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The effectiveness of simvastatin compared to atorvastatin - a feasibility study

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Registration date 09/12/2009	**Overall study status** Completed	
Last Edited 26/05/2015	**Condition category** Circulatory System	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
043464; 09_056R

Study information

Scientific Title
The effectiveness of simvastatin compared to atorvastatin: an e-clinical randomised feasibility trial within a research database in routine clinical practice

Acronym
RETRO-PRO

Study objectives
This is a feasibility study on a relatively small number of patients to assess whether the "simple study methodology" whereby patients are randomised in routine clinical care and the data collected from within the standard NHS records, could be used to run much larger 'real world' studies - larger in the sense of sheer number of patients required to provide statistically significant results on all outcomes; real world in the sense that there is only the normal at point of clinical care inclusion, exclusion criteria and that there is no attempt to alter normal care. The study involves patients being randomised to one of two statins (lipid-lowering drugs) for heart disease to assess which statin provides the better outcome; in this feasibility study changes in laboratory measures of lipids (low density lipoprotein [LDL] and high density lipoprotein [HDL]) will be statistically significant which is important as there are laboratory data that suggest that some types of statins may be better than others. However there remains a question mark over which statin to prefer in the real world.

If and when a full study is performed it will be powered for end points such as myocardial infarction (MI) and death. In this feasibility study these outcomes will be monitored to show the full capability of the study methodology.

In this study GP sites will be from practices who are regular contributors to the General Practice Research Database (GPRD) that has ethics approval (Trent REC, ref: 05/MRE04/87) to download the practices pseudonymised observational data. In this study the flags that show patient consent and to which treatment the patient was randomised will also be downloaded.

The primary objective is to test the feasibility of a "simple methodology" for randomised clinical trials - randomisation at the point of care of real world patients with data collection from the routine clinical NHS records. This feasibility study uses two methods to enable a study that might otherwise not take place:
1. Randomisation in everyday clinical care where patients who would normally be prescribed a statin (the type of statin would be determined by randomisation rather than by the GP; both statins in this study are routinely prescribed in the UK), and
2. The data required to analyse the outcomes are available from either the primary care datasets or hospital data

Randomised clinical trials make major contributions to medical research. But the costs of conducting these studies can often be prohibitive. A considerable amount of the data needed in clinical studies is increasingly collected as part of routine health care. A major opportunity in extending research opportunities could be for trials to use information that is routinely collected. A randomised clinical trial could be conducted by prospectively randomising subjects to treatment with subsequent data collection and follow up conducted by using the routinely collected data (also known as "randomised clinical trial within the database" [RCTdb]). This type of study evaluates the drug effectiveness (i.e., the outcomes within routine health care system) rather than drug efficacy (i.e., the outcomes in ideal circumstances).

The present protocol describes a feasibility trial of RCTdb. General practitioners (GPs) play a key role in the UK health care system, as they are responsible for primary health care and specialist referrals. Hospitals are required to inform GPs of any significant medical events that occur. Long-term care of chronic conditions is typically managed by GPs. As a consequence, subjects' medical records as managed by the GPs contain longitudinal information on all significant medical events and prescribing. They are essentially the life-long record for each patient and include the key secondary care information as well laboratory, other investigations and details of all medications prescribed within general practice. Data from practices in England can now be linked anonymously at the person level to various other NHS datasets, including the death certificates, the national registry in England of hospital admission, prospective disease registries (such as the cancer registries or the Central Cardiac Audit Database, that records, among others clinical details on subjects admitted to hospitals in England for myocardial infarction). These records contain unique information for research.

The secondary objective is to measure laboratory and clinical outcomes and compare these outcomes between the two randomly allocated statins. The trial is large enough to show differences in laboratory measures of lipid levels (HDL and LDL).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Multicentre pragmatic randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
GP practice

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Cardiovascular illness

Interventions
Potentially eligible trial subjects will be "anonymously" identified by the Principal Investigator within the anonymous GPRD records. To ensure patients who are eligible under statin SPCs and the guidelines for the use of statins, the 10-year risk of developing cardiovascular disease, based on Framingham 1991, will be estimated for each patient aged 40 years or older. All patients with

a 10-year risk of 20% or greater (based on Framingham) and who have no prior record in GPRD of statin prescribing, pregnancy within the last 4 years or serious liver disease will then be noted within the GP medical record software system by the use of two anonymisation keys (described earlier). Trial recruitment procedures will be initiated for the potentially eligible trial subjects (using a flagging system in the GP software) if any of the following activities occur in the GP medical record software system:
1. Review of a laboratory test for lipids with abnormal values for total cholesterol or LDL
2. Data entry of a medical code of hyperlipidaemia during a subject's visit to the GP Investigator
3. Data entry of a statin prescription during a subject's visit to the GP Investigator

The GP Investigator will then review and confirm the eligibility criteria and record this in the electronic case report form in a web-based secure clinical trial management system. For patients that agree to potentially participate in the study, the system will allow printing a study information form and consent form for the patient to sign. The basis of the information sheet is that both statins in the study are widely prescribed and this trial will help decide whether a large simple RCT can be undertaken in this routine medical care with long-term follow-up of representative patient populations.

Consenting patients can be provided with a statin prescription at the same visit as the recruitment. But consenting patients will be informed that they can 'opt-out' of the RCTdb by not redeeming the prescription for the study drug (and starting actual statin exposure) and that they can return for a consultation. The information sheet will note that, in case of 'opt-out', the GP may still prescribe them the same drug but that they have a right to request not to further participate in the RCTdb.

Trial subjects will be followed for a period of 3 months. Within 3 months after the baseline visit, trial subjects should provide two blood samples for the study (at the same time as the repeat liver function tests as recommended in the 2008 NICE guideline on lipid modification).

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Atorvastatin, simvastatin

Primary outcome measure
1. Methodological endpoint evaluating the feasibility of conducting RCTdb
2. Clinical endpoint evaluating the percent change of total cholesterol, high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL), comparing the baseline values to a repeat measurement within 3 months

The feasibility evaluation will include the recruitment rate of GPs and of subjects and an assessment of the technical challenges in conducting RCTdb. No formal threshold for success will be applied but results will be published.

The blood samples for total cholesterol, HDL, and LDL should be taken at the same time as the routine blood samples. The 2008 guideline on lipid modification from NICE and the National Collaborating Centre for Primary Care recommends that fasting total cholesterol, HDL, fasting

blood glucose, liver function tests and renal function are measured prior to start of statin treatment. In addition, a repeat liver function test is recommended to be done within 3 months.

Secondary outcome measures
1. Persistence to statin treatment at month 3
2. Myocardial infarction
3. Stroke
4. Death (any cause)
5. Death with cardiovascular disease as primary cause
6. Feasibility of collecting biological samples in RCTdb

Given the small number of subjects in this study, these secondary outcomes will serve as pilot data for power calculations for larger studies in the future. The study will not be powered statistically to detect a difference between simvastatin and atorvastatin in the rate of secondary outcomes.

Overall study start date
15/02/2010

Completion date
01/07/2012

Eligibility

Key inclusion criteria
1. Aged 40 years or over, either sex
2. Able and willing to provide informed consent to study participation
3. Fully registered with the general practice for at least 6 months (i.e. subjects who are newly registered with the practice will not be eligible)
4. Subjects who had not been prescribed a statin previously
5. Subjects who in the opinion of the GP Investigator should be prescribed a statin
6. Subjects who in the opinion of the GP Investigator have primary hypercholesterolaemia (cholesterol of 5.0 mmol/l or above) and have not responded adequately to diet or other appropriate measures (i.e. one of licensed indications of statins)
7. Subjects who in the opinion of the GP Investigator would require a statin for primary prevention according to the 2008 NICE guideline on lipid modification: adults over 40 who have a 20% or greater 10-year risk of developing cardiovascular disease, based on Framingham 1991 10-year risk equations and clinical judgement

Further details can be found in the British National Formulary (section 2.12) and in the 2008 NICE guideline on lipid modification [5], which will be available on the study website.

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
300

Key exclusion criteria
Statins are contra-indicated in active liver disease (or persistently abnormal liver function tests), in pregnancy (adequate contraception required during treatment and for 1 months afterwards) and breast-feeding. Further details can be found in the British National Formulary (section 2.12).

Date of first enrolment
15/02/2010

Date of final enrolment
01/07/2012

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
GPRD
London
United Kingdom
SW8 5NQ

Sponsor information

Organisation
University of Liverpool (UK)

Sponsor details
Brownlow Hill
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L69 3BX

Sponsor type
University/education

Website
http://www.liv.ac.uk/

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Charity

Funder Name
The Wellcome Trust (UK) (grant ref: 043464)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/07/2014		Yes	No