**PROTOCOL**

**Observational Study of Cardiovascular Disease**

## Study Title

Long-term Study of LDL-c Lowering with Evolocumab: Observational Follow-up after the FOURIER OUTCOMES Trial

## Study Name: FOURIER LEGACY Study

## NHMRC CTC protocol number

CTC 0173

## International Sponsor:

The University of Sydney

NSW 2006 Australia

This study is a collaboration between the NHMRC Clinical Trials Centre, University of Sydney, TIMI Study Group, Brigham and Women's Hospital, Imperial College, London and University of Oslo, Oslo

## Protocol version number and date

Version 1.3 dated 26th September 2019

**CONFIDENTIAL**

## STUDY MANAGEMENT

**Lead Investigators:** Professor Anthony Keech and Professor Peter Sever

**Co-ordinating Center:**

NHMRC Clinical Trials Centre
92-94 Parramatta Road
Camperdown, Sydney, NSW 2050
Telephone: 61-2-9562-5000
Fax: 61-2-9565-1863
Email: FOURIER.LEGACY@ctc.usyd.edu.au

| Region | Regional Study Chair | Regional Co-ordinating Center | Project Manager |
|---|---|---|---|
| Asia Pacific/Australasia | Anthony Keech | NHMRC Clinical Trials Centre | Annie Yeung |
| North & South America | Marc Sabatine<br>Robert Giugliano | TIMI Study Group | Polly Fish<br>Alexandra Pricken |
| Europe/South Africa | Peter Sever | Imperial College | Judith Mackay<br>Vanita Vij Narang |
| Nordic countries | Dan Atar | University of Oslo | Arnhild Bakken |

**Senior Statisticians:** Professor Val Gebski, NHMRC Clinical Trials Centre
Sabina Murphy, TIMI Study Group

**Global Project Manager:** Rebecca Mister, NHMRC Clinical Trials Centre

**Abbreviations**

| | |
|---|---|
| ACS | Acute coronary syndrome |
| CHD | Coronary heart disease |
| CRF | Case report form (e-CRF = electronic CRF) |
| CTC | NHMRC Clinical Trials Centre |
| CVOT | Cardiovascular outcomes trial |
| GP | General practitioner |
| CV | Cardiovascular |
| GCC | Global co-ordinating center |
| NCC | National co-ordinating center |
| RCC | Regional co-ordinating center |
| LDL-C | Low density lipoprotein cholesterol |
| PCSK9 | Proprotein convertase subtilisin kexin type 9 |
| UAP | Unstable angina pectoris |

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# SYNOPSIS

| | |
|---|---|
| **Background** | This observational study will follow participants who completed follow-up in the FOURIER OUTCOMES trial to evaluate the long-term effects of evolocumab treatment. Long-term post-trial (legacy) beneficial effects have been reported with statins, niacin, hypoglycemic therapy and fibrates. Whether similar effects are seen after LDL cholesterol (LDL-c) lowering by PCSK9 inhibition is currently unknown. Evolocumab therapy causes a profound reduction in LDL cholesterol of approximately 60%. Statins have shown legacy effects over 5 years post-trial, including a 7% reduction in total mortality in meta-analysis and 12% reduction in coronary mortality. It would therefore be hypothesized that additional effects beyond the trial period would be conferred by previous evolocumab treatment. It is also important to assess the long-term safety of prior evolocumab treatment. |
| **Aim** | To evaluate potential long-term effects on cardiovascular outcomes of evolocumab treatment in participants who have completed follow-up in the FOURIER OUTCOMES trial. |
| **Primary objective** | 1. To evaluate the potential long-term effect of evolocumab treatment on a composite of CV death, MI, stroke or coronary revascularization in patients completing participation in the FOURIER OUTCOMES trial. |
| **Secondary objectives** | 2. To evaluate the long-term effect of evolocumab treatment on CV death, MI and stroke.<br>3. To evaluate the long-term effect of evolocumab treatment on CV death.<br>4. To evaluate the long-term effects of evolocumab treatment on CHD death.<br>5. To evaluate the long-term effect of evolocumab treatment on the individual components of the primary endpoint and any other CV hospitalizations.<br>6. To evaluate the long-term effect of evolocumab treatment on amputations and peripheral revascularization.<br>7. To evaluate the long-term effect of evolocumab treatment in terms of all-cause death (and non-CV, including cancer, death). |
| **Exploratory objective** | 8. To assess the effect of use of lipid-lowering treatment classes (statins, cholesterol absorption inhibitors, PCSK9i).<br>9. To assess the effect modification by baseline characteristics on defined study outcomes above. |
| **Design** | International multi-center observational, longitudinal follow-up study of participants who participated in the FOURIER OUTCOMES trial. |
| **Population** | Participants in selected countries who completed the FOURIER OUTCOMES trial. |
| **Study treatments** | None. |
| **Assessments** | Participants will be remotely assessed (via questionnaire) upon entry into the FOURIER LEGACY study, approximately 6 and 12 months later and |

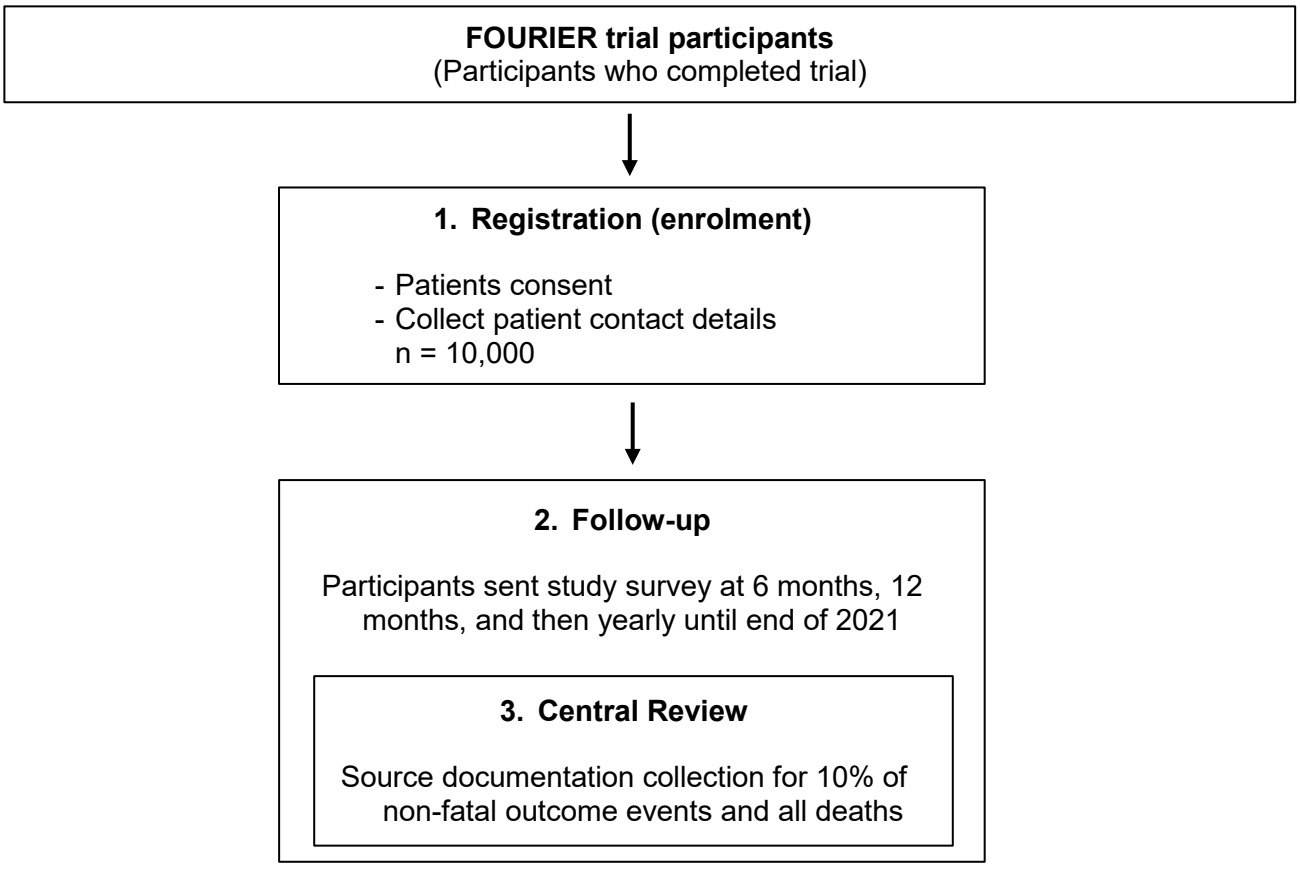
then approximately annually to obtain a total of 5 years' follow-up after the date of last contact in the FOURIER OUTCOMES trial to collect details of cardiovascular hospitalizations, mortality and lipid-lowering therapy classes.

**Statistical considerations**

A minimum of 10,000 participants, followed over 5 years post-trial, with an assumed average post-trial event rate of 5% per annum for the primary endpoint, would have over 95% power at 2P=0.05 to detect a 20% proportional event reduction accruing post-trial. It will also offer 80% power at 2P=0.05 to detect a 23% reduction in CVD (from 4.94% to 3.8%).

Interim analyses of accrued data may be conducted annually post-trial as agreed from time to time by the study Steering Committee and funder. Analyses will be by intention-to-treat based on original allocated treatment in the parent FOURIER OUTCOMES trial.

# Study Schema



# 1 BACKGROUND

On-going and additional clinical benefits of statin therapy after trial completion have been demonstrated to accrue from a number of trials (including the 4S Study[1] and the LIPID Study[2,3] in secondary prevention patients, and the WOSCOPS Study[4,5] and ASCOT study[6] in primary prevention). Furthermore, collectively in all those trials contributing to the Cholesterol Treatment Trialists' Collaboration[7] with accessible published follow-up data, in patients who received active treatment rather than placebo over (the 3–6 years of) the original trial period, the same pattern of on-going advantage and additional risk reduction is seen.[8] This is seen despite mostly identical usage rates of lipid-lowering therapy between the original groups for many years after completion of the trials.

In meta-analysis of the trials with accessible published post-trial data, an 8% additional reduction in total mortality at 2 years after trial close, 18% reduction in coronary mortality, and 7% reduction in total mortality and 12% reduction in coronary mortality over the next 5 years after trial close was recently reported.[8] Collectively, these findings could have a major impact on how early initiation of lipid-lowering treatment should be considered in patients at risk. Also, because of greater emerging absolute risk differences than those apparent immediately at trial end, the net clinical benefits estimated relative to treatment costs becomes more favorable for earlier (vs deferred) intervention attributable to the original treatment assignment.

The same may or may not be true of PCSK9 inhibitor therapy, and so this needs to be examined prospectively and systematically. Similarly, in terms of potential safety issues, longer-term data after exposure provides more reliable evidence about the safety of therapy intended to be used for many years.

The FOURIER OUTCOMES trial was a randomized double-blind placebo-controlled trial that demonstrated significant clinical benefits, with a 15% reduction in the composite endpoint of CVD death, MI, stroke, UAP or urgent revascularization over a median of 2.2 years follow-up, and a 20% reduction in CVD death, MI, and stroke, with no excess of any important adverse events.[9,10] However, while beneficial over just a few years, these treatments will be designed for long-term use, such that high confidence in the value of the therapy can be better established with longer-term efficacy and safety data related to the treatment received during the FOURIER OUTCOMES trial.

The ODYSSEY OUTCOMES trial showed that among patients who had a previous acute coronary syndrome (ACS) and who were receiving high-intensity statin therapy, the risk of recurrent ischemic cardiovascular events was lower among those who received alirocumab than among those who received placebo.[11]

We hypothesize that, in this observational study of participants who had taken part in the FOURIER OUTCOMES trial, prior use of evolocumab compared with placebo during the randomized FOURIER OUTCOMES trial, irrespective of post-trial treatment with or without further evolocumab, will confer additional effects post-trial on cardiovascular events and mortality beyond those observed at the end of the randomized study period; and that this will occur without any adverse signal on non-cardiovascular mortality.

# 2 AIM AND OBJECTIVES

The aim of this study is to determine potential long-term effects on cardiovascular outcomes of evolocumab treatment in patients enrolled in the FOURIER OUTCOMES trial through extended follow-up of selected participants beyond the treatment period.

The **primary objective** is to evaluate potential long-term effects of evolocumab treatment on a composite of CV death, MI, stroke or coronary revascularization in patients completing participation in the FOURIER OUTCOMES trial over a period of up to 5 years following completion of the FOURIER OUTCOMES trial.

The **secondary objectives**, each over a period of up to 5 years following completion of the FOURIER OUTCOMES trial, are:

1. To evaluate the long-term effect of evolocumab treatment on CV death, MI and stroke.
2. To evaluate the long-term effect of evolocumab treatment on CV death.
3. To evaluate the long-term effect of evolocumab on CHD death.
4. To evaluate the long-term effect of evolocumab treatment on the individual components of the primary endpoint and any other cardiovascular hospitalizations.
5. To evaluate the long-term effect of evolocumab treatment on amputation and peripheral revascularization.
6. To evaluate the long-term effect of evolocumab treatment in terms of all-cause death (and non-CV, including cancer, death).

Two exploratory analyses will be performed:

1. To assess effect modification of use of prescription lipid-lowering treatment classes (statins, cholesterol absorption inhibitors, PCSK9i) administered at FOURIER OUTCOMES trial entry on the outcomes above.
2. To assess the effect modification by baseline characteristics on defined study outcomes above.

# 3 DESIGN

International multi-center, longitudinal observational study of selected participants who completed the FOURIER OUTCOMES trial.

## *3.1 Target Population*

Participants in selected countries who completed the FOURIER OUTCOMES trial, irrespective of non-fatal on-study events during FOURIER OUTCOMES trial, and who agree to take part in the FOURIER LEGACY study following study completion will be enrolled into this trial.

## *3.2 Study Enrolment*

Subjects who completed the FOURIER OUTCOMES trial (defined as attendance at close-out visit irrespective of treatment compliance) will be approached by FOURIER OUTCOMES site investigators and asked about their interest in taking part in this trial. Contact details of those interested in taking part will be forwarded to the national co-ordinating center (NCC), who will contact participants to confirm consent.

**Assent:** Confirmation by site staff of the participant's agreement to be contacted for consent by the NCC will be provided to the NCC.

**Consent:** Participation will require a specific consent by each participant to allow on-going contact to be made periodically to achieve follow-up for a total of approximately 5 years from completion of the FOURIER OUTCOMES trial. Telephone consent may be acceptable if allowed by local

regulations and approved by the Ethics Committee. Additionally, approval to hold each participant's contact details (in addition to contact details for at least one relative not living with the participant) and details of treating physician(s) will be sought to facilitate reliable on-going follow-up, and signed authorization for study staff to seek supplementary information and source documentation about health events will be collected. Participants will provide details of the preferred mode of communication (SMS, email, letter, phone) at the time of consent. Personal data identifying trial participants will be held securely solely at each NCC for the purpose of follow-up.

### 3.2.1 Informed consent

Informed consent must be signed and dated by the participant, and signed and dated by the investigator, prior to registration and participation in the study.

### 3.2.2 Registration

Registration will be done according to the instructions in the Study Manual. Once the registration process has been completed, the participant will be identified using their original FOURIER OUTCOMES patient ID. Individuals may only be registered once in this trial.

# 4 TREATMENT PLAN

This is a purely observational study, and as such there are no study treatments. Participants remain under the care of their treating physician.

## *4.1 Concomitant Medication Reporting*

Use of concomitant medications is solely at the discretion of participants and their treating physicians, including any lipid-modifying medication (including PCSK9 inhibitors). Use of lipid-modifying therapy classes will be recorded.

# 5 ASSESSMENT PLAN

## *5.1 Schedule of Assessments*

| | Study entry, 6 and 12 months later and then annually to a total of 5 years post-end of FOURIER OUTCOMES trial |
|---|---|
| MI | X |
| Stroke | X |
| Coronary revascularization | X |
| Other CV hospitalization | X |
| CV death | X |
| CHD death | X |
| Amputation/peripheral revascularization | X |
| Non-CV death | X |
| Lipid-lowering therapies | X |
| Any adverse drug reactions from evolocumab treatment | X |

## *5.2 Details of Assessments*

Participants will be contacted upon entry into the FOURIER LEGACY study, and then approximately 6 months later. Following this, contact will be made approximately annually to obtain follow-up for a total of 5 years after the date of last contact in the FOURIER OUTCOMES trial. Each participant will be sent a unique link to a secure website and asked to provide details of any cardiovascular events and lipid-lowering therapy classes used since the last contact (Appendix 1 lists data to be collected). A proportion of events will be adjudicated as detailed in Section 8.1.

Participants will be contacted directly (by their preferred method of communication) or via a proxy, as agreed and in accordance with local regulations.

Participants who do not complete the required information despite reminders will be contacted directly by the relevant NCC.

Where permitted by local regulations, permission will be sought to collect data from any available national/local registries.

All consenting participants are expected to be followed up to the end of the study. All efforts must be made to maintain follow-up per the visit schedule. If this is not possible, follow-up should still occur wherever possible via periodic contact, the participant's other nominated contacts, their usual doctors, contact at study closure and any available national/local registries, as permitted by local regulations.

To ensure no bias is introduced into the assessment of possible late safety signals from prior evolocumab treatment in the FOURIER OUTCOMES trial, every effort will be made to ascertain causes of death for participants who may have died since the FOURIER OUTCOMES trial close-out and prior to the commencement of this study.

### *5.3 Withdrawal From Contact or From Follow-up*

Withdrawal from on-going contact by the designated NCC may occur at any time by participant request, with confirmation to be documented clearly. Withdrawal of consent should only occur if the participant refuses any further assessments or contact whatsoever. Any data collected prior to a participant's withdrawal of consent will be maintained in the database and analyzed.

It is expected that all options for continued participation are explained to the participant and the reason for refusal is documented.

For participants who formally withdraw consent from the study, direct ascertainment of health status at the end of the study or vital status via public records will be performed in compliance with local privacy laws/practices. If specifically requested, in accordance with local regulations, participant data can be removed completely.

# 6 OUTCOMES, ENDPOINTS AND OTHER MEASUREMENTS

### *6.1 Cardiovascular Outcomes*

Wherever possible the definitions applied in the FOURIER OUTCOMES trial will be used in this study.

- Myocardial infarction is defined as presence of cardiac symptoms consistent with an ACS plus elevated cardiac biomarkers (e.g., elevated troponin); ECG changes consistent with myocardial ischemia or infarction (e.g., ST segment changes) can be used to support on confirm the diagnosis.
- Stroke is defined as any neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction or a focal neurologic deficit that persists for >24 hours without other obvious cause.
- Coronary revascularization is defined as any procedure intended to restore coronary blood flow either percutaneously (including angioplasty and stenting) or via coronary artery bypass surgery.

### *6.2 Cardiovascular Death and Coronary Heart Death*

Cardiovascular death is defined as one of the following: death due to MI, stroke, heart failure, or other cardiovascular causes. Coronary heart death is defined as death due to acute MI or sudden cardiac death.

### *6.3 Non-cardiovascular Death*

Non-cardiovascular death is defined as death from any non-cardiovascular cause.

### *6.4 Cardiovascular Hospitalization*

Cardiovascular hospitalization is defined as hospitalization for any cardiovascular reason.

### *6.5 Amputation and Peripheral Revascularization*

Amputation is defined as non-traumatic amputation of an extremity more proximal than the distal phalanx.

Peripheral revascularization is defined as revascularization of any peripheral artery either surgically or percutaneously.

### *6.6 Prescription Lipid-lowering Treatment Use*

Use of prescription lipid-lowering treatment classes during follow-up period.

# 7 SAFETY REPORTING

### *7.1 Reporting of Serious Adverse Events (including SUSARs*

No information for adverse events on specific drugs will be collected in this trial for the following reasons:

- Extensive safety data for evolocumab was already gathered in a rigorous, double-blind, placebo-controlled manner in a very large number of individuals in the FOURIER OUTCOMES trial.
- Amgen, the maker of evolocumab, is conducting two open-label extension studies of evolocumab in 6700 patients who received evolocumab in FOURIER OUTCOMES trial, thereby extending the duration of exposure to evolocumab to 7 years. (ClinicalTrials.gov Identifiers: NCT02867813 and NCT03080935).

Participants will be under the clinical care of their primary physician with no care provided by the NCC. If the investigator suspects or becomes aware of an adverse drug reaction(s) (serious or non-serious) or product complaints related to evolocumab use (past or current), this information shall be reported to Amgen within one (1) business day of the investigators' awareness or to the concerned competent authority via the national spontaneous reporting system. If it is not known what PCSK9i inhibitor a subject was on at the time of the event, this information will still be reported.

# 8 CENTRAL REVIEW

### *8.1 Endpoint Adjudication*

Event information (masked to previous FOURIER OUTCOMES trial treatment allocation) will be adjudicated centrally by each RCC. At least 10% of non-fatal CV events and all deaths will be selected for central adjudication by RCCs, and NCCs will be asked to collect source data for these events.

Further details of outcome definitions for adjudication can be found in the adjudication guidelines which will be based on definitions used in the FOURIER OUTCOMES trial endpoint committee charter.

# 9 STATISTICAL CONSIDERATIONS

## *9.1 Sample Size*

The event rate for the primary endpoint in the parent FOURIER OUTCOMES trial among participants allocated to placebo was 11.3% over a median follow-up of 2.2 years (i.e., 5% per annum). For a minimum of 10,000 participants, followed over 5 years post-trial, with an assumed average post-trial event rate of 5% per annum for the primary endpoint excluding hospitalization for unstable angina pectoris (UAP), then the observational FOURIER LEGACY study would have over 95% power at 2P=0.05 to detect an additional 20% proportional event reduction accruing post-trial, and over 90% power to detect an additional 15% proportional event reduction. The study would also offer 80% power at 2P=0.05 to detect a 23% reduction in CVD death from 4.94% to 3.8% over up to 5 years.

## *9.2 Statistical Analysis*

The analyses will examine the effects of long-term evolocumab therapy on cardiovascular events, total mortality, and cause-specific mortality. Analyses will include all participants who entered the FOURIER LEGACY study in participating countries, irrespective of whether they completed the FOURIER LEGACY study. (Data including baseline characteristics, medications, event history and during follow-up etc. will be incorporated into the follow-up database from the FOURIER OUTCOMES trial database). The characteristics of participants at participating sites/countries who did and did not contribute to the FOURIER LEGACY study will be compared. Likewise, the characteristics of subjects who complete the FOURIER LEGACY study vs. those who do not will be compared.

Qualitative and quantitative data will be described using counts, means, medians, and percentages with ranges or standard deviations as appropriate. Event data will be analyzed according to the participants' original randomly assigned therapy in the OUTCOMES study, on an intention-to-treat basis. Time to event information will be presented using Kaplan-Meier curves, and described according to Cox proportional hazard ratios (and 95% CIs), with comparisons between curves using standard log-rank tests. Similar methodology will be used for analyses of any pre-specified subgroups (e.g., baseline participant characteristics). In the circumstance that the hazards violate the test of proportionality, methods such as time-partitioned regression techniques will be utilized. Tests for interaction will be used to evaluate for evidence of differences in treatment effects between subgroups. Recurrent event analysis will be performed using the methods of Wei, Lin and Weissfeld[12] . Analyses, both unadjusted and adjusted for baseline measures, will be performed. Cause-specific mortality will also be analyzed using competing risks methods.

Further analysis investigating the impact of baseline characteristics (at time of randomization into the OUTCOMES study) on events will be performed using regression methods (linear, logistic, and proportional hazards) as appropriate.

Separate analyses examining effects post study close will be performed to evaluate the trajectory of effects long-term using appropriate methods (e.g., landmark analysis and conditional probability plots), again by original treatment assignment, among the FOURIER LEGACY study cohort from the time of randomization.

No adjustments will be made for multiple comparisons. Statistical inferences will be drawn based on the 5% level of significance. Expanded details will be provided in a separate Statistical Analysis Plan prepared prior to interim analysis.

## *9.3 Interim Analyses*

Interim analyses of accrued data may be conducted annually during FOURIER LEGACY study follow-up. No formal early stopping rules will be used.

# 10 STUDY ORGANIZATION and COMMITTEES

## *10.1 Study Coordination*

The study is an international collaborative group study that will be coordinated by the NHMRC CTC and other RCCs.

Global statistical analysis will be performed by the NHMRC CTC in collaboration with the TIMI Study group.

## *10.2 Trial Executive Committee*

The Study Executive Committee will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g., ethics committees). The Executive Committee of the FOURIER LEGACY study will comprise of members of the FOURIER OUTCOMES Trial Executive Committee (comprising the members of the RCCs).

The Executive Committee will consider whether to continue the study as planned or modify the protocol, or stop it, based on interim analyses or other information subject to the funding agency (Amgen's) agreement.

The detailed responsibilities of the Executive Committee, its relationship with the other parties responsible for the management and conduct of the study, its membership, and the purpose and timing of its meetings will be detailed in a separate charter.

## *10.3 Trial Management Committee*

The TMC will oversee study progress with reporting from the Executive Committee and will be involved in major decisions impacting the progress and success of the trial.

The detailed responsibilities of the TMC, its relationship with the other parties responsible for the management and conduct of the study, its membership, and the purpose and timing of its meetings will be detailed in a separate charter.

The TMC will be comprised of members of the FOURIER LEGACY Trial Executive Committee and representatives from each of the participating NCCs.

## *10.4 Independent Safety and Data Monitoring Committee*

No ISDMC will be required, as the observational follow-up study involves no specific treatment.

The Executive Committee will review all interim analyses, in addition to other information that might influence decisions to continue the study.

# 11 ADMINISTRATIVE ASPECTS

## *11.1 Ethics and Regulatory Compliance*

This study will be conducted according to ICH Good Clinical Practice 1995 (Integrated Addendum to ICH E6 (R1): Guidelines for Good Clinical Practice ICH E6(R2)) and local regulations.

The study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with any local comments and in compliance with applicable laws and regulations in each country. The study will be performed in accordance with the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008.

To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided written informed consent.

## *11.2 Confidentiality*

The study will be conducted in accordance with applicable privacy acts and regulations. All data generated in this study will remain confidential. All information will be stored securely at the NHMRC CTC, University of Sydney, and will only be available to people directly involved with the study. The results of this study and a copy of the anonymised database will be provided to the TIMI Study Group and Amgen (if requested).

All regulatory requirements for protecting patient privacy, confidentiality and locally-approved methods for electronic data linkage will be complied with. All analyses will be by study ID, without patient names or other identifiers used. Strict access restrictions to all personal information will be adhered to at all times, as compatible with approvals granted for the performance of the study.

Personal data identifying trial participants will be held securely solely at each NCC for the purpose of follow-up. Storage of, and access to, pseudonymized data will be managed by the University of Sydney.

## *11.3 Protocol Amendments*

Changes and amendments to the protocol can only be made by the Executive Committee. Approval of amendments by the Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the data collected, if required, will be incorporated in the amendment.

The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial participant(s).

## *11.4 Data Handling and Record Keeping*

All trial data required for the monitoring and analysis of the study will be recorded on the (e)CRFs provided. All required data entry fields must be completed. Data corrections will be done according to the instructions provided.

Source documents pertaining to the trial must be maintained by NCCs. Source documents may include a participant's medical records, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a participant's study-related data.

The following information should be entered into the participant's file:

a. The participant’s protocol identification.

b. The date that the participant entered the study, and participant number.

c. A statement that informed consent was obtained (including the date)

d. Relevant medical history

e. Occurrence and status of any identified Adverse Drug Reactions reportable to pharmaceutical company

f. The date the participant exited the study, and a notation as to whether the participant completed the study or reason for discontinuation.

All study-related documentation at study sites will be maintained for at least 15 years following completion of the study.

### *11.5 Monitoring, Audit and Inspection*

Monitoring will be in accordance with the monitoring plan. This study may be participant to inspection by representatives of the Trial Executive Committee, the funding agency Amgen, the CTC, representatives of other RCCs, or representatives of regulatory bodies.

### *11.6 Clinical Study Report*

A Clinical Study Report which summarises and interprets all the pertinent study data collected will be issued which may form the basis of a manuscript intended for publication. The Clinical Study Report or summary thereof will be provided to the manufacturer of the study medication if requested.

### *11.7 Publication Policy*

The Trial Executive Committee will act as the Writing Committee to draft manuscript(s) based on the trial data. Manuscript(s) will be submitted to peer-reviewed journal(s). The Writing Committee will develop a publication plan, including authorship, target journals and expected dates of publication. All manuscripts will be available prior to submission for comment from the study funder. Publication authorship will abide by the ICJME Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.

The Executive Committee support the spirit and intent of sharing of clinical trial data.

# 12 PROTOCOL AMENDMENTS

| Amendment No. | Date | Summary of Change |
|---|---|---|
| 1.2 | 23 April 2019 | Clarification of survey question text. Section 14.1 Appendix 1. Questionnaire to Patients, question (vii) Been admitted to hospital for your heart condition?<br>Changed to (vii) Been admitted to hospital for your heart condition? **(cardiovascular hospitalization is defined as hospitalization for any cardiovascular (heart or blood vessel) reason)?** |
| 1.3 | 18 August 2019 | Added survey question response option 'Unsure' for consistency.<br>Section 14.1 Appendix 1. Questionnaire to Patients, response to question (viii), (ix) and (x). Response options previously available (Yes/ No). This has changed to (Yes / No / **Unsure**)<br>Addition of Study Schema after the Synopsis<br>Addition of text to section 11.2 Confidentiality with wording about the study results and anonymised database being shared with TIMI and Amgen.<br>Addition of section 11.4 Data Handling and Record Keeping<br>Addition of section 11.6 Clinical Study Report |

# 13 REFERENCES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# 14 APPENDICES

## *14.1 Appendix 1. Questionnaire to Patients*

Since you last made contact with us, have you suffered from any of the following new health events?

(i) A new heart attack? (Y/N/Unsure)

(ii) A new stroke? (Y/N/Unsure)

(iii) Had one or more new coronary angioplasties (balloon treatment) or coronary stenting? (Y/N/Unsure)

(iv) Had new coronary artery bypass surgery? (Y/N/Unsure)

(v) Had a new angioplasty (balloon treatment) or stenting to the leg vessels? (Y/N/Unsure)

(vi) Had an amputation of any limb (not relating to injury or accident)? (Y/N/Unsure)

(vii) Been admitted to hospital for your heart condition (cardiovascular hospitalization is defined as hospitalization for any cardiovascular (heart or blood vessel) reason)? (Y/N/Unsure)

[For each of the above, if yes, please give month and year]

*[If response is "unsure", then "thank you, we will contact you directly to help clarify your answer"]*

Please also answer the following questions:

(viii) Are you still taking a statin tablet to lower your cholesterol (you needed to be taking one to take part in the FOURIER trial)? (Y/N/Unsure)

(ix) Are you still taking a cholesterol lowering injection (PCSK9 inhibitor drug) similar to as in the FOURIER trial (you needed to start one when you joined the FOURIER trial)? (Y/N/Unsure)

(x) Are you taking a medication (e.g., ezetimibe or Zetia) to slow absorption of cholesterol from your diet? (Y/N/Unsure)

PLEASE INDICATE BELOW IF YOU WISH TO BE CONTACTED BY THE STUDY TEAM TO DISCUSS ANY NEW HEALTH ISSUES SINCE WE LAST CONTACTED YOU (Y/N)

Thank you very much for your participation, and for keeping us updated about your health. We will contact you again in 1 years' time to stay in touch. If you have told us that you have had one of the above health events, then we may contact you sooner, to learn more about it if necessary.