TRI Faces the Future

TRI announce ETHIC, a clinical trial funded by Sanofi p.4
VTE prevention in COVID-19 patients p5
Research opportunities in a time of pandemic p7

"We’ve had to think on our feet like all organisations, but agility is one of our strengths as a smaller institute. The work goes on."
## CONTENTS

<table>
<thead>
<tr>
<th>Page</th>
<th>Section</th>
</tr>
</thead>
</table>
| 3    | TRI Faces the Future  
Opportunities and research priorities in the coming months       |
| 4    | Announcing ETHIC  
A new clinical trial                                               |
| 5    | VTE Prevention in COVID-19 Patients  
Professor Sylvia Haas                                             |
| 6    | A Tribute to TRI founder, Professor Vijay Kakkar  
Professor Sylvia Haas                                             |
| 7    | Opportunity in the Time of Pandemic  
Harry Gibbs addresses occupational stress, healthcare systems and the thrombosis angle to COVID-19 |
| 9    | Staff Profile  
TRI biostatistician Alfredo Farjat on work and life in London     |
| 11   | In the Works  
Ongoing and upcoming research                                       |
| 12   | Data Sciences  
Head Statistician Karen Pieper on TRI’s Data Sciences service  |

© Thrombosis Research Institute 2020
Registered Charity No. 800365
TRI Faces the Future

COO Gloria Kayani talks research priorities and commercial opportunities for the coming months.

Though already known for research on an international scale, it has nonetheless been a remarkable decade for TRI, largely focused on effectively managing and disseminating data from our large global registry programmes. Combined the studies recruited over 75,000 patients in 40+ countries, focusing on bringing a real world perspective to venous thromboembolism, cancer-associated thrombosis and stroke prevention in atrial fibrillation.

Gloria reflected on a heady time:
“We can be proud. Our work will aid clinician treatment decisions for better patient outcomes, we’ve published a significant amount of scientific papers, and our various steering committees have presented findings at packed symposia at a number of conferences in recent years.”

With three large global studies in the close out phase, TRI is facing the future and focusing on some exciting new projects. The COVID-19 pandemic prompted a few changes to TRI’s priorities, including the delaying of ‘grand finale’ GARFIELD symposia lined up in Milan and Amsterdam, and TRI’s own London congress, now scheduled for early next year. However, the pandemic has also presented some opportunities for TRI to extend their experience.

“Initially COVID-19 put a handful of our projects on hold. But then there emerged this thrombotic element to the COVID story, suddenly making our core expertise relevant in the race to understand the virus. Our new clinical trial ETHIC is the result”.

ETHIC will evaluate whether progression of COVID-19 to a severe stage can be halted with early administration of enoxaparin to prevent thrombosis in symptomatic patients. The trial is funded by Sanofi and will involve around 1,400 patients in eight countries.

So the research continues, though much of TRI’s operations work is now remote in compliance with public health advice. How did staff cope with the transition to remote working?
“From an operations standpoint, we’ve been able to proceed smoothly so far and the technology is there to facilitate that. Closing our labs and facilities was more challenging, but we are starting to reopen our labs and return our researchers to work safely. Overall, we’ve missed the social interactions – though we’ve learned new skills on how to work together through adapting to remote working”. All the while TRI is continuing to develop key partnerships in industry and academia, helped by the gradual return to working norms.

“We’re in a promising position. We have so much to offer. For example, a new partnership with Cyte, a global clinical research organisation has improved TRI’s ability to deliver effective research programs (more on Cyte at cyteglobal.org), and standalone services such as data sciences and medical writing give partners access to the expertise of specific teams across the Institute”.

So despite the strange times, you are optimistic?
“We’ve had to think on our feet like all organisations, but agility is one of our strengths. The work goes on.”

We can be proud. Our work will aid clinician treatment decisions for better patient outcomes...
NEW CLINICAL TRIAL

Announcing ETHIC

A new clinical trial to evaluate if progression of COVID-19 to a severe stage requiring hospital admission can be halted with early administration of enoxaparin to prevent thrombosis.

ETHIC

Funded by

• Approx. 1,400 patients in 8 countries participating in the study starting in July
• Participants randomised with half receiving enoxaparin for 3 weeks and half receiving no treatment (the current standard of care)
• Objective is to demonstrate the superiority of prophylactic enoxaparin compared to the current standard of care

TRI will conduct an open-label randomised controlled trial of community-based early thromboprophylaxis named ETHIC (Early Thromboprophylaxis in COVID-19). Patients will be eligible if they are > 55 years of age, with a BMI > 25 kg/m2 and possess one other additional risk factor (e.g. cardiovascular disease).

The study was designed in response to recent evidence suggesting that severe COVID-19 infections are associated with dangerous thrombotic states. This is now thought to contribute significantly to disease progression and overall morbidity and mortality.

Given the efficacy of low weight molecular heparin (LMWH) in treating thrombosis, and the benefit of avoiding progression of the disease to a severe stage, there is a clear need to evaluate the role of early administration of LMWH thromboprophylaxis in COVID-19 patients.

...amid this pandemic our core expertise has become vital in understanding the disease.

In the trial symptomatic COVID-19 patients receiving enoxaparin will be compared with patients receiving no treatment. Follow up period for assessing hospitalisation/death is at 21 days, with further assessments at 50 days and 90 days.

TRI Director Ajay Kakkar said:

“TRI pioneered the use of LMWH to treat thrombosis, and amid this pandemic our core expertise has become vital in understanding the disease. We are pleased to have the funding of Sanofi as we engage our network of researchers in countries with pronounced COVID-19 where we will conduct the trial in high risk community settings.”

ETHIC is funded by Sanofi.

More information at www.tri-ethic.com
When we think about VTE prevention in COVID-19 patients, I think we should first look back to the beginnings of pharmacological prophylaxis of the condition.

As long ago as 1969 TRI founder Professor Vijay Kakkar described the problems of thrombosis in deep veins of the leg in his Hunterian Lecture at the Royal College of Surgeons of England. In 1975 he was the first to describe the use of low-dose heparin to prevent post-operative fatal PE, published in The Lancet.

In the associated trial, 4,121 patients undergoing a variety of elective major surgical procedures were randomly allocated to receive either 5,000 IU unfractionated heparin (UFH) three times daily or no prophylaxis. The primary endpoint was autopsy-proven fatal PE. The difference in outcomes was highly significant.

It was Professor Kakkar’s vision that resulted in the concept of prophylactic UFH for surgical patients. This prompted the development of low molecular weight heparin (LMWH) and the eventual identification of antithrombotic oligosaccharides, leading to the development of synthetic oligosaccharides such as fondaparinux.

When we think about VTE prevention in COVID-19 patients, we should first look back to the beginnings of pharmacological prophylaxis of the condition.

Sylvia Haas MD, PhD
Emeritus Professor of Medicine,
Technical University of Munich

The journey from the first prescription of low-dose heparin for prevention of post-operative fatal PE to venous thromboembolism (VTE) prevention in COVID-19 patients.

As long ago as 1969 TRI founder Professor Vijay Kakkar described the problems of thrombosis in deep veins of the leg in his Hunterian Lecture at the Royal College of Surgeons of England. In 1975 he was the first to describe the use of low-dose heparin to prevent post-operative fatal PE, published in The Lancet.

In the associated trial, 4,121 patients undergoing a variety of elective major surgical procedures were randomly allocated to receive either 5,000 IU unfractionated heparin (UFH) three times daily or no prophylaxis. The primary endpoint was autopsy-proven fatal PE. The difference in outcomes was highly significant.

It was Professor Kakkar’s vision that resulted in the concept of prophylactic UFH for surgical patients. This prompted the development of low molecular weight heparin (LMWH) and the eventual identification of antithrombotic oligosaccharides, leading to the development of synthetic oligosaccharides such as fondaparinux.

... Real World Evidence studies are absolutely crucial. I am pleased to note TRI is on the case.

The corona pandemic has suddenly revived the issue of VTE prevention, as we often don’t know whether our patients die from or with COVID-19. It is amazing how quickly the recognition of COVID-19 as a thromboinflammatory process is impacting clinical care for hospitalised, especially ICU patients and heparin based. I am confident that the recommendations of D-dimer determination and heparin prophylaxis/treatment are now widely accepted.

However, a burning question remains: to what extent can we prevent hypercoagulability and disseminated intravascular coagulation in the outpatient setting by starting VTE prophylaxis in COVID-19 patients at an early stage? Could this mitigate the course of the disease and perhaps prevent hospitalisation? Here we urgently need evidence-based recommendations. In order to get there, Real World Evidence studies are absolutely crucial. I am pleased to note TRI is on the case.
A Tribute to Professor Vijay Kakkar

Professor Vijay Kakkar’s insights on VTE prevention may guide efforts to treat the condition in COVID-19 patients. Dr Sylvia Haas pays tribute to a mentor, friend and the founder of TRI.

Sylvia Haas, MD, PhD

In 1989 Professor Kakkar established the Thrombosis Research Institute (TRI) in London as a multidisciplinary resource dedicated to the study of thrombosis and related disorders. His publication credits include 680 original articles and 6 books, with contributions to many others. He was also a founding member of the British Society of Haemostasis and Thrombosis. Upon his retirement in 2009 he was appointed Emeritus Professor at the University of London and was awarded an OBE the following year.

I knew him personally to be a kind and humble man. On one occasion, after operating on a woman from Pakistan, he left theatre to speak to her husband. Their young son ran up to Professor Kakkar asking about his mother. Embracing the boy, Professor Kakkar reassured him that she would live. When the boy’s father asked about a fee, Professor Kakkar gently suggested that the man need only buy a toy for his son.

Outside work, Professor Kakkar was not a man for hobbies per se; his focus was his family, to whom he was devoted, and cricket. “I don’t play golf,” he told The Daily Telegraph. “What else am I going to do? My hobby is thrombosis!” This certainly benefitted the field.

Throughout his career, Professor Kakkar established groundbreaking research and education programmes across the globe, and he trained some of the leading vascular surgeons and clinicians in this area. He also contributed to the introduction of new diagnostic methods for thrombosis. His vision, leadership and teaching profoundly improved outcomes for patients in the entire field of haemostasis and thrombosis. He was truly an inspiration to many of us, and he was an inspiring mentor and good friend to me.
Opportunity in the Time of Pandemic

Managing stress, adapting systems and the thrombotic angle to COVID-19.

Harry Gibbs
FRACP, FCSANZ
Program Director, Outpatient Program, Alfred Health
Deputy Director, General Medicine, Alfred Health
Associate Professor of Medicine, Monash University

The COVID-19 pandemic has been a time of great stress – stress for those infected and their families, stress for healthcare workers, stress for health systems and stress for economies. The consequences of this cannot be understated. However, it is also a time of opportunity – opportunity for system change and opportunity for advancement in knowledge and treatment – and we should maximise the potential of these opportunities.

I have had clinical responsibilities for COVID-19 patients and so, for the first time in my career, I have faced a real risk of personal illness and even death due to my work, and of transmitting this risk to my family. In short, this is a time of heightened occupational stress.

Occupational stress

Occupational stress occurs when there is an imbalance between work demands and a person’s knowledge, skills, or expectations and occurs more frequently with excessive workloads. Unrelenting occupational stress may lead to burnout, characterised by reduced efficacy, fatigue and cynicism.

Much has been written recently about burnout in healthcare and its consequent psychological and organisational harm. The physical harm due to burnout is less well appreciated. Many cardiologists are unaware that burnout carries a high risk of the development of coronary artery events.

In the Copenhagen City Heart Study, burnout conferred the highest risk of future coronary events in men, with a higher risk than traditional risk factors such as hypertension and dyslipidaemia and was second only to smoking in women.

The mechanism of this increased risk may be explained by increased activity of the amygdalae which are the cerebral nuclei that mediate the stress response. Increased amygdalar activity, which occurs with chronic stress, is associated with increased bone marrow activity and the production of inflammatory cells. There is associated arterial inflammation, possibly due to an increase in these inflammatory cells within atherosclerotic plaque, and this, in turn, leads to plaque instability, rupture and cardiac events.

The association with stress and heart attack is clear and now part of the mechanism may be explained; the remaining vital issue is whether methods to reduce occupational stress will reduce cardiac events. Perhaps we will find that reasonable rosters and workloads, more exercise, better sleep and meditation are as important as smoking cessation, lipid lowering and blood pressure control in the prevention of cardiac events.
Agility

This pandemic has also highlighted that individuals and organisations have a remarkable resilience and agility to respond to a crisis. The innovations and adaptations that have occurred will lead to permanent change and, in spite of the tragedy and disruption, we must ensure that we capitalise on the opportunity for improvement that exists as we move out of the acute pandemic phase.

At my hospital, a screening clinic for SARS-CoV-2 suspected patients was created in the hospital café within 36 hours. Patients self-swabbed under nursing supervision to maximise throughput and so that nursing staff did not have to change personal protective equipment for each patient. Over 900 individuals underwent testing in the first 2 days.

To allow for an increase in inpatient beds, 2 floors of an outpatient facility were transformed into inpatient beds. Most outpatient activity was converted to Telehealth. The Telehealth activity increased from 164 appointments in February to 4,866 appointments in April. We plan to expand this service to include remote monitoring and therapy.

These changes show that health systems are able to adapt rapidly when required and we should capitalise on the current acceptance of change to continue to improve our processes rather than returning to business as usual.

The thrombosis angle

Finally, SARS-CoV-2 seemed initially to cause a viral pneumonia but it has become increasingly apparent that it is a potent cause of thrombosis\(^8\),\(^9\). Venous thromboembolism, stroke, atheroembolism and other thrombotic complications have been increasingly reported.

This infection offers an opportunity to investigate the pathogenesis of these thrombotic phenomena and for our thrombosis community to study the benefit of antithrombotic therapies.

It has certainly been a challenging time but one with opportunity to improve our knowledge and treatments. We must seize the moment.

Please visit this link for a full list of references:
www.tri-london.ac.uk/references-harry-gibbs-tri-in-focus-may-2020/
With respect to modelling the problem, I am always mindful of the old George Box quip: “All models are wrong but some are useful.” Our models are mere approximations of the phenomena we are attempting to describe – none are perfect. However, if we are aware of the underlying assumptions and limitations, we can identify the models likely to produce meaningful results.

Tell us about the team you are a part of at TRI. Be nice!
I am part of the Stats/Medical Writing team. What to say about this group of superheroes...

We have programmers Madhu and Uma, who are invaluable. Their deep technical knowledge is rivalled only by their exquisite taste in Indian food – they bring in spicy treats for us now and then.

Then we’ve got three excellent medical writers in Nick, Surekha and Rebecca. These guys are behind all our scientific publications, symposiums and so on. Their gift is disseminating our findings in a clear and elegant way.

And Saverio and Karen are my fellow statisticians. We enjoy having nerdy stats discussions about methods of analysis. Saverio is the go-to person for our GARFIELD-AF and RIVER registries (as well as intel on south London’s finest Italian restaurants). Karen heads the group and given her vast experience, we are lucky to have her.

Are there any particular projects you have been a part of you are especially proud of?

We did a project on comparing oral anticoagulants in GARFIELD-VTE patients lead by Professors Henri Bounnameaux and Sylvia Haas, which has been recently accepted for publication in Thrombosis Research. I think this kind of study is particularly valuable since it helps physicians make better decisions when treating patients.
How have you adjusted to working from home during COVID-19?

It has been challenging – my wife and I both work from home and we have three young children. But we’ve adapted... Of course, I have had to take on additional roles as teacher, entertainer and assistant to our mini-bosses!

How do you relax?

Cooking! I enjoy making pasta from scratch, and grilling outdoors when the weather is nice. In more normal times I enjoy running, cycling and playing football – sadly, not much lately. Oh, and when the kids let me, I play the bass guitar.

Prior to joining TRI you completed a PhD at North Carolina State, before working at the Duke University Medical Centre. How did you find the adjustment moving from the southern US to London?

Raleigh (capital of North Carolina) is completely different from London. The first shock was adapting to public transport. I went from driving my car everywhere to taking the tube and cycling. I also had to re-train my brain to learn how to drive on the ‘wrong’ side of the road. Then there was learning some words not used in American English e.g. chips, trousers. And of course, I now really appreciate a sunny day...

What attracted you to TRI?

The scale of the research and TRI’s international profile. I was hooked by the possibility of collaborating with researchers from Universities across the world.

When I joined, Karen Pieper was splitting her time between Duke and TRI. Now we have collaborators at Duke and we are also building connexions with local universities.

You hail from Buenos Aires. What do you miss about your hometown? Should we visit?

Historically, Buenos Aires port received immigrants from all over the world, making the city a melting pot. My family tree extends to Italy, Spain and Syria. Visitors can expect a European flavour reflected in its architecture, an incredible collection of bars and restaurants, art museums, theatres and an intense nightlife.

Personally, I miss my old neighbourhood, the tall sycamore trees across the city, the river (Rio de la Plata) that is so wide you cannot see the shore on the other side... And like any expat, what you end up missing the most are your friends and family. 

Personally, I miss my old neighbourhood, the tall sycamore trees across the city, the river (Rio de la Plata) that is so wide you cannot see the shore on the other side... And like any expat, what you end up missing the most are your friends and family.
Current Institute Activity

Even in uncertain times, our research goes on to the greatest extent possible. Below is a summary of current lab research, projects in development and projects in closing at TRI.

In development

**ETHIC** – In response to a strong body of research showing thrombosis to be a damaging clinical manifestation of COVID-19, TRI is preparing a clinical trial funded by Sanofi involving the administering of low molecular weight heparin early in the natural history of the disease to improve patient outcomes.

**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).

**TRI fellows** – We are delighted to welcome our first fellow, Dr Jelle Himmelreich of the Amsterdam UMC, who will be working on a project on managing patients with atrial fibrillation and coagulation disorders. TRI Fellows was created to expand the capabilities of TRI, and allow external researchers learn more about our research interests.

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.

In closing

**GARFIELD-AF registry** – atrial fibrillation patient management and outcomes.
No. patients: 57,000

**GARFIELD-VTE registry** – venous thromboembolism patient management and outcomes.
No. patients: 10,000

**RIVER** – use of Rivaroxaban in management of atrial fibrillation and stroke patients.
No. patients: 5,000
Here’s to the Statisticians!

We spoke with Karen Pieper about TRI’s Data Sciences service.

Behind all great empirical research is a great statistician! Statisticians draw meaning from unwieldy banks of data. In turn, researchers can draw conclusions, with implications for practice, therapy development and future research.

Karen Pieper leads the stats team at TRI. After 30 years at Duke Clinical Research Institute in North Carolina which included a gratifying collaboration with TRI on the GARFIELD registries beginning in 2014, she retired in 2019 and agreed to manage the TRI stats and medical writing teams.

Her multi-skilled team is composed of biostatisticians, programmers and medical writers.

“We are fortunate to have such a diverse base of skills in-house. Though a small institute, we can design a study, collect data, do the analysis and produce a manuscript independently, often without the overhead and red tape a larger organisation might deal with. This is a key part of our appeal to our industry partners.”

Despite the disruption caused by COVID-19 lockdown, the past three months proved a busy period. There is a growing body of literature indicating a relationship between COVID-19 patient outcomes and thrombosis. With no time to be lost, TRI are designing studies to shed light on this.

Karen also oversees TRI Data Sciences, which provides analytics as a service for biotech, pharma and clinical investigators in protocol and grant development, presentations for major meetings and publication in peer reviewed journals.

“Our edge is always that we work quickly, we are experienced and we have a clear house style for presenting findings. We can also provide additional medical writing services should the client not have that capacity.”

You can contact Karen about your research needs at kpieper@tri-london.ac.uk

To learn more, visit www.tri-london.ac.uk/services