Responding to COVID-19
New ways of working, new research programmes

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The purpose of this quarterly newsletter is to keep our global network of partners, trustees and friends of the Institute updated on the exciting and innovative work ongoing at the TRI.

In the last issue, I was pleased to announce ETHIC, a randomised controlled trial of prophylactic enoxaparin versus standard of care in community-based COVID-19 patients. We are on the cusp of enrolling our first patients in South Africa and Australia and I commend our Clinical Study teams who continue to collaborate with our Steering Committee and local teams in each participating country to achieve the many milestones successfully met so far. It is a fascinating study and we are proud to rise to the challenge of contributing to the global fight to constrain and eradicate the virus.

2020 has unleashed an unprecedented and difficult period for many institutions with an impact on life that will undoubtedly be long lasting.

2020 has unleashed an unprecedented and difficult period for many institutions with an impact on life that will undoubtedly be long lasting. The coronavirus has prompted a shift in focus and an opportunity to re-evaluate our priorities and in response we have two additional COVID-19 projects in progress and we will provide a broad overview of them in this issue.

I am also pleased to note the successful closure of the GARFIELD-AF, GARFIELD-VTE and RIVER studies (a decade in the running!). Alongside the publications these studies have yielded, they have become a vast source of data, which will undoubtedly prove very valuable in enabling us to further our research and improve treatments options for patients.

All the while, our facilities and administration teams have remained committed to ensuring our building is secure and safe, in line with public health advice and government restrictions for our team of laboratory scientists who continue to do great research. We have achieved an awful lot in the past 9 months and though the future is uncertain, I believe we are in a strong position to roll with events as they unfold and continue to produce meaningful, valuable contributions to our field.

My best wishes to you all.

Gloria Kayani

Responding to COVID-19

COO Gloria Kayani talks how COVID-19 has impacted TRI and the successful closure of our GARFIELD studies.
TRI AND THE PANDEMIC

Responding to COVID-19

Adapting our working practices in the light of the pandemic, two new studies and a vaccine.

Going remote and securing the office

From March 2020 TRI responded quickly and incisively to the situation in London, moving with rapidly evolving public health guidance. With TRI and CYTE primarily being office-based, a committee was formed to monitor the pandemic and prepare to move our operations fully remote. The committee was successful in this, navigating both the technical challenge (ensuring every staff member had a fully functional and secure IT set up in their home at short notice) as well as addressing health and safety.

Despite the circumstances, during the last six months of remote working we were able to mitigate disruption remarkably well. Staff took to collaboration via Microsoft Teams quickly, and our committee continued to monitor government regulations as we worked to get TRI HQ operational and safe for staff who rely on the usage of our lab facilities.

Our doors opened again in July for these lab-based staff members, and for those unable to work from home for other reasons. This was the culmination of a period of diligent preparations; our admin and facilities team undertook Coronavirus awareness courses in June in order to learn about making the building safer for staff. They then conducted a risk assessment for the building, presenting their findings during regular meetings with management. Steps taken to make the building safer include installing hand sanitiser stations, regular cleaning, safety measures around air ventilation, social distancing, and separate entry and exit routes.

It has been an unusual and challenging year for staff. However, it also revealed our resilience as a team and an ability to adapt to new work surroundings. 

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ETHIC
There is an urgent need to find a safe and effective treatment for COVID-19 to prevent worsening of the disease. Evidence has shown that COVID-19 infections can lead to an increased risk of blood clots. Unfortunately, these blood clots can lead to individuals being admitted to hospital, and in severe cases, death.

Successful intervention early in the natural history of the disease to prevent clotting would save lives and lessen the burden on healthcare systems.

ETHIC will pit prophylactic enoxaparin (a blood thinner) against the current standard treatment in community-based COVID-19 patients. Enoxaparin is a standard treatment for blood clots, identified as one of the damaging clinical manifestations in severe cases. Successful intervention early in the natural history of the disease to prevent clotting would save lives and lessen the burden on healthcare systems.

Website
The trial website is now live and you can view it at www.tri-ethic.com It will evolve as the trial moves forward and should anyone external express an interest in learning more about ETHIC, the site is an excellent resource.

Scale and how it will work
The study will take place in 10 countries, in approximately 30 to 50 centres. Patients will be allowed to take part if they have had a confirmed COVID-19 infection, are 55+ years of age and have at least two of the following additional risk factors; age ≥ 70 years, body mass index > 25 kg/m², chronic obstructive pulmonary disease, diabetes, cardiovascular disease, or corticosteroid use.

Half the patients in the study will receive the blood-thinning drug enoxaparin for three weeks, and half will receive no enoxaparin. Individuals will be randomly allocated to one of these groups.

After 21 days, the number of patients in each group who were either admitted to hospital, or died, will be compared. The number of patients in each group who developed a blood clot (venous thromboembolism) will also be compared. For safety, major bleeding and stroke will also be collected. Further comparisons will be made at both 50 and 90 days after the beginning of the study.

Atherovac
Atherovac is TRI’s lab work on solutions for the prevention and treatment of atherosclerosis and atherosclerosis complications. Atherosclerosis is the build up of plaque in arteries, a major risk factor for cardiovascular diseases (CVDs) such as coronary heart disease and stroke. CVDs in turn are responsible for 3.9 millions deaths each year in Europe alone.

This project has been a long term TRI effort carried out by our molecular immunology department led by Professor Xinjie Lu.

Our recent efforts explore the use of the Atherovac technology platform for its potential to develop COVID-19 and other zoonotic infection therapies. This involves replacing loops in the old vaccine construct with the COVID-19 spike protein that plays a critical role in virus entry prior to the replication and infection process.

TICEL
(Thrombosis in COVID-19 in East London)
TICEL is a retrospective, observational study to understand the risk factors and outcomes of COVID-19 patients in East London, and is led by Peter McCallum, with sponsorship from Queen Mary University of London.

Barts’ Thrombosis Service has been asked to advise on Trust-wide preventative and treatment strategies for venous thrombosis and coagulopathy in COVID.

In the absence of data from clinical trials to inform these strategies, TRI proposes to analyse the hospital’s own dataset, which includes 2,422 confirmed cases and 5,887 suspected cases. Using this TRI analysis Barts can then set out their approach.

Funded by SANOFI
Dr Cools is a steering committee member as well as serving as the national coordinator for Belgium in the ETHIC trial. He contributed this piece:

We have learned much about the novel COVID-19 virus since the start of the pandemic. However, there remains a great need for solid scientific data as well as for well-designed clinical trials.

The ETHIC trial will give us an answer to an important clinical question. However, organising the trial presents a practical challenge for the national coordinators in each country. Namely, this trial aims to include only non-hospitalised patients, in a trial-inexperienced environment. So how do we reach these patients?

In Belgium, testing for Coronavirus is organised in so-called triage centers, manned by dedicated nurses and general practitioners. We aim to cooperate with these centers to identify potential study patients. A ‘flying study nurse’ (who will work with and visit the centers) will do the practical work-up.

Should the test results come back positive, the nurse will contact the patient and his general practitioner to check inclusion and exclusion criteria, explain the study to the patient and guide them through the consent process. Dedicated mobile nurses will visit the patients at home and give instructions to patients on how to administer study medication (for patients in the enoxaparin group) and how to fill out the patient diary. Whenever possible, we will provide remote care.

Still, there will be further challenges. After battling with this virus for 6 months, many physicians show signs of ‘Corona-fatigue’. It can also be difficult to find high-risk patients, as most positive tests appear to be in younger, lesser-risk patients (who do not fit the inclusion criteria of ETHIC). Additionally the unpredictable behavior of the pandemic can be a problem. At times when the pandemic is accelerating, there is a risk that centers will be overwhelmed, leaving little time for study related procedures. This is why we chose to have the bulk of the work done by a centrally steered ‘flying’ study nurse, in order to cope with most of the administrative burden.

All told, ETHIC is an example of a pragmatic trial with a novel study design that will try to answer an important clinical question. We are keenly aware of the challenges that lie ahead, but such challenges will always invite innovative solutions, and we believe the trial can be a meaningful contribution to the research.
Talk about your approach to overseeing large projects

I can’t overstate the importance of teamwork and collaboration. Studies are multifaceted (particularly those on the scale of ETHIC), so it’s vital that all involved are committed and work together. I also believe a level of flexibility and lateral thinking are required in order to ensure the success of a project in times like these. Thankfully, the team more than measure up!

We are a small team with a BIG heart...

Tell us about the team you are a part of at TRI. Be nice!

We are a small team with a BIG heart and broooooaad skill set. We manage a significant scope of work, pull together when we need to and celebrate even the smallest wins! I think we have the good humour and spirit to see us through difficult days, and it is a pleasure to work with them. I want to mention that our youngest members, Bradley and Abel, have grown so much in the past year, and they ensure there is at least a modicum of cool about us!

Talk us through your role at TRI

I lead our small Clinical Operations team at TRI and am responsible for the day-to-day running of the trials, ensuring that we deliver quality studies within the approved budget and timelines. My team and I work closely with all other departments and I generally consider us the ‘glue’ that helps bring different (but equally important) aspects of the trial together.

Alice Fernandez

Alice Fernandez is one of our talented project managers at TRI. We sat down with her to talk about her role, balancing work and family, and the high wire act of coordinating an international clinical trial during a pandemic…
Are there any particular projects you have been a part of (presently on or in previous years) you are especially proud of?

I was privileged to work on a high profile study committed to finding a more effective Tuberculosis vaccine. The resulting M72 vaccine candidate is the first promising TB vaccine candidate in 100 years and has moved on to the next phase of trials. In addition, I am extremely proud to be involved in the work we are doing on the ETHIC study here at TRI. The COVID-19 pandemic takes centre stage in almost everything we do and talk about these days. To be part of a team working on the ETHIC trial that has the potential of benefitting both individual people and healthcare systems in the way the disease is treated is so relevant and important, and very meaningful to me.

How have you adjusted to working from home during COVID-19?

With the incredible technology we have available these days, working from home has been rather easy and effective. Home schooling… not so easy. When Ofsted came to inspect me, they gave me a rating of ‘AWFUL’!

How do you relax?

Mmmm, not much time to relax with three boys aged 5, 7 and 44 – whilst working on a COVID study – during COVID but I do love a good romcom!

You previously worked in South Africa. What was your focus there?

I worked for an amazing non-profit Biotech for almost 8 years that focused on vaccine development in Tuberculosis. Tuberculosis is the leading cause of natural death in South Africa and finding a new, more effective vaccine is critical. I was extremely passionate and proud to be a part of this mission. Outside of work, my focus was the beach, my friends and my amazing family.

What is challenging/different about project managing a clinical trial amidst a pandemic?

The most challenging part of managing a COVID study is that the situation is ever changing and unpredictable. We have the pressure of working faster than normal to get the study up and running but all the while the environment is unpredictable. We are constantly required to think on our feet. That said, I’ve seen my team really rise to the occasion. TRI has quite a bit of experience coordinating studies of this size and scale, so I would say we have some confidence and experience to draw upon.
Even in uncertain times, our research goes on to the greatest extent possible. Below is a summary of current lab research, and ongoing projects at TRI.

**Active lab research**

**Oncology** – experimental investigation of the mechanism by which heparin prolongs the survival of cancer patients.

**Atherosclerosis** – the development of a dendroaspin-based vaccine to control restenosis, a common cause of the failure of atherosclerosis treatments.

**Tri Fellowship Program** – We are delighted to welcome our new fellow, Dr Jelle Himmelreich of the Amsterdam UMC, who will be working on a project on managing patients with atrial fibrillation and coagulation disorders. The TRI fellowship programme has run for many years, created to educate and train upcoming researchers through hands-on experience in a variety of areas in clinical research, to expand the capabilities of TRI, and allow external researchers to learn more about our research interests.

**Pipeline**

**CVD population health** – working with a prospective sponsor to leverage new technologies and methods to understand population health and management in cardiovascular disease.

**Cancer associated thrombosis registry** led by Dr Peter McCallum. If you and your organisation are interested in speaking with us about a partnership, please contact us.

**Renal disease registry** in difficult populations (e.g. rapid progressors, rare kidney disease, diabetic nephropathy).
GARFIELD Draws to a Successful Close

In this issue, we will take a high-level look at the GARFIELD-AF study.

TRI is pleased to announce the successful closure of the GARFIELD-AF, VTE and RIVER studies. The data amassed from GARFIELD-AF has been fully cleaned and secured, offering a rich source of clinical insight beyond the ongoing run of publications the studies have yielded.

GARFIELD-AF (Global Anticoagulant Registry in the FIELD-Atrial Fibrillation) is the largest worldwide prospective registry involving 35 countries and over 1,000 randomly selected sites representing all care settings and real-world practice.

The registry followed historical changes in the treatment of AF, from the period leading up to the introduction of NOACs through the acceptance and common use of these treatments in clinical practice. The registry offered insight into the changes in outcomes with the use in these new therapies (death, stroke... bleeding).

"GARFIELD-AF showed that AF should not simply be considered as a localised cardiac arrhythmia but rather a systemic disease requiring comprehensive management of risk factors and comorbidities."
New insights

GARFIELD-AF showed that AF should not simply be considered as a localised cardiac arrhythmia but rather a systemic disease requiring comprehensive management of risk factors and comorbidities.

Among other insights, GARFIELD-AF has shown:

- Death was the most frequent major event occurring in patients with newly diagnosed atrial fibrillation (AF) at a rate threefold as high as stroke/SE and major bleeding
- Oral anticoagulant therapy was associated with a 30% lower risk of death, far a greater than might be expected from the reduction of stroke-related risk of death. This suggests that other mechanisms than stroke/SE risk reduction may affect the risk of death
- Heart failure, prior coronary artery disease/acute coronary syndrome and chronic kidney disease were three common comorbidities in patients with newly diagnosed AF and each of them affecting treatment strategies and outcomes.

The GARFIELD-AF risk score

GARFIELD-AF also made it possible to develop a new risk calculator that provides estimates of risk of all three major clinical outcomes (death, stroke and major bleeding) and assesses the impact of different anticoagulation strategies in a single reading. You can try the calculator at af.garfieldregistry.org/garfield-af-risk-calculator or access it via the QxMD app.

We are pleased to note the calculator was cited in the ESC Guidelines for the diagnosis and management of atrial fibrillation for 2020.

Future research directions

GARFIELD-AF has set a foundation for innovative trial methodologies such as observational studies looking at comparative effectiveness and pragmatic studies providing real-world reference arms for RCTs.

Learn more about GARFIELD-AF at af.garfieldregistry.org