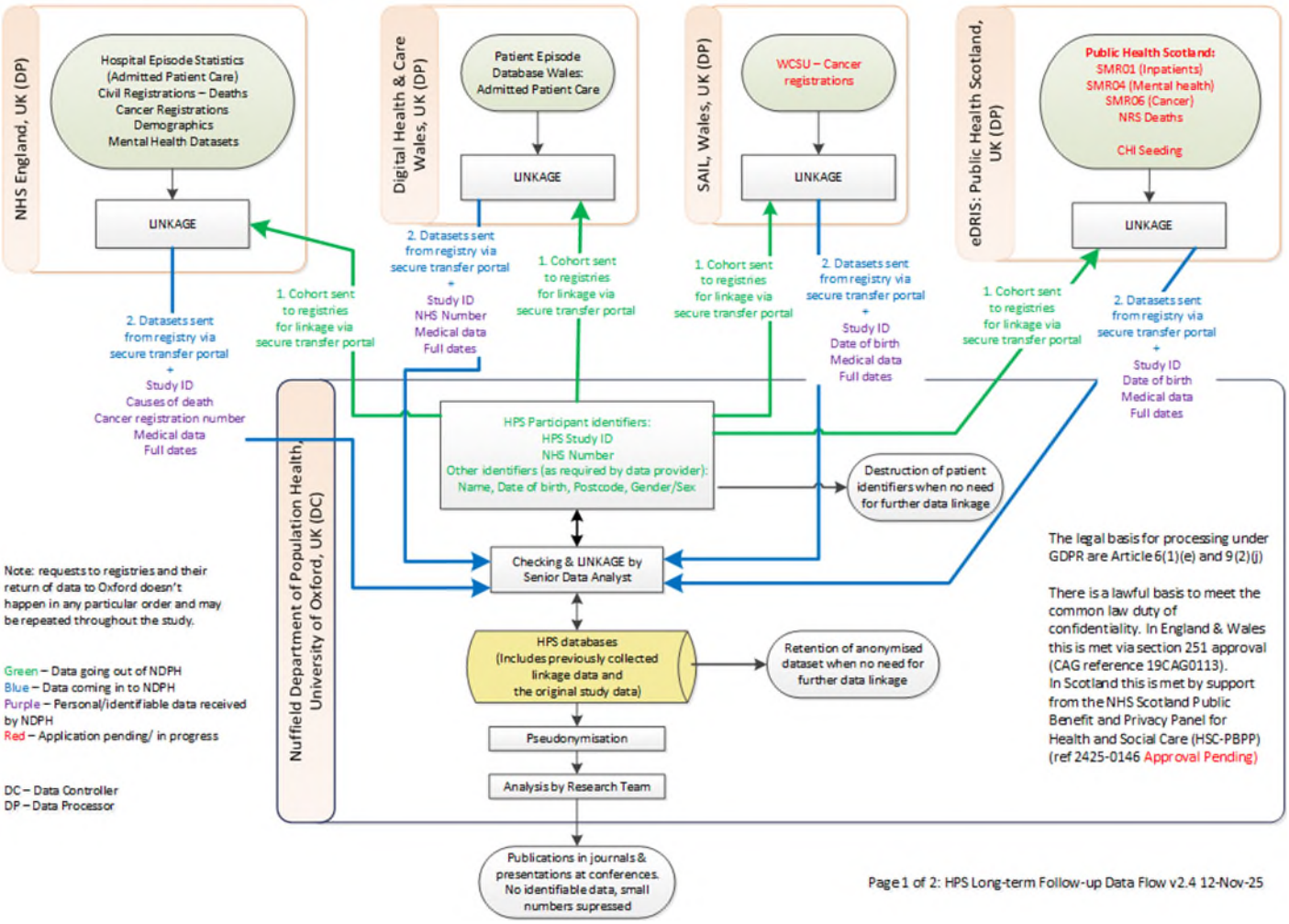
The data will be stored at the Nuffield Department of Population Health (NDPH), Richard Doll Building and the Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, Old Road Campus, University of Oxford. Any NDPH researchers involved will have appropriate training in information governance and in handling confidential and participant sensitive data.

The NDPH servers are protected against unauthorised external access by an appropriate strength firewall. Access to patient identifiable information is protected by the appropriate authentication procedures (user IDs and passwords). Authentication is only given to personnel with an approved need, and authorisation, to access the required data. Only personnel involved in the long-term follow-up study for HPS (processing and analysing data) will have authorised access to this data. Data processing will take place in-line with the NDPH Information Governance Security Policies and Procedures. The University of Oxford ICO data protection Registration Number is Z575783X. All HPS data is held within an NDPH NHS Data Security & Protection (DSP) Toolkit compliant environment with Standards Met (Organisation code: EE133863-MSD-NDOPH-NDPH).

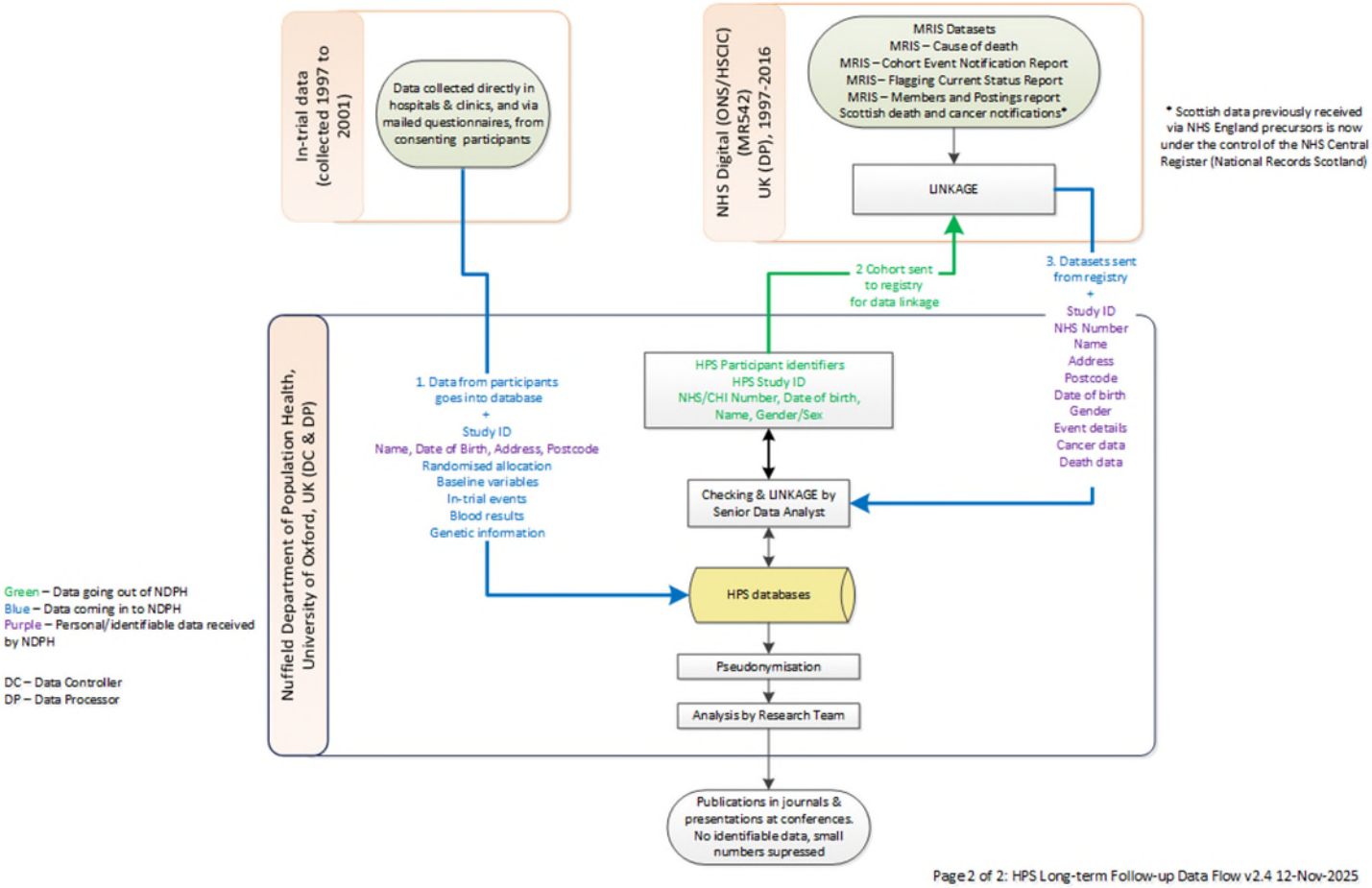
De-identified datasets will be kept indefinitely to provide: an audit trail for published findings, ability to respond to regulatory requests for further information and for further analysis.

Data Flow Diagrams

(1) HPS Data Flow Diagram – Data requested from 2022 onwards



(2) HPS Data Flow Diagram – Data previously received (1997 to 2016)



Page 2 of 2: HPS Long-term Follow-up Data Flow v2.4 12-Nov-2025

Appendix iii: 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).

Appendix iv: Protocol HPS/P/2/0894

HPS/P/2/0894: Original Protocol (1994)

See separate document

HPS/P/2/0894/ADD010519: Addendum (2019)

See separate document

HPS/P/2/0894/ADD100821: Addendum (2021)

See separate document

Appendix v: Amendment History

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
01	ADD010519	01-May-19		Inclusion of genomic and relevant blood-based analytic studies of cardiovascular disease using existing blood samples donated from MRC/BHF Heart Protection Study (HPS) participants.
02	ADD100821	10-Aug-21	Richard Bulbulia	Inclusion of long-term routine healthcare and registry data to the existing MRC/BHF Heart Protection Study (HPS) database.
03	ADD121125	12-Nov-25	Michelle Nunn Richard Bulbulia	• Change of Chief Investigator from Rory Collins to Louise Bowman • Change of Principal Investigator from Rory Collins to Richard Bulbulia • Protocol has been updated to reflect more recent information about the long-term follow-up work. This includes: o Update of datasets being used for linkage o Use of 'NHS Data Custodians' as collective term for Data Providers o Correction of names of providers e.g. NHS Digital

				is now NHS England, Information and Services Division Scotland is now Public Health Scotland, and removal of Northern Ireland. o Addition of SAIL as a data provider o Addition of the Big Data institute as data storage location o Update to Data Flow Diagram to include correct provider names and addition of SAIL.