STUDY NEWSLETTER

Issue No. 7, 6th November 2020

A welcome from the NCC Principal Investigator

Dear Study Teams,

Thank you for your continued support with the FOURIER LEGACY study, especially during the coronavirus pandemic.

Due to the surge of sites resuming activities from COVID-19 hold, we now have a total of **49 sites** activated which is 82% of our target in the UK.

From these activated sites, we have been able to fully enrol **424 participants** on to the study, that is 42% of our national target of which 49 (8%) are deceased patients.

We have also gone on to complete 364 baseline questionnaires in the UK. Globally, 227 outcomes that have been reported.

We are also happy to tell you that South Africa is now open for recruitment for FOURIER LEGACY alongside the UK and Netherlands.

Dr Judy Mackay

Fourier LEGACY has been recruiting relatively well. As assenting potential participants can be done over the phone, some sites have processed their patient lists in as quickly as **A DAY** whilst others have the flexibility to sporadically recruit around other priorities.

Out of the 49 sites activated, 25 have fully completed recruitment and 24 sites are currently recruiting or open for recruitment. Only 11 sites are remaining to be open, with 2 of these currently still on COVID-19 hold.

Scotland & PBPP

We are also very close to opening our Scottish sites once we have approval from Public Benefit and Privacy Panel for Health and Social Care (PBPP) to collect data on deceased patients.

Synexus (AES)

We are also in the process of initiating our Synexus (AES) sites in Lancashire, Manchester, Merseyside, Midlands, North East, Thames Valley, Wales, and Scotland.

UK STUDY RECRUITMENT

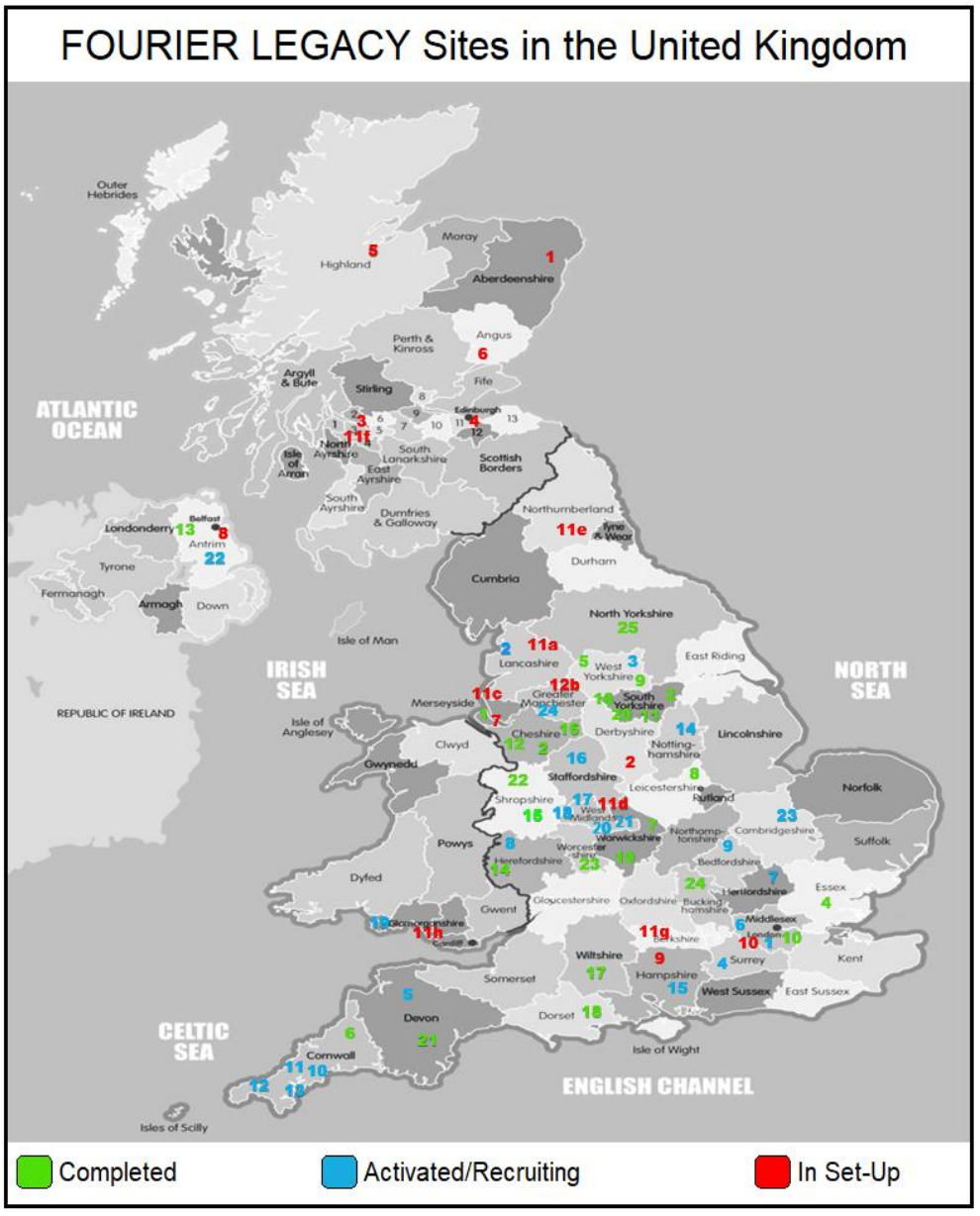
Congratulations to our team members across the UK

Thank you to the following 25 sites whose participants have completed recruitment with us:

Arrowe Park Hospital (1)
Ashfields Primary Care Centre (2)
Barnsley Hospital (3)
Basildon and Thurrock University Hospital (4)
Bradford on Avon and Melksham Health Centre (5)
Brannel Surgery (6)
George Eliot Hospital (7)
Glenfield Hospital [Leicester] (8)
Leeds General Infirmary (9)
New Cross Hospital [Wolverhampton] (10)
Northern General Hospital (11)
Northwick Park Hospital (12)
Ormeau Clinical Trials Ltd. (13)
Portmill Surgery (14)
Princess Royal Hospital [Shrewsbury] (15)
Rotherham General Hospital (16)
Rowden Surgery (17)
Royal Bournemouth Hospital (18)
Sherbourne Medical Centre (19)
South Axholme Practice (20)
Torbay Hospital (21)
Whitby Group Practice (22)
Worcestershire Acute Hospitals (23)
Wrexham Maelor Hospital (24)
York Hospital (25)

The following 24 sites are currently activated or open for recruitment:

William Harvey Clinical Research Centre [Barts] (1)
Blackpool Teaching Hospitals (2)
Castle Hill Hospital [Hull] (3)
Crouch Oak Family Practice (4)
Derriford Hospital [Plymouth] (5)
Hammersmith Hospital [Imperial College Healthcare] (6)
Lister Hospital (7) , and Queen Elizabeth II ([East & North Hertfordshire] (8)
Luton & Dunstable Hospital (9)
Mounts Bay Medical Ltd [Morrab Surgery (10), Penalverne Surgery (11), Connor Downs Surgery (12), and Cape Cornwall Surgery (13)]
Nottingham University Hospitals (14)
Queen Alexandra Hospital [Portsmouth] (15)
Royal Stoke University Hospital (16)
Sandwell General Hospital*** (17) and City Hospital*** (18)
Joint Clinical Research Facility [Swansea] (19)
Cardiology and Stroke Unit, and Hospital of St Cross [University Hospitals Coventry] (20), (21)
Ulster Hospital (22)
West Suffolk Hospital (23)
Cardiovascular Research Hub [Manchester University NHS Foundation Trust] (24)



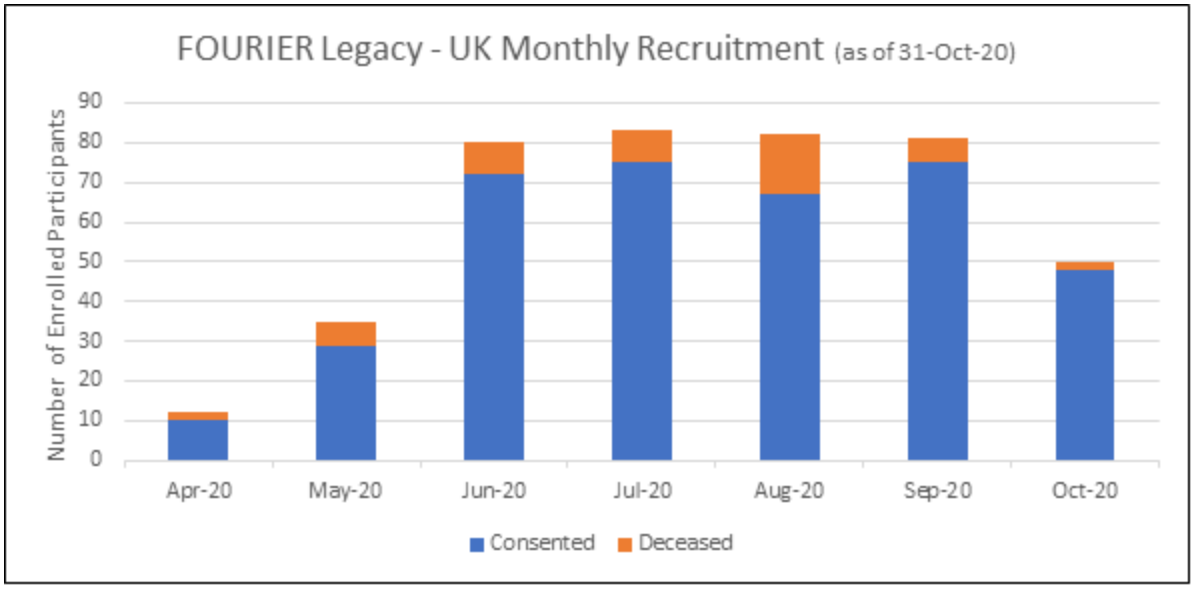
The following 11 sites are currently in set-up:

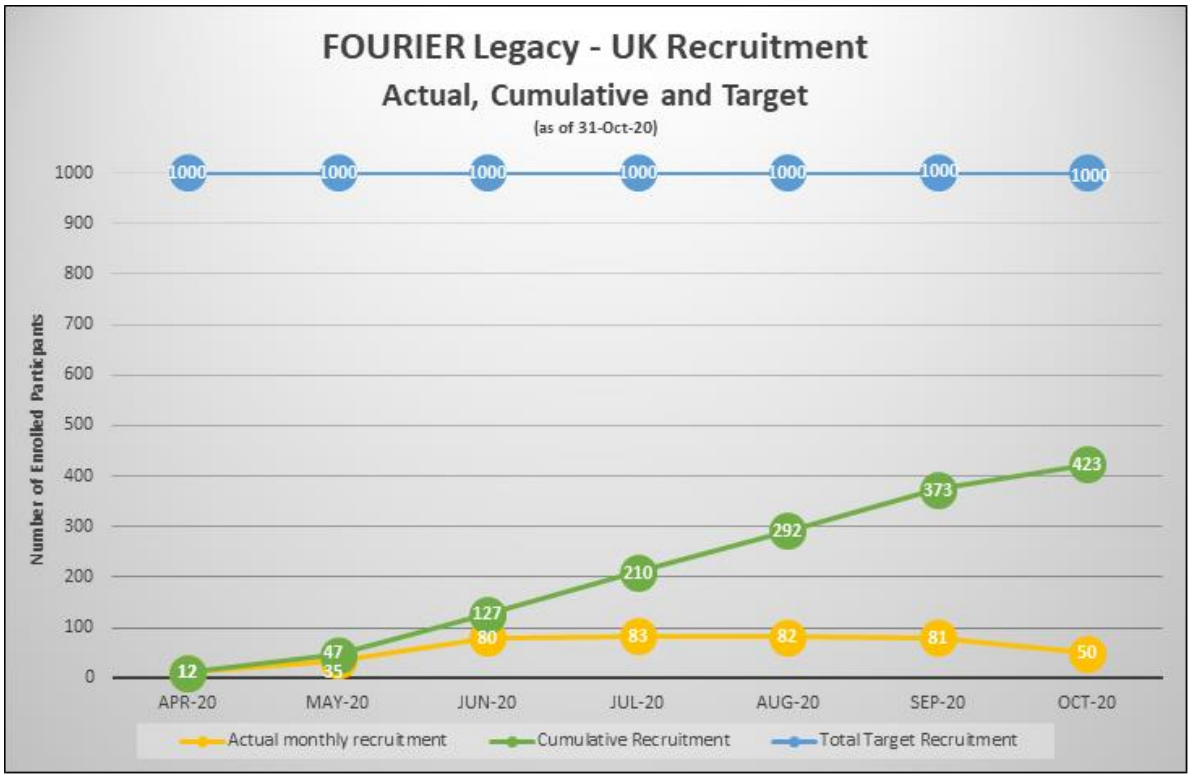
Aberdeen Royal Infirmary+++ (1), Ashgate (Avondale) Medical Practice*** (2)., Castlemilk Group Practice [Glasgow & Clyde]+++(3), Edinburgh Royal Infirmary [Lothian]+++ (4), Centre for Health Science [Highland]+++ (5), Ninewells Hospital and Medical School Dundee [Tayside]+++ (6), Royal Liverpool Hospital (7), Royal Victoria Hospital [Belfast] (8), Vectasearch Clinic [St Mary's Hospital]*** (9), St Thomas' Clinical Research Facility [Guys and St Thomas] (10), Synexus Lancashire Clinical (11a), Synexus Manchester Clinical Research Centre (11b), Synexus Merseyside Clinical Research Centre (11c), Synexus Midlands Clinical Research Centre (11d), Synexus North East Clinical Research Centre (11e), Synexus Scotland Clinical Research Centre (11f), Synexus Thames Valley Clinical Research Centre (11g), and Synexus Wales Clinical Research Centre (11h)

*** Activities of these sites are on hold due to COVID-19 Pandemic.

+++ Activities of these sites are pending by PBPP.

UK RECRUITMENT NUMBERS *(AS OF 03 Nov 2020)*





UK FIGURES (Number of Patients)	
Processed by sites: 604 (89%)	Interested in participating: 453 (93%)
Deceased: 49 (8%)	Consented: 375 (63%)
Assented: 489 (84%)	Withdrawn: 0
Declined: 32 (7%)	Enrolled (consented + deceased): 424

Consenting experiences

Our conversion rate of participant IDs from Fourier OUTCOMES that end up enrolled into Fourier LEGACY remains high at 75%. The best method of contact for participants is still over the phone which is when participants also complete their baseline surveys.

The consenting process is still lengthy as it is conducted over the phone and via post. However, once we have patients consented, subsequent follow-up surveys can be done electronically via text or email which will help to speed up the follow-up phase.

Patient surveys and reported outcomes

We have now completed 365 baseline questionnaires which is 97% of those enrolled. Some of our first participants to join the study are now completing their six-month survey.

Additionally, we now have 227 global outcomes reported, of which 47 are confirmed deaths from the UK.

Data review and adjudication

We are scheduled to begin our first round of event adjudications in November.

Thank you again for your continued support with collecting source documentation for deceased patients as well as other selected outcomes where needed. As you may recall from the training, all death data and at least 10% non-fatal events are to be chosen for adjudication. Below are some examples of possible source documents that would help us adjudicate death outcomes:

- Death/Discharge Summary (if death occurred in-hospital)
- Death Certificate
- Relevant Progress or Consultation Notes
- Event summary signed/dated by Principal Investigator if there are no source documents available

Currently, we have 50 global events selected for adjudication with the UK source documents fully secured from either the participating PIC sites or patient's GPs. Please continue to ensure that source documents are fully redacted with only the patient's study number before sending them over to us.

Other important study information

Substantial Amendment 3

We now have REC favourable opinion and HRA/ HCRW approval for the recent substantial amendment 3. Recruiting sites can now implement this amendment now or by the **28th Oct 2020**.

The main updates that are applicable to PIC sites include:

- Updated verbal consent form v2.0 23.07.20 (assent) to allow site to collect patient's date of birth details
- Updated group-specific appendix v3.0 22.09.20 (GSA) providing clarifications around the collection of deceased patient data
- Extending the study recruitment from December 2020 through until 30 June 2021
- Addition of tele-script (for Synexus sites only).

Reminder: To avoid potential data breaches

A reminder to sites (not applicable to those using the secure file transfer portal) to please ensure that Patient identifiable details are ***only*** sent to a nhs.net email account and ***not*** an Imperial College email account. The secure email addresses to send any patient identifiable details to are:

- Candy Coghlan at: **c.coghlan@nhs.net**
- Andrew Whitehouse at: **andrew.whitehouse2@nhs.net**
- Judy Mackay at: **judith.mackay1@nhs.net**

Once we receive first batch of patient data, your site will be allocated to one of our NHS Imperial team members who will send you an introductory email of receipt and be your point of contact going forward.

COVID-19 & FOURIER LEGACY

A message from RCC investigator regarding COVID-19 and FOURIER Legacy

Covid-19 has affected all our lives in one way or another. Many of our investigators, particularly those working in hospitals will have been on the front line looking after sick patients during the peak of admissions in the early summer. Fortunately, hospitalisations for Covid-19 are currently much lower, but numbers are increasing during the second wave which we are now experiencing. Hopefully new measures to protect virus transmission will prevent a return to the high levels we experienced earlier this year.

Inevitably most clinical trial activities operating from hospital sites were suspended in March and this has applied to a number of FOURIER sites. Several of these are now back in action with others coming on board in the next few weeks. GP sites have been less affected by restrictions and since site activity is essentially based on telephone contact with patients this has continued unhindered by Covid-19. In fact, largely because of lockdown, we have found it surprisingly easy to contact patients. So far, our UK recruitment rate is around 72% of those potentially eligible for our legacy study, which is very encouraging. We are very appreciative for the commitment of our sites to the recruitment of patients during these difficult times and we are hopefully on course to meet our goal of around 1000 patients for the UK.

To our patients who have agreed to be followed up, we are very thankful for their participation in this important study and we look forward to keeping in touch with them over the next 18 months.

Professor Peter Sever

Whist we are all working from home currently, it's business as usual. We're busy working together and meeting regularly on Zoom.

PUBLICATIONS

There continues to be a proliferation of major publications arising from the FOURIER Study. Of 25 publications so far, 9 have been published in 2020.

1 Nick Marston and colleagues showed that combining a conventional risk prediction based on the number of risk factors with a genetic risk score derived from a 27 single-nucleotide polyporphism, that high genetic risk regardless of clinical risk was associated with high event rates and greatest benefit from evolocumab. *Marston NA, Kamanu FK, Nordio F, Gurmu Y, Roselli C, Sever PS, et al. Predicting benefit from evolocumab therapy in patients with atherosclerotic disease using a genetic risk score. Results from the FOURIER Trial. Circulation 2020;141:616-623.*

2 In a separate paper the same authors reported an extremely novel finding that PCSK9 inhibition with evolocumab reduced the risk of venous thromboembolism and that this benefit may have been mediated by a reduction in Lp(a). *Marston NA, Gurmu Y, Melloni GEM, Bonaca M, Gencer B, Sever PS, et al. The effect of PCSK9 inhibition on the risk of venous thromboembolism. Circulation 2020;141:1600.1607.*

3 Guigliano and colleagues extended the preliminary observations reported in the main FOURIER outcome paper and showed that evolocumab in combination with statins reduced the incidence of stroke including recurrent ischaemic stroke. *Giugliano RP, Pedersen TR, Saver JL, Sever PS, Keech AC, Bohula EA, et al. Stroke prevention with the PCSK9 (proprotein convertase subtilisin-kexin type 9) inhibitor evolocumab added to statin in high-risk patients with stable atherosclerosis. Stroke 2020;51:1546-1554.*

4 Bergmark and colleagues reported the results of an exploratory analysis in which Lp(a) levels were found to be associated with a higher risk of aortic stenosis events in the trial and that PCSK9 inhibition showed a trend , particularly after the first year of treatment to reduce the incidence of these events. *Bergmark BA, O'Donoghue ML, Murphy SA, Kuder JF, Ezhov MV, Ceška R, et al. An exploratory analysis of proprotein convertase subtilisin/kexin Type 9 inhibition and aortic stenosis in the FOURIER Trial. JAMA Cardiol 2020;5(6):709-713.*

5 Gencer and colleagues looked at those patients in FOURIER who had had a recent myocardial infarct prior to entry into the trial. Such patients are at much higher risk than those whose infarction occurred at a longer time interval prior to randomisation. *Gencer B, Mach F, Murphy SA, De Ferrari GM, Huber K, Lewis BS, et al. Efficacy of evolocumab on cardiovascular outcomes in patients with recent myocardial infarction: A prespecified secondary analysis from the FOURIER Trial. JAMA Cardiol. Published online May 20, 2020. doi:10.1001/jamacardio.2020.0882.*

6 Patients with a recent MI experienced higher absolute risk reduction than those with more remote MIs which supported the guidelines concept to aggressively lower LDL-cholesterol in very high risk papers. There have been a number of reports claiming that very low LDL-cholesterol levels could be associated with cognitive impairment, although meta-analyses have failed to confirm this. Ebbinghaus- a substudy of FOURIER showed that there was no evidence that low LDL- cholesterol was associated with a decline in cognitive function. In the other publication Gencer et al showed that in over 22,000 patients who completed a detailed survey on a number of aspects of cognition, that evolocumab had no impact on patient-reported cognition after 2.2 years of treatment , even among those patients who achieved very low cholesterol levels. *Gencer B , Mach F, Guo J, Im K, Ruzza A, Wang H, et al. Cognition after lowering LDL-cholesterol with evolocumab. J Am Coll Cardiol, 2020;75(18):2283-2293.*

7 Sever and colleagues carried out a prespecified analysis of the FOURIER outcomes to evaluate the effects of increasing age and gender on the benefits of evolocumab. Despite some suggestions that older patients might not achieve the full benefits of statins and some unfounded reports that women do not share the same benefits of lipid lowering as men, in FOURIER we showed conclusively that the benefits of PCSK9 inhibition continued throughout the whole age range , including the very elderly and that women benefited to the same extent as men. *Sever P, Gouni-Berthold I, Keech A, Giugliano R, Pedersen TR, Im K, et al. LDL-cholesterol lowering with evolocumab, and outcome according to age and sex in patients in the FOURIER Trial. Euro J of Preventive Cardiol 2020 Feb 4:2047487320902750.*

8 Deedwania and colleagues emphasised that patients with atherosclerotic disease and the metabolic syndrome were at very high residual risk despite statin treatment. They showed that evolocumab reduced their cardiovascular risk without increasing new-onset diabetes, worsening glycemic control or other adverse events. *Deedwania P, Murphy SA , Scheen A , Badariene J , Pineda AL, Honarpour N, et al. Efficacy and safety of PCSK9 inhibition with evolocumab in reducing cardiovascular events in patients with metabolic syndrome receiving statin therapy: secondary analysis from the FOURIER Randomized Clinical Trial. JAMA Cardiol 2020 Aug 12. doi: 10.1001/jamacardio.2020.3151. Online ahead of print.*

9 Finally, prior to writing this update, Wiviott and colleagues subdivided MI outcomes by size(severity) and whether they were STEMI or non-STEMI. Outcomes in the evolocumab arm of the trial were similar irrespective of the size or type of the MI. *Wiviott SD, Giugliano RP, Morrow DA, De Ferrari GM, Lewis BS, Huber K, et al. Effect of evolocumab on type and size of subsequent myocardial infarction: A prespecified analysis of the FOURIER Randomized Clinical Trial. JAMA Cardiol 2020;5(7):787-793.*

Many analyses are ongoing and further publications in the pipeline.

Watch this space!

UK NATIONAL COORDINATING CENTRE CONTACT LIST

Our Imperial Teams have been very busy, and we have some new staff who have come to join us. Our updated contacts list is below:

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We are here to help! Please do not hesitate to contact us if you have any queries or questions about the study.

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