fourierLEGACY

Newsletter (International)

Number 4. **Nov 2019**

Dear Colleagues,

We are pleased to announce that we are making slow but steady progress with the FOURIER LEGACY study. We were pleased to see some of our National Leads at the recent European Society of Cardiology meeting in Paris (photos below).

BREAKING NEWS

We have just heard that the definitive agreement between University of Sydney and Amgen is now ready for signing. This means that we are finally in a position to prepare and sign our own definitive agreement and progress with the study. At long last!

We wish you and your teams a very happy festive season !

New Protocol

There is now a new version of the study protocol, v1.3, which is sent as an attachment to this email.

The main changes are as follows:-

Section 11.2 - Confidentiality

- The study results and anonymised database will be shared with TIMI and Amgen, for research and analysis.

- Added response option of 'Unsure' for consistency to the questions about lipid lowering therapy.

- Other minor editorial changes including addition of Study Schema, addition of sections on Data Handling/Record Keeping and Clinical Study Report

Group Specific Appendix (GSA)
If there are variations to the protocol specific to any country, these will be added as a Group-Specific Appendix to the protocol for each country.

For example, for countries in which sites are performing the follow-up for participants (rather than the NCC doing the consent and follow-up), this can be described in the Group Specific Appendix before submission to Ethics.

Revised Participant Information Sheet
There is a revision to the Global template, incorporating the updates in data sharing. The new version of the global template is v1.2 (attached).

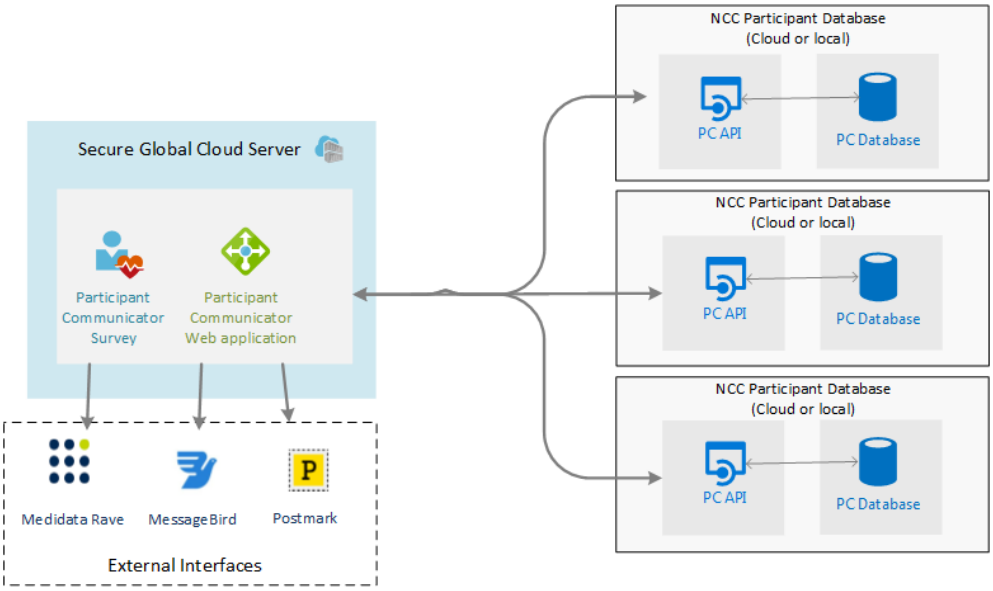
Obtaining Information on Patients Who Have Died
One of the most discussed issues with data collection in FOURIER LEGACY is how we may be able to obtain information on deaths that have occurred since the end of the FOURIER OUTCOMES study.

In the UK, we have approached the Confidentiality Advisory Group (for England, Scotland and Wales) and the Privacy Advisory Committee (for Northern Ireland).

The responses that we received from both groups were positive. 'Death certificates are not usually considered to be confidential patient information as they are publicly available on request from the General Register's Office (GRO). A member of the CAG Chair Team reviewed the application and advised that requesting the death certificates from patient's GPs, rather than the GRO, does not affect the view that the certificates are not confidential patient information'.

NCC Contracts Update
We are at final draft stage with NCC contracts. These are currently with the legal department at Imperial College and will be sent to all NLIs within the next two weeks.
There is one section (Schedule X) that relates to any specific data transfer requirements for data to be sent from non-EEA countries to the UK. This is to be filled in, if required, by the NCC

IT
The patient communicator is the system set up to record participants' confidential information and to send messages to participants to prompt them to complete their questionnaires.



This will be housed within each NCC country and no confidential information will leave that country.

There are two ways of hosting the participant communicator

- using a cloud-based system, hosted by Azure. Probably the easiest option, requires no financial outlay for server, has access to back up and support for users.
- using a separate server within the NCC

Further information on the IT systems used in the study are attached to this newsletter.

Once contracts between NCC and Imperial have been agreed, we will arrange a telephone conference between National Leads, their IT departments and the IT lead at University of Sydney.

Update on FOURIER Publications
The following papers have been published since the end of the trial:-

1. **Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease**. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators. *N Engl J Med*. 2017;376:1713-1722.

Main paper showing that evolocumab reduced LDL-cholesterol by 59%. This was associated with a reduction in the primary endpoint of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina and coronary revascularisation, by 15% (p<0.001) and the key secondary endpoint of cardiovascular death, myocardial infarction and stroke, by 20% (p< 0.001).

2. **Cognitive Function in a Randomized Trial of Evolocumab.** Giugliano RP, Mach F, Zavitz K, Kurtz C, Im K, Kanevsky E, Schneider J, Wang H, Keech A, Pedersen TR, Sabatine MS, Sever PS, Robinson JG, Honarpour N, Wasserman SM, Ott BR; EBBINGHAUS Investigators.
N Engl J Med. 2017;377:633-643.

Major substudy (Ebbinghaus) showing that compared with placebo, evolocumab had no adverse effects on cognitive function assessed by a variety of tests of memory and executive function

3. **Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial**. Sabatine MS, Leiter LA, Wiviott SD, Giugliano RP, Deedwania P, De Ferrari GM, Murphy SA, Kuder JF, Gouni-Berthold I, Lewis BS, Handelsman Y, Pineda AL, Honarpour N, Keech AC, Sever PS, Pedersen TR.
Lancet Diabetes Endocrinol. 2017 ;5:941-950.

Benefits of evolocumab in patients with diabetes similar to those observed in non-diabetic subjects. No evidence that evolocumab increased the risk of new-onset diabetes.

4. **Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk).** Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, Kuder J, Murphy SA, Jukema JW, Lewis BS, Tokgozoglu L, Somaratne R, Sever PS, Pedersen TR, Sabatine MS.
Circulation. 2018 ;137338-350.

Substantial benefits on cardiovascular outcomes seen with evolocumab in patients with peripheral vascular disease, including a 42% reduction in the risk of adverse limb events (p<0.0093).

5. **Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial**.
Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Gaciong ZA, Ceska R, Toth K, Gouni-Berthold I, Lopez-Miranda J, Schiele F, Mach F, Ott BR, Kanevsky E, Pineda AL, Somaratne R, Wasserman SM, Keech AC, Sever PS, Sabatine MS; FOURIER Investigators.
Lancet. 2017;3901962-1971.

Highly significant relationship between low LDL-cholesterol levels and lower risk of cardiovascular endpoints extending to levels < 0.2 mmol/L. No safety concerns observed with achieving very low levels of cholesterol.

6. **Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease**.
Sabatine MS, De Ferrari GM, Giugliano RP, Huber K, Lewis BS, Ferreira J, Kuder JF, Murphy SA, Wiviott SD, Kurtz CE, Honarpour N, Keech AC, Sever PS, Pedersen TR.
Circulation. 2018;138:756-766

Patients recruited into Fourier closer to their most recent myocardial infarction ,those with a history of multiple myocardial infarctions and those with multivessel coronary disease, were at high risk of cardiovascular events and experienced substantial reductions in cardiovascular endpoints.

7. **Clinical Efficacy and Safety of Evolocumab in High-Risk Patients Receiving a Statin: Secondary Analysis of Patients with Low LDL Cholesterol Levels and in Those Already Receiving a Maximal-Potency Statin in a Randomized Clinical Trial.** Giugliano RP, Keech A, Murphy SA, Huber K, Tokgozoglu SL, Lewis BS, Ferreira J, Pineda AL, Somaratne R, Sever PS, Pedersen TR, Sabatine MS.
JAMA Cardiol. 2017 ;2:1385-1391

Evolocumab was equally effective in reducing cardiovascular events in patients with stable atherosclerotic cardiovascular disease regardless of whether the baseline LDL-C was less than 70 or at least 70 mg/dL and whether the background statin was of maximal or submaximal potency.

8. **Cost-effectiveness of Evolocumab Therapy for Reducing Cardiovascular Events in Patients with Atherosclerotic Cardiovascular Disease**. Fonarow GC, Keech AC, Pedersen TR, Giugliano RP, Sever PS, Lindgren P, van Hout B, Villa G, Qian Y, Somaratne R, Sabatine MS.
JAMA Cardiol. 2017 ;2:1069-1078

Initial cost effectiveness analyses of evolocumab based on Fourier data

9. I**nflammatory and Cholesterol Risk in the FOURIER Trial.** Bohula EA, Giugliano RP, Leiter LA, Verma S, Park JG, Sever PS, Lira Pineda A, Honarpour N, Wang H, Murphy SA, Keech A, Pedersen TR, Sabatine MS.
Circulation. 2018 ;138;131-140

This paper addresses the question of whether the benefits of evolocumab are modified by baseline inflammatory risk as assessed by high sensitivity (hs) CRP. LDL-C reduction with evolocumab reduces cardiovascular events across hsCRP strata with greater absolute risk reductions in patients with higher-baseline hsCRP. Event rates were lowest in patients with the lowest hsCRP and LDL-C.

10. **Effect of the PCSK9 Inhibitor Evolocumab on Total Cardiovascular Events in Patients with Cardiovascular Disease: A Prespecified Analysis From the FOURIER Trial.** Murphy SA, Pedersen TR, Gaciong ZA, Ceska R, Ezhov MV, Connolly DL, Jukema JW, Toth K, Tikkanen MJ, Im K, Wiviott SD, Kurtz CE, Honarpour N, Giugliano RP, Keech AC, Sever PS, Sabatine MS.
JAMA Cardiol. 2019;4:613-619

This paper shows that when analyses incorporated all cardiovascular events occurring during the trial rather than time to first event analyses, more than double the number of events were recorded and the risk reductions associated with evolocumab were substantial.

11. **Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk.** O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I, Im K, Lira Pineda A, Wasserman SM, Češka R, Ezhov MV, Jukema JW, Jensen HK, Tokgözoğlu SL, Mach F, Huber K, Sever PS, Keech AC, Pedersen TR, Sabatine MS.
Circulation. 2019 ;139:1483-1492

Higher levels of Lp(a) are associated with an increased risk of cardiovascular events in patients with established cardiovascular disease irrespective of low-density lipoprotein cholesterol. Evolocumab significantly reduced Lp(a) levels, and patients with higher baseline Lp(a) levels experienced greater absolute reductions in Lp(a) and tended to derive greater coronary benefit from PCSK9 inhibition.

12. **Efficacy and Safety of Evolocumab in Chronic Kidney Disease in the FOURIER Trial.** Charytan DM, Sabatine MS, Pedersen TR, Im K, Park JG, Pineda AL, Wasserman SM, Deedwania P, Olsson AG, Sever PS, Keech AC, Giugliano RP; FOURIER Steering Committee and Investigators.
J Am Coll Cardiol. 2019 ;73:2961-2970

LDL-C lowering and relative clinical efficacy and safety of evolocumab versus placebo were consistent across all CKD groups. Absolute reduction in the composite of cardiovascular death, MI, or stroke with evolocumab was numerically greater with more advanced CKD.

13. **Interindividual Variation in Low-Density Lipoprotein Cholesterol Level Reduction with Evolocumab: An Analysis of FOURIER Trial Data.** Qamar A, Giugliano RP, Keech AC, Kuder JF, Murphy SA, Kurtz CE, Wasserman SM, Sever PS, Pedersen TR, Sabatine MS.
JAMA Cardiol. 2019;4:59-63

Paper shows highly consistent and robust reduction in LDL-cholesterol levels with evolocumab. Interesting variability in response demonstrated in both evolocumab and placebo groups.

FOURIER LEGACY team contact details:
Peter Sever (Chief Investigator for UK) p.sever@imperial.ac.uk, 0207 594 1099
Andrew Whitehouse (Clinical Research Fellow) a.whitehouse@imperial.ac.uk, 0207 594 3437
Judy Mackay (Honorary Research Fellow) j.mackay@imperial.ac.uk, 0207 594 9890
Vanita Vij Narang (Project Manager), v.vij-narang@imperial.ac.uk, 0207 594 3414
Candy Coghlan (Lead Research Nurse) c.coghlan@imperial.ac.uk, 0207 594 2911
Yvonne Green (Administrator and PA to Peter Sever) y.green@imperial.ac.uk, 0207 594 1100

Study email: fourier.legacy@imperial.ac.uk
Website: https://www.imperial.ac.uk/medicine/fourier-legacy