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Great Expectations for 2021

Gloria Kayani
COO

It’s a pleasure to welcome you to this edition of TRI in Focus. We are still living and working in uncertain times, but there are grounds for optimism.

It is my hope that the vaccination programmes we’re seeing internationally bring a gradual return to normality. I hope our care systems can pull through this moment, the vulnerable can be vaccinated quickly, and we see an easing of the wearisome constraints on our work and social lives. In the meantime, there is work to be done!

Though some activity in the life sciences has slowed since the pandemic outbreak (I’m thinking in particular of the congresses that do so much to bring brilliant minds from all around the world together), TRI has remained active. We were compelled to; thrombosis was shown early on to be a damaging clinical manifestation of COVID-19. This was the basis for our ETHIC trial, which we are using to help validate effective treatment of at risk patients in community settings.

Our offering is compelling – a global network of research sites, our cardiovascular specialism and our new research platform.

Meanwhile, Cyte (our clinical research subsidiary) is refining its capabilities and speaking to prospective partners to work with this year. I believe our offering is compelling – a global network of research sites, our cardiovascular specialism and our new research platform. I am very proud of how the team brought everything together. We now stand to deliver some important work in the coming months.

And of course, our lab work goes on. Lab research is at the heart of what TRI does, so we’ve worked hard to make our facilities safe for our team. They are back working every day on novel solutions to conditions such as atherosclerosis (often the cause of life-threatening problems, such as heart attacks and strokes). Their work has drawn some positive attention, and I am excited to see what this year will bring.

I hope you enjoy this issue, and we’d be delighted to hear from you if you have feedback, or an article you would like to contribute next time out. I am pleased to note we have a guest contribution from Dr Juan Muntaner (CMC-Tucumán, Argentina) in this issue. Please contact Stephen if you would like to be involved: smulvey@tri-london.ac.uk.

All the best,

Gloria Kayani
TRI AND THE PANDEMIC

Why the ETHIC Clinical Trial Matters

ETHIC will evaluate standard of care for COVID-19 patients in community settings.

The use of LMWH (low molecular weight heparin) in hospitalised patients with COVID-19 has become standard of care. However, there is no hard data supporting the use of these anticoagulants in a community setting. This means that any kind of pharmacological prophylaxis is still off-label use due to the lack of randomised trials. Gathering evidence to establish the benefit or harm of prescribing LMWH to individuals with COVID-19 in the community is imperative. This treatment cannot become routine clinical practice until there is sufficient evidence to support such a decision. The purpose of ETHIC is to provide that evidence.

Specifically, ETHIC aims to assess whether prophylactic doses of enoxaparin (compared to no enoxaparin) can reduce hospital admission and/or death within 21 days of randomisation in symptomatic individuals with COVID-19 in a community setting.

Why LMWH?

Severe COVID-19 infections are associated with a profound prothrombotic state, with large and small vessel thrombosis. Prophylactic anticoagulation with LMWH has been shown to reduce mortality in hospitalised patients [1]. However, we remain in uncertainty regarding the use of LMWH in COVID-19 patients in the out-patient-care setting. ETHIC will answer this critical question.

Trial status

Our investigators continue to recruit patients in the UK, Spain, South Africa, Australia, Belgium, Brazil and Russia. If you are a clinician treating COVID-19 patients in one of these countries and are interested in enrolling patients, please reach out to us: ethic@tri-london.ac.uk.

Dr Frank Cools, a member of our steering committee based in Belgium has created a video for clinicians on why he is motivated to continue recruiting despite the other demands of hectic days in hospital.

Take a look at: https://www.tri-ethic.com/for-clinicians
Learn more about ETHIC at: www.tri-ethic.com

The epicenter of the COVID-19 pandemic is currently in the American continent.

The TET Strategy for COVID-19 Patients in Tucumán, Argentina

Dr Juan Antonio Muntaner
CMC-Tucumán
Argentina

Dr Juan Antonio Muntaner has worked with TRI as a national coordinator on the GARFIELD-VTE registry. Here he discusses the TET (triple early treatment) strategy for COVID-19 patients in Argentina.

The epicenter of the COVID-19 pandemic is currently in the American continent.

In February 2020, the first imported case was reported in Argentina. As of December 2020, Argentina reached 1,466,306 infected and 40,009 deaths.

Infections and deaths are not uniform throughout Argentina. The most populated region, the province of Buenos Aires, has 630,000 infections, and the city of Buenos Aires (separate to the province) has 160,996. The city of Tucumán had 64,826 infections, making it the most affected in the NW, and sixth overall in the country.

The main aim of the TET strategy is to reduce the number of patients in the intensive care unit, mechanically ventilated patients, and overall mortality rate.

An early pharmacological strategy adopted for Tucumán patients with risk factors (obesity, hypertension, asthma, coronary heart disease, etc.) involved medicating patients early on with rivaroxaban (10mg/day for 15 days) and dexamethasone at low doses (2mg/day) or colchicine (0.5mg/day).

When early treatment is possible, it can help prevent the cytokine storm and the consequent vascular thrombotic complications. Treatments started in patients hospitalised for COVID-19 are late when initiated in ICU, even in hypoxemic patients, since immune-inflammatory activation is greatly increased. Therefore, it is best to focus on intervening early in the natural history of the disease.

In summary, for preventing the disease progressing to a severe state, the inhibition of the cytokine storm through immuno-regulatory drugs (dexamethasone plus colchicine) that limit the host response is our proposed best treatment. For preventing microcirculation thrombosis and improving patient evolution, the use of LMWH or direct oral anticoagulants is supported when there is an increase in plasma d dimer.
Rebecca Watkin

Rebecca Watkin is a medical writer at TRI. She spoke to us about her work, hobbies and a strange Irish sport called hurling...

What does your role at TRI involve?
I work with the steering committee members and the stats team to produce publications. I am currently working on abstract submissions for the ISTH conference this summer.

Talk about your approach to writing
My approach to writing is fairly structured. I go through the current literature for the topic first. I’ve also made a habit of noting points in papers that might be relevant for future manuscripts. This really saves time down the line.
Secondly, I generally don’t write chronologically. It is faster to start with the data we want to present. Then I can tailor the methodology and literature review accordingly, which makes the paper more focused and coherent. Once I have my initial (usually lengthy) draft, I refine until I am happy and share it with the team.

Getting used to the job during lockdown was strange but daily check-ins on Microsoft Teams with everyone made a big difference.

Tell us about your team at TRI. Be nice!
Everyone is lovely. Getting used to the job during lockdown was strange but daily check-ins on Microsoft Teams during the year made a big difference – a quick friendly chat about anything at all was a great let-up to working alone.

Anything projects you are particularly proud of?
Everything published so far!

Prior to joining TRI you studied in Ireland – tell us about that!
Yes, I lived Dublin for 11 years! I moved to Dublin to study Genetics at University College Dublin and stayed to do my PhD in the Royal College of Surgeons in the city centre.
Dublin is a cool city, with lots of gems to stumble across. It is not as varied as London, but the atmosphere is great.

What research areas in the field you would like to tackle in future?
My background is primarily based in genetics and molecular signalling in the cardiovascular system. I’ve done a lot of research into the role of miRNA signalling in the host cardiovascular response to infection and would be interested in looking into the role of miRNA signalling in thrombosis.
I would also like to take part in international congresses again. I had the opportunity to present at a few congresses in recent years, including the 2017 ISTH in Berlin. I really enjoyed communicating with the wider scientific community because it puts into perspective how much a single researcher or team can contribute to research across the world.

How do you relax?

I am really into theatre and love both going to shows and auditioning myself. I used to work in a theatre, but lockdown restrictions saw most shows postponed. But there’s a lot of online sessions cropping up, so I do classes with a director who usually teaches in London.

Reading is a must – fantasy, sci-fi, and non-fiction are my top choices – I recommend *The Name of the Wind* by Patrick Rothfuss, it’s amazing! I’m a big fan of video games too, such as Witcher, Red Dead Redemption, Skyrim, etc. Mostly fantasy games (I’m sensing a theme).

I’m not much of a sports fan (that’s a lie, I’m just bad at team sports) but I like running and take part in annual races, charity runs etc. I love archery too, but it isn’t an option at the moment. My housemates object to practising in the house (weird).

You hail from County Kilkenny, Ireland. What do you miss about your hometown? Why should we visit?

I’m from a tiny village in Kilkenny called Inistioge, which sites on the banks of a river, and close to a beautiful country estate called Woodstock Gardens. Kilkenny City itself is a really vibrant place in the summer. There’s the Kilkenny Cat Laughs comedy festival and the Kilkenny Arts festival which both take place most years. The Watergate Theatre is close to the heart of most – it hosts all major shows that come to Kilkenny, but also a lot of amateur productions, so most people get a chance to perform there while in school. I miss that the most, it was brilliant. There’s also a cool music bar somewhere called the ‘Hole in the Wall’, a secret venue with no signs or advertisement. You just turn up and see what band you get. I’ve never found it.

Places to visit… check out Kilkenny Castle if the weather is good. The castle itself and surrounding park is gorgeous. Kilkenny is a major hurling city (hurling is an Irish sport – Google it!). The All-Ireland Hurling final in September is always a major event. If you happen to be in the city when a match is on, head to a sports bar to watch, the atmosphere is awesome.
Current Institute Activity

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.

Ongoing

**ETHIC** – In response to a strong body of research showing thrombosis to be a damaging clinical manifestation of COVID-19, TRI is currently running a clinical trial funded by Sanofi involving the administering of enoxaparin early in the natural history of the disease to improve patient outcomes. Our investigators continue to recruit patients in the UK, Spain, South Africa, Australia, Belgium, Brazil and Russia.

**TRI Fellowship Program** – Our current fellow, Dr Jelle Himmelreich of the Amsterdam UMC is working primarily on the ETHIC trial and statistical work on data assembled in the GARFIELD studies.

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).

**TRI Data Warehouse** – using de-identified data gathered in previous studies for new research.
How CROs Have Evolved to Get Research Done During COVID-19

Cyte has adapted its services to address key challenges during the pandemic.

The cardiovascular drugs market is predicted to reach a value of $64 billion by 2026. This growth is driven by a growing need for advanced and effective drugs to combat prevalent heart stroke and cardiovascular disease. According to the American Heart Association, cardiovascular disease (CVD) accounts for approximately 1 in every 4 deaths in the US.

Cyte’s cardiovascular specialism stems from its parentage, TRI. TRI’s program of research in this field reaches back as far as the 1960s. In time TRI became familiar with the recurring challenges in coordinating research studies, and learned to work through them. Cyte now acts as TRI’s delivery arm.

Like many CROs, Cyte introduced measures in 2020 to mitigate COVID-19 disruptions to research. These include remote working for personnel who are not engaging with participants, effective systems for online document management, signing and storage, and conducting site monitoring on a remote basis.

But there are a number of preexisting challenges relating to set up, sites, and operations. These include:

- Rising site and patient recruitment costs
- Long contracting and budget negotiations
- Wavering patient and site engagement as the study goes on
- Juggling multiple clinical systems and data sources
Cyte’s three services were developed to address these key problems. They include a network of research sites with prenegotiated contracts, a collaborative platform for study stakeholders and ad hoc services to handle bottleneck issues and move studies to compilation.

2021 stands to be an interesting, challenging year for CROs and Cyte is no exception. But there are vital projects in the offing, and the prospect of rolled back restrictions assuming vaccination programmes are effective. Watch this space.

You can find more information at: cyteglobal.com and if you want to make enquiries about services, email us at: g.kayani@tri-london.ac.uk
Behind the Demand for Data in Healthcare

Efficient use of resources, personalized medicine and AI.

We argue there are three contemporary factors making demand greater than before. Firstly, governments in developed countries are spending less on healthcare in recent years. At the same time, costs are increasing owing to the greater instances of chronic disease in aging populations. Accordingly, providers and payers are seeking to use their resources more efficiently. That makes cost-effective approaches like real world evidence an attractive means of testing the effectiveness of treatments.

Secondly, we’re seeing a move toward personalized medicine. This is driven by 1) chronic disease, 2) instances where patients carry two or more conditions long term, and 3) patients requiring multiple medications simultaneously. Personalised medical decisions and interventions are based on a patient’s predicted response to treatment (or risk of disease in the first place). These risks are calculated using large banks of patient data. For example, TRI produced a calculator comparing three treatment options for atrial fibrillation patients powered by data from the GARFIELD-AF registry (57,000 patients in 40 countries). You can try it for yourself here: af.garfieldregistry.org/garfield-af-risk-calculator

Finally, data inputs will be required to realise the promise of AI and machine learning. Encouragingly, healthcare has been the top industry for investment in AI. Healthcare providers, insurers and the pharmaceutical industry are incorporating AI into their existing services, tech industry leaders are adding healthcare to their core business, and start-ups are raising capital at record rates (the venture industry grew by 4% this year).

The technology and finances are available; data is the missing ingredient.

Applications of this technology include risk prediction, imaging and diagnostics, and remote monitoring. The technology and finances are available; data is the missing ingredient.

TRI has amassed large data sets as part of previous research programmes. This includes (70,000+ patient lives, 160,000+ patient years of follow-up data). Once properly de-indentified (to protect the identity of patients) it can be used for further research. Our research network will generate further clinical data and real world evidence in the coming years. This in turn can be put to good use beyond the study in which it is first generated.●