PROTOCOL FOR NIHR HEALTH TECHNOLOGY ASSESSMENT 17/140/02

1. Full Title of Project

COST-EFFECTIVENESS OF STATIN THERAPIES EVALUATED USING INDIVIDUAL PARTICIPANT DATA FROM LARGE RANDOMISED CLINICAL TRIALS

2. Background and Rationale

Large randomised clinical trials have repeatedly reported that statin therapy reduces the risk of heart attacks, strokes and vascular mortality in different categories of patients. Since the 1990s, the Cholesterol Treatment Trialists' (CTT) Collaboration has coordinated a prospective meta-analysis of all large statin trials (1). This work has reliably demonstrated that statins produce similar proportional reductions of about a quarter in cardiovascular disease (CVD) risk per 1 mmol/L reduction in LDL cholesterol in a wide range of people (eg, men and women; older and younger; primary and secondary prevention; patients with high and low CVD risk, patients with diabetes or non-dialysis dependent CKD), and that further reductions in LDL cholesterol with more intensive statin therapy produce further reductions in CVD incidence (2-8).

There is some controversy, however, over the size of net benefits for individuals at low CVD risk, and in the elderly, and there are concerns about the safety of statins. Many of the safety concerns originate from non-randomised studies(9, 10) and may be unreliable (11). Nevertheless, in randomised trials, standard statin dose regimens have been associated with a proportional increase of about 10% in incident diabetes(12), and more intensive statin regimens with about a 10% further increase(13). Such adverse effects should be considered in evaluating the net effects of statins particularly in people at low CVD risk. Statins are now cheap(14) and the direct costs to the NHS are less of a concern, but the efforts required to initiate and support people on treatment should not be understated. The latest cardiovascular disease prevention NICE Clinical Guideline 181(15) recommends medium intensity statins for people with 10% or greater 10‑year risk of developing CVD and for those with diabetes, and high intensity statins for people with pre-existing CVD. The NICE guidance affects a large section of the population (about 37% of 30-84 year olds(16)) and unreliable cost-effectiveness results could lead to people who do not derive worthwhile health benefit being recommended for treatment and, conversely, people who could derive worthwhile benefit not being recommended for statin treatment or recommended suboptimal treatment intensity. Uncertainty in evidence can also affect the strength of implementation of guideline recommendations with ample evidence indicating suboptimal statin use among people recommended for treatment(17-19) with both individual patient and prescriber factors likely contributing.

Cost-effectiveness analyses help decision-makers obtain better value for money by targeting health care at interventions and population groups where the net health gain is greatest in relation to the net cost. However, questions remain as to how such analyses should be performed, which leads decision-makers to question their reliability. Decision analytic models, typically developed using summary data from multiple sources, and (summary) treatment effects from randomised clinical trials, are commonly used. Such an approach was followed in the evaluation of statin therapy for CVD prevention in the NICE Clinical Guideline CG181(15). An evaluative cost-effectiveness framework based on published summary data, however, does not allow for reliable assessment of disease risks and treatment effects over time or in categories of patients (e.g. by disease risk, age, gender, comorbidity). Furthermore, in the absence of an assessment of model validity, the reliability of results is unclear. Consequently, a research recommendation was made in

NICE CG181 for the development of a cost-effectiveness analysis of statins informed by the individual participant data (IPD) of randomised clinical trials, a recommendation taken forward in this project.

At present there is no comprehensive individual patient data (IPD)-based cost-effectiveness analysis of statin therapies in the UK. Therefore, the following priority research areas were identified: (1) use of IPD from randomised clinical trials of statins to develop more detailed and reliable (e.g. based on time-to-event analysis) cost-effectiveness analyses; and (2) the use of such analyses to produce detailed results for effectiveness and cost-effectiveness of statin therapies in categories of patients by CVD risk (e.g. 10-year and lifetime risks) and other patient characteristics (e.g. age, sex, comorbidities). These areas are timely in view of: the increasing availability of statins (i.e. all widely used statins are now available generically in the UK); the growing evidence for effectiveness of new treatments (e.g. ezetimibe, PCSK9 inhibitors); and the recent developments in UK CVD risk scoring (QRISK3 10-year CVD risk score was recently published(20)) and growing interest in lifetime CVD risk(21, 22).

Cost-effectiveness studies embedded within individual statin trials have demonstrated an ability to evaluate cost-effectiveness of statin regimens in categories of patients (23-27). By combining IPD-based multivariate time-to-event disease risk equations and estimates of the relative effects of statins on disease risks into interlinked disease models, such frameworks have evaluated statins' cost-effectiveness reliably in particular categories of participants (e.g. by CVD risk, age and gender)(24, 26). The CTT database is a unique resource for the development of further more detailed analyses to guide statin recommendations for individual patients. It currently includes IPD from 28 large statin trials among nearly 180,000 participants with well-documented baseline characteristics and first occurrence of major vascular, cancer and mortality events during studies' follow-up (Table 1), as well as information on the effects of statin regimens on lipid values (which allows trial-level adjustment for the effects of non-adherence). The database is currently being augmented to include (or facilitate access to) IPD for all vascular and non-vascular adverse events (that is, not just the first event of each type) recorded during the studies to address further the uncertainties about statin safety (28).

In this project we aim to substantially strengthen the evidence about the cost-effectiveness of statins using the augmented CTT IPD of all types of events (either adverse or beneficial; first or subsequent)(28) and other UK population IPD databases. This work is timely in view of the richness of data in these databases. The cost-effectiveness analysis of statin regimens, developed using these data, will account for the timing of disease events, the beneficial and adverse effects of statins and would produce more reliable estimates of net effects on quality-adjusted life expectancy and health care costs in categories of patients. The evaluative model itself will be made freely available for further use. The web-based interface to the model will facilitate its use by policy makers, analysts, clinicians and other interested users to interrogate the model functioning and findings and employ it in further appraisals.

3. Aims and objectives

The research question addressed in the project is "What is the cost-effectiveness of different statin therapies in different categories of people?". We will study the cost-effectiveness of statin regimens (i.e. of different intensity) for categories of people with and without previous CVD. The CTT database, augmented with data on all events (adverse and beneficial), enables detailed analyses of safety concerns (eg incident diabetes, an important consideration in people at low cardiovascular risk) as well as impact of statins on recurrent events.

Outcomes of interest will include nonfatal and fatal CVD events and incident diabetes; (quality-adjusted) life years; health and social-care costs; the effects of statin therapies on these outcomes; and cost-effectiveness of statin therapies. We will:

1) evaluate risks over time of major vascular events (i.e. myocardial infarction, stroke, cardiovascular death) and incident diabetes in people with particular demographic characteristics and cardiovascular risk factors;
2) evaluate the impact of vascular events on healthcare costs in people with particular demographic and disease risk characteristics and source the health-related quality of life impacts of these events from external data;
3) develop and validate, internally and externally, the CTT cost-effectiveness model to project CVD risks, incident diabetes and mortality, and statins' effects on these in categories of people;
4) evaluate the cost-effectiveness of different statin therapies in different categories of people; and
5) develop and make available a web-based interface to the CTT cost-effectiveness model.

4. Research Plan / Methods

The project will be organised into five work packages.

Work Package 1: CTT cost-effectiveness model

Data: CTT Collaboration's database; post-trial long-term follow up data from the Heart Protection Study (HPS)

The CTT Collaboration's individual participant data (IPD) of large randomised statin trials(6) (Table 1) will be used to develop the CTT cost-effectiveness model, a decision-analytic Markov cost-effectiveness model with an annual cycle of transition, to simulate progression of CVD, evolving diabetes and mortality. The endpoints considered in the model will include those events that are influenced by statin therapy, such as myocardial infarction, stroke, cardiovascular mortality, and incident diabetes. Rarer safety outcomes attributable to statins (ie, myopathy and rhabdomyolysis) will also be considered. The data on all trial participants will contribute to model estimation with allowance for treatment allocation and treatment intensity (per 1 mmol/L reduction in LDL cholesterol). The trials included in the CTT database were conducted in different geographic locations and across a 20-year time period. These features of the data will be accounted for in the development of the disease risk equations(5), and UK data (five large studies in the CTT database recruited predominantly in the UK) will be used to guide estimation of baseline disease hazards.

We plan to use the long-term follow-up data in the 20,000-patient Heart Protection Study (HPS)(29) (~15 years follow-up beyond the 5-year trial duration is now available) and the 10,000-large Whitehall II study(30) (~30 years of follow-up) to increase reliability of the long-term modelling and guide the assessment of longer term model performance.

Methods:

A set of parametric time-to-event multivariate risk equations will be estimated for each endpoint of interest to be included in the model. Different parameterizations of the model in categories of patients by gender and prior CVD history will be investigated (i.e. four separate model parametrisations for men and women with and without previous CVD). Risk equations will include information on patient characteristics,

including socio-demographic characteristics, blood pressure, lipid levels and comorbidities such as CVD and diabetes, and will evaluate risk of first and subsequent disease events. Previous work has demonstrated that experience of non-fatal vascular events and increasing age strongly predict the absolute risk of subsequent cardiovascular morbidity and mortality(25). Proportional hazards models will be considered, as both external evidence and data-driven Cox modelling suggest the suitability of the proportional hazards assumption for modelling CVD risks(31, 32). Initially, the Andersen-Gill generalisation of the Cox proportional hazards model will be used(33, 34), with all potentially relevant covariates included into the equations. An automatic procedure based on selecting a model with the lowest Akaike Information Criterion (AIC) and forward/backward selection will be used. Variables that are only marginally significant, both statistically and clinically, will be removed. Model comparisons will be performed using the likelihood ratio test, with p-values of <0.01 considered significant. Proportional hazards assumptions will be tested using the Schoenfeld residuals (35) and plots depicting log(-log(survival)) versus log(survival time). To account for multiple events per participant, robust standard errors will be estimated. Once a set of covariates is finalised, parametric proportional hazards survival models will be fitted to allow extrapolation to lifetime analyses. Exponential, Weibull and Gompertz proportional hazards models will be considered with the appropriate survival distribution selected on the basis of the AIC(36). An internal assessment and statistical modelling in the long-term individual participant follow-up data in the HPS and other long-term post-trial follow-up data(37, 38) will guide further the choice of parametric survival models.

Bootstrapping with replacement approach to risk equations' estimation will be used to jointly estimate parameter uncertainty(39). In internal validation, vascular events rates, simulated by the model, will be compared with the corresponding observed event rates during follow-up in participant categories by study, CVD risk, age, gender and comorbidities.

Following validation and further development of the model (work package 2), and completion of the healthcare costs models (work package 3), the CTT cost-effectiveness model will be fully coded in R and prepared to support the cost-effectiveness analyses of statin therapies (work package 4).

Work Package 2: Validation and further development of the CTT cost-effectiveness model in external datasets

Data: UK Biobank study; Whitehall II study

To ensure that the results of the CTT cost-effectiveness model are reliable and widely accepted, the model will be further validated in two external datasets: the UK Biobank study(40, 41), a cohort of 500,000 UK adults aged 40-70 years followed for (currently) about 10 years, and the Whitehall II study(30), a cohort of 10,000 men and women aged 35-55-years at recruitment followed for 30 years.

The UK Biobank study with detailed characterization of participants at study entry and comprehensive linkage with routine primary and secondary healthcare data and cancer registrations and mortality for health outcomes (~ 9500 participants experienced MIs, 5000 strokes, 3400 died from cardiovascular causes during follow-up), presents a unique opportunity to validate the CTT cost-effectiveness model in a range of participants (eg, at recruitment 20% of participants are younger than 48 years; 20% older than 68 years; more than half are women; participants predominantly without prior cardiovascular disease at recruitment)(40, 41). A key feature of the CTT cost-effectiveness model will be its ability to project outcomes in categories of participants (and individual risk profiles) and, therefore, the ability to study model performance in categories of participants in the UK Biobank cohort is a key strength. The UK Biobank population differs in a number of respects from the general UK population and exhibits the "healthy volunteer effect" (42). However, the focus of the CTT cost-effectiveness model is on categories of

participants, particularly by cardiovascular disease risk. As noted above, there is a good representation of these categories of the general UK population in the UK Biobank cohort to support such work. The Whitehall II study data will importantly contribute to the longer-term assessment of the model as well as its performance in older men and women.

Methods:

We will use the UK Biobank, and separately, Whitehall II participants' data at entry into the respective studies and the CTT cost-effectiveness model to project each participant's CVD risks and mortality and compare these projections with the observed risks in categories of UK Biobank/Whitehall II participants over time. Model-simulated cumulative rates of CVD events will be compared with the respective Kaplan-Meier product-limit estimates.

Any evidence for suboptimal model performance will be investigated and, if necessary, the model revised. While the proportional hazards assumptions, under appropriate specification of risk factors, are typically met (eg, Framingham risk(31), QRISK(43), ASSIGN(44)), it may be necessary to calibrate some of the model components (e.g. individual CTT risk equations) in the target population/s.

Work Package 3: UK healthcare costs related to cardiovascular and other disease events and sourcing QoL related to disease events

Data: UK Biobank cohort study

The UK Biobank data (500,000 participants aged 40-69 years old at recruitment in 2006-2010) will be used to assess the annual hospital and primary healthcare costs associated with CVD events in categories of patients.

Methods:

<u>Annual costs of hospital and primary care of UK Biobank participants</u>

Hospital and primary care costs will be calculated to align with the structure of the model while adhering to accepted costing standards. Hospital Episode Statistics (HES) data are available for UK Biobank participants, including detailed cause-specific information on participants' hospital admissions. The NHS reference cost grouper will be used to assign Healthcare Resource Groups (HRGs)(45) to all finished consultant episodes (FCE: the unit of data in HES; refers to care under a particular consultant)(46) across all years of follow-up in UK Biobank. The cost of hospital episodes, determined based on the hospital admission type, procedures, diagnoses, length of stay and patient's age, will be calculated using NHS reference costs(47).

Linked UK routine primary care data for UK Biobank participants will be available to researchers later in 2019. The primary healthcare data includes information on all visits and telephone consultations, with a general practitioner, a nurse, or allied health/social care professional; monitoring and diagnostic tests; and prescription items. NHS costs will be applied to categories of consultations and tests.(47, 48). Average costs per prescription item at the BNF paragraph level will be calculated(49) from the NHS Prescription Cost Analysis(50), and will be applied to each prescription item issued based on the BNF paragraph recorded in the primary care data.

Annual costs for, respectively, hospital and primary healthcare will be calculated for each participant and each year of follow-up.

Statistical methods: Generalised linear models (GLM) will estimate annual secondary, and separately, primary care costs related to categories of participant and types of vascular and other event histories. Statistical model selection will be performed using common specification tests to select appropriate GLMs for the annual hospital care costs and annual primary care costs(51). All models will be estimated using cluster robust standard errors to account for the lack of independence between observations of annual costs for the same participant. The covariates included in the model will include demographic, clinical characteristics and cardiovascular event histories, corresponding to the structure of the CTT cost-effectiveness model. The impact of events on healthcare in the years events occur and in subsequent years will be examined. These predictive models will inform the annual healthcare costs in the CTT cost-effectiveness model.

We will study the evidence on QoL in categories of individuals (e.g. from national surveys) and the effects of disease events of interest on QoL to inform the QoL parameters in the model.

Work package 4: Cost-effectiveness of statin therapies in the UK

Data: UK Biobank and Whitehall II study data

Methods:

The cost-effectiveness for particular statin therapies in categories of patients will be developed and summarised. We will use the UK Biobank and Whitehall II individual participant data and the CTT cost-effectiveness model to evaluate effectiveness and cost-effectiveness for different statin therapies in categories of UK Biobank/Whitehall II participants.

The effects of statin therapies on vascular and other events in the CTT cost-effectiveness model will be informed by results from the CTT Collaboration database following the intention-to-treat principle. Previous CTT meta-analyses have showed that the principal source of between-trial heterogeneity in the effects of statins on vascular events is the size of the differences in the achieved absolute LDL cholesterol reduction at 1 year(2, 4-6). Therefore, the effect of particular statin regimen in a particular category of participant will be estimated by applying the proportional effect of that therapy on LDL cholesterol, based on published data, to the mean LDL cholesterol level observed among participants in that category and using the proportional effect of statin therapy on particular outcomes per 1 mmol/L reduction in LDL cholesterol derived in meta analyses in CTT database. The cost-effectiveness assessments will use the latest NHS drug tariff costs (14) for statin therapies and present results from the perspective of the NHS and personal social services following the NICE reference case(52). The results will be relevant across UK healthcare settings.

Target population: Patients considered for statin therapy for primary or secondary CVD prevention; categories by 10-year and lifetime CVD risk, age, gender, and comorbidities. We will investigate the use of QRISK 2, QRISK 3(20, 43) and QRISK lifetime(22) risk scores to stratify participants in risk categories.

Health technologies assessed: We will present results for statin therapies used in UK: atorvastatin 10, 20, 40, 80mg/day; simvastatin 10, 20, 40, 80mg/day; rosuvastatin 5, 10, 20, 40mg/day; and pravastatin 20, 40mg/day.

Sample size: There are sufficient numbers of participants and events in the proposed large databases: 180,000 participants, followed for an average of 5 years in CTT (8600 participants experienced nonfatal MIs, 6000 strokes, 10700 died from cardiovascular causes); 500,000 participants followed for about 10 years in

UK Biobank (~ 9500 participants experienced MIs, 5000 strokes, 3400 died from cardiovascular causes); and 10,300 participants in Whitehall II study.

Difference between current and planned care pathways: There might be changes in statin treatment recommendations in categories of people. The treatment scenarios will include potential effects on services related to initiation, monitoring, switching or discontinuation of therapies.

The risk, cost and, if relevant, QoL equations and the model itself will be published open access and widely available, and we propose to provide and facilitate open access to the model in the public domain. We will also develop the key cost-effectiveness scenarios and will make key cost-effectiveness results widely available to inform major current areas of uncertainty relevant to use of statins (e.g. individuals at low cardiovascular disease risk).

Work Package 5: Web-based user interface to CTT cost-effectiveness model

Methods:

A user-friendly web interface will be developed to allow the model's external use and to facilitate adaptations (eg, effects of treatments, costs, quality of life) to the model. We will use the R Shiny package to develop the front (data input) and back (results)-end of the model.

We intend developing the model functionality to allow projections for individual patients as well as for populations using user-supplied individual patient data. In all simulations, the projections of long-term event rates, quality-adjusted life years, costs and cost-effectiveness, including uncertainty estimates, will be summarised. Users would have the option to supply alternative sets of treatment effects, healthcare costs, QoL and other model parameters.

5. Dissemination, outputs and anticipated Impact

The project findings will be disseminated at scientific meetings and published open access in peer reviewed publications. We will also widely share findings from the project with policymakers, stakeholders, and key organisations such as the British Heart Foundation and patient groups. We will work with our PPI members and media teams to develop an effective dissemination strategy achieving the widest and most effective reach. The project will be directly relevant to policy recommendations for the use of statin therapies in categories of patients in the NHS. The CTT cost-effectiveness model web interface together with the user manual and examples for its use will be freely available to clinicians, analysts and members of the public and could inform individual decisions and further evaluations of CVD preventative interventions.

6. Project / research timetable

It is envisaged that the whole project will take 36 months. Figure 1 presents a diagram of the flow of work packages in the project.

Work Package 1 [M1-13 and M19-24] CTT cost-effectiveness model will be developed over months 1 to 13 and 19-24.

Work Package 2 [M12-20] Validation and further development of the CTT cost-effectiveness model in other datasets

Work Package 3 [M6-18] UK healthcare costs related to CVD morbidity; source QoL related to CVD morbidity

Work Package 4 [M25-36] Cost-effectiveness of statin therapies in the UK

Work Package 5 [M25 – 36] Web-based user interface to CTT cost-effectiveness model.

7. Project management

The PI (Prof. Borislava Mihaylova) will take overall responsibility for the progress of each work package. She will be supported by Co-PI Prof. Colin Baigent. The project will be managed by the Project Management group consisting of the Principal, Co-Principal and other Investigators and the research staff working on the project at the University of Oxford and QMUL. The Project Management Group will have face-to-face meetings quarterly to review progress on the project. Progress reports on the respective work packages will be discussed and notes from the meetings will be produced.

Annually, the Project Oversight Group (including clinical practitioners, a public health physician and a public and patient representative(PPI)) will join the Programme management group meetings and review and discuss progress on the project.

8. Ethics

The use of all planned data sources will be under the auspices of the ethics arrangement for the individual data sources. All individual trials participating in The Cholesterol Treatment Trialists' (CTT) Collaboration Database, including Heart Protection Study, have received ethics approvals and consented individual participants. The CTT database has also received a favourable opinion by the South Central - Oxford C Research Ethics Committee (REC Reference 16/SC/0094) as a resource enabling comprehensive understanding of the balance of benefits and harms of statins in specific types of individuals. The UK Biobank has received an approval from the North West Multi-centre Research Ethics Committee (MREC), which covers the UK. The Whitehall II study was approved by the NHS National Research Ethics Service and the local Research Ethics Committee (UCL).

9. Patient and Public Involvement

Our steering group will include a public and patient representative(PPI), clinical practitioners and public health physician. This group will contribute throughout the project to the development of research and emerging results, outputs and their interpretation and use. We will seek our panel views on drafts of our presentations, publications, other outputs and outreach materials to improve their clarity, accessibility and ultimately impact. We will further disseminate our findings to the public by presenting at public meetings in Oxford and London.

10. Funding acknowledgement

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11. Project team

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Table 1: Randomised clinical trials, participating in the CTT Collaborators database

Study	Participants	Median follow-up in survivors (years)*	Treatment comparison	Number of participants†
Statin vs control				
SSSS	SP (Angina/MI)	5.4	S20-40 vs. placebo	4,444
WOSCOPS	PP	4.8	P40 vs. placebo	6,595
CARE	SP (MI)	5.0	P40 vs. placebo	4,159
Post CABG	SP (CABG)	4.3	L40-80 vs. L2.5-5	1,351
AFCAPS/TexCaps	PP	5.2	L20-40 vs. placebo	6,605
LIPID	SP (MI/angina)	6.0	P40 vs. placebo	9,014
GISSI-P	SP (recent MI)	2.0	P20 vs. no treatment	4,271
LIPS	SP (previous PCI)	3.9	F80 vs. placebo	1,677
HPS	SP/Diab (CHD/diabetes)	5.4	S40 vs. placebo	20,536
PROSPER	PP/SP	3.3	P40 vs. placebo	5,804
ALLHAT-LLT	PP/SP	4.9	P40 vs. usual care	10,355
ASCOT-LLA	PP/SP	3.3	A10 vs. placebo	10,305
ALERT	Renal transplant	5.5	F40 vs. placebo	2,102
CARDS	PP+ diabetes	4.1	A10 vs. placebo	2,838
ALLIANCE	SP	4.7	A10-80 vs. usual care	2,442
4D	Renal dialysis	4.0	A20 vs. placebo	1,255
ASPEN	PP/SP+diabetes	4.0	A10 vs. placebo	2,410
MEGA††	PP	5.0	P10-20 vs. usual care	8,214
JUPITER	PP	2.0	R20 vs. placebo	17,802
GISSI-HF	HF	4.2	R10 vs. placebo	4,574
AURORA	Renal dialysis	4.6	R10 vs. placebo	2,773
CORONA	HF	3.0	R10 vs. placebo	5,011
SPARCL	SP (recent Stroke/TIA)	4.9	A80 vs placebo	4,731
Subtotal: All 23 trials		**4.8**		**139,268**
More vs less trials				
PROVE-IT	SP	2.1	A80 vs. P40	4,162
A to Z	SP	2.0	S40 then S80 vs. placebo then S20	4,497
TNT	SP	5.0	A80 vs. A10	10,001
IDEAL	SP	4.8	A40-80 vs. S20-40	8,888
SEARCH	SP	7.0	S80 vs. S20	12,064
Subtotal: All 5 trials		**5.1**		**39,612**
Total: All 28 trials		**4.9**		**178,880**

* Estimated using standard Kaplan-Meier methods with participants censored at their date of death.

††Includes 382 randomised patients who were excluded from the original publication.

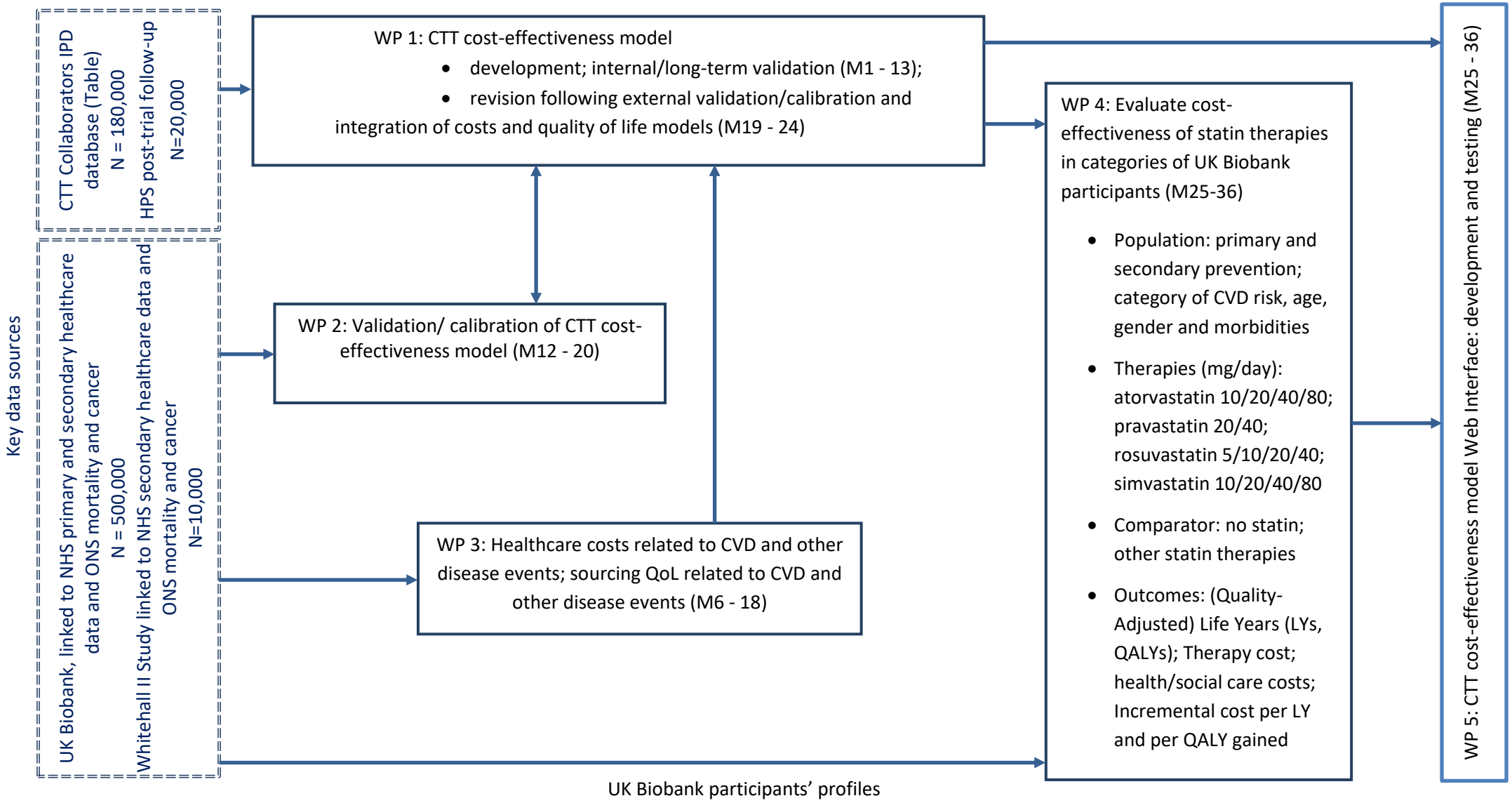
SSSS=Scandinavian Simvastatin Survival Study; WOSCOPS=West of Scotland Coronary Prevention Study; CARE=Cholesterol And Recurrent Events; Post-CABG=Post-Coronary Artery Bypass Graft; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease; GISSI-P=Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; LIPS=Lescol Intervention Prevention Study; HPS=Heart Protection Study; PROSPER=PROspective Study of Pravastatin in the Elderly at Risk; ALLHAT-LLT=Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; ALERT=Assessment of Lescol in Renal Transplantation;

CARDS=Collaborative Atorvastatin Diabetes Study; ALLIANCE=Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; ASPEN=Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study Group; JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin study group; AURORA=A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: an Assessment of Survival and Cardiovascular Events; CORONA=Controlled Rosuvastatin Multinational Trial in Heart Failure; SPARCL=Stroke Prevention by Aggressive Reduction in Cholesterol Levels; PROVE-IT=Pravastatin or Atorvastatin Evaluation and Infection Therapy; A to Z=Aggrastat to Zocor; TNT=Treating to New Targets; IDEAL=Incremental Decrease in End Points Through Aggressive Lipid Lowering Study Group; SEARCH=Study of the effectiveness of additional reductions in cholesterol and homocysteine.

SP, secondary prevention; PP, primary prevention; MI, myocardial infarction; CABG, Coronary artery bypass surgery; CHD, coronary heart disease; TIA, transient ischaemic attack; HF, heart failure.

A, atorvastatin; F, fluvastatin; P, pravastatin, S, simvastatin, L, lovastatin; R, rosuvastatin.

Figure 1: Flow Diagram of work packages of project "Cost-effectiveness of statin therapies evaluated using IPD from large randomised clinical trials"



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