VISITING
AMSTERDAM RHEUMATOLOGY & IMMUNOLOGY CENTRE
AND
MAYO CLINIC USA

BEST OF BOTH WORLDS

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Introduction

I was appointed as Consultant Rheumatologist & Physician at Luton & Dunstable University Hospital NHS Foundation Trust having completed my Rheumatology & Internal Medicine speciality training in the East of England in 2013.

I grew up in Lahore Pakistan and studied Medicine at Bahauddin Zakariya University. I obtained MRCP in March, 2007 and commenced my dual training in Rheumatology & Medicine at Watford General Hospital before joining Addenbrooke’s Hospital Cambridge to pursue clinical research with Dr Andrew Östör in 2010. Same year, I achieved MRCP in Rheumatology as well. I finished research in 2012 and joined Luton Hospital as a final year registrar until was appointed in the current role.

In order to enhance my research portfolio, I wanted an international perspective. Hence I saw John Glyn bursary as a golden opportunity to visit a research centre of excellence to learn how to set up a successful clinical trials unit. Two units kindly agreed to host me to help acquire a true Trans-Atlantic view. I visited USA’s most prestigious Mayo Clinic in Rochester Minnesota and EULAR centre of excellence Amsterdam Rheumatology & Immunology Centre, both of which are world-renowned centres for Rheumatology research.

Objectives

The aim of the visits was to help broaden my understanding of different models of conducting scientific research and apply the learnt skills in my unit to shape the trajectory of clinical research and build a strong foundation for a research active hub.

Amsterdam Rheumatology & immunology Centre

My host was Dr Mike T Nurmohamed, Professor at Amsterdam Rheumatology and immunology Centre (ARC) – a European League against Rheumatism (EULAR) centre of Excellence. Prof Nurmohamed is an internationally acclaimed rheumatologist with
special interest in epidemiology and leads on research in cardiovascular comorbidity in rheumatic diseases.

The ARC encompasses three leading rheumatology units in Amsterdam – VU university medical centre (VUmc), Academic medical centre (AMC) and Reade institute wherein rheumatology research and education has been brought together in one Organisation. This has resulted in the ARC being the biggest centre for research in the Netherlands. The ARC is led by Prof Ronald van Vollenhoven and, together with Prof Nurmoshef and a highly effective team of more than 80 researchers, work on the origin and treatment of rheumatic and immunological disorders.

Day 1

My visit started with a very well attended bi-monthly ARC educational meeting. The theme was ‘Mechanisms of immune regulation and tolerance to prevent or restrain autoimmunity’. In his typically unique way, Prof van Vollenhoven commenced the proceedings with an overview of world affairs and its impact on the research environment. He extended a warm welcome to the two visiting physicians including myself and Dr Jens Geginat from Istituto Nazionale Genetica Molecolare "Romeo ed Enrica Invernizzi", Milan, Italy.

The meeting was chaired by Prof Sander Tas who introduced the speakers for the morning. Dr Geginat discussed the opposing roles of IL-10 in the pathogenesis of systemic lupus. I learnt, for the first time, that there was a ‘dark side’ to IL-10 as well.
The next two talks focused on Autoimmune Regulator (AIRE) expressing cells. Though some basic concepts were more difficult to understand for a clinical researcher, the speakers were exceptionally clear in their presentations which helped the uninitiated like me. In my moments of slumber, my attention periodically strayed to a long bamboo stick next to the lecturers which could certainly poke me to ensure heightened level of awareness. I am sure that was not the purpose of the cane though!

Second part of the morning comprised a visit to Sanquin laboratories hosted by Profs Gertjan Wolbink and Annick de Vries Head of Biologicals Lab Diagnostic Services. Sanquin is responsible for safe and efficient blood supply in the Netherlands on a not-for-profit basis. In addition, Sanquin also offers service testing for the pharmacokinetics and immunogenicity of an expanding array of biologicals, using assays developed in-house. The institute is now the frontrunner in the development of new tests for most biologic agents.

I was greeted by four PhD fellows who provided an overview of the completed and ongoing trials utilising drug level testing and its implications in clinical practice. There is certainly a belief that these studies have helped apply the principles of personalised medicine with added dimension of cost effectiveness. I learnt about their recently published trial which demonstrated that adalimumab trough levels reached a maximal effect on RA disease activity at 5 to 8 μg/ml. Levels higher than 8 μg/ml had no additional benefit. In patients with higher concentrations the dose interval may be prolonged without losing clinical efficacy, thereby saving cost. I was impressed to know that these findings have led to routine application in a clinical setting with further data to be published soon.
In the afternoon, I had the privilege to visit the laboratory and observe live drug level testing. Anti-drug antibodies are quantified using state-of-the-art validated antigen-binding radio-immunoassay. ELISAs are utilised to measure drug levels and help decide the therapeutic choice. It certainly was a surreal experience to see a world-class laboratory in action bringing immunogenicity research from bench to bedside.

It was now time for me to see the bench to bedside transition in person. My final visit of the first day was to meet Dr Wilfred van de Weele at Reade. Dr van de Weele is a well-recognised rheumatologist who works with a large team of ARC clinicians. It was interesting to hear about the challenges of clinical practice and how closely these were related to issues at home. Still they manage to consent over 90% of their patient cohort for trials and the use of electronic database EPIC helps identify the appropriate participants with few clicks. PhD fellows spend 20% of their time in clinics thereby bridging the gap between their projects and recruitment targets. It certainly was a model which I felt could help push research positively at home.

Day two

The day started with a visit to ARC clinical research bureau. I was welcomed by Iris Oving who chairs the bureau and ensures smooth working of this rapidly transforming unit. The unit is undergoing a major overhaul in an attempt to bring all three rheumatology research facilities under one system. It was interesting to hear the complexities of developing one SOP for three sites and standardising the procedures for seamless research activities – challenges perhaps similar to clinical research networks in the UK. Nevertheless, the organisation remains highly productive with 200 publications in 2016 and rapidly expanding repertoire of dynamic members.

I was quite impressed by the high profile studies running with European network partners and funded by EU grants. There was an opportunity for me to see the clinical research facility and meet research nurses who had a solid clinical background and were well supported by infrastructure and dedicated administrative staff. Overall, I felt that the unit has a strong focus on clinical research trying to answer pertinent questions a clinician wishes to know when encountered with a complex inflammatory arthritis patient.

In the early afternoon, I visited state of the art PET imaging facility in VUMC and heard from two PhD fellows about the research in novel macrophage-based imaging markers employed in scan acquisition to enhance synovial uptake and help with early diagnosis as well as therapy monitoring. I met with Prof Dr Conny van der Laken who is leading on these exciting translational projects starting with animal models ultimately transitioning to arthritis patients in the same facility. It was great to meet the highly passionate team with clear objective of improving patient journey throughout their disease career.

In the latter half of the afternoon, I met with the research team at the Reade Institute. Again, there was strong focus on projects addressing clinically relevant questions. I also met with the lead pharmacist in the specialised rheumatology pharmacy. It was inspiring to see that the pharmacist was actively involved in patient recruitment to
biologic studies. Their role also included therapy discussion thus helping shared decision making and preparing therapies for blinded administration.

Having met 12 PhD fellows over the two days, I was impressed to note that nearly 40% were not even doctors. In contrast to the UK where PhD in Rheumatology is almost solely undertaken by committed speciality trainees, the Netherlands works a completely different model. The applications are invited from a wider pool of candidates which brings a wealth of skills and ideas different from destined doctors or more specifically rheumatologists. For instance, Annelies Blanken with prior imaging experience was able to utilise her skills in setting up PET study to answer a rheumatology question. In addition, there are government subsidies and interest free loans to help pursue the doctorate. Most would commence a project without worrying too much about grants or funds. Once they are nearing completion, there would be an expectation to submit grant application for the next incumbent. As they understand the project and relevant data, they feel more confident in presenting their case to the awards committee thereby achieving a successful outcome.

**Final day**

I joined clinical round led by Prof Niek de Vries at AMC. His focus of research is ‘adaptive immunomics’ - Immunogenomic approaches to selectively monitor and target adaptive immune responses in immune-mediated inflammatory disease. He is also the coordinator of the Amsterdam RA genetics network (GENRA). It was interesting to note the similarities in clinical terminology for the cases presented and how much I could infer from investigation results in Dutch!

Later, I accompanied Prof de Vries to a fascinating thesis defence session at the ancient city centre campus of University of Amsterdam. The 15th century Agnietenkapel, where the university was founded, was first constructed as a monastery chapel around 1470. It was later converted for use by the Athenaeum Illustre in 1631. The Agnes Gate in front of the Agnietenkapel is a major symbol of the university and dates back to 1571. It was renovated and moved to its current location in 1631.
Firstly, Mrs. Karin Maijer presented her thesis titled ‘Rheumatoid arthritis: from the at risk phases all the way up to the development of the disease’. She was questioned by six professors including independent experts about her work before being presented with the certificate at the end of this beautiful ceremony. Mrs. Frieda Koopman was the second presenter with her thesis titled ‘Balancing the autonomic nervous system: towards new therapeutic options for rheumatoid arthritis?’ Both topics were highly captivating and I learnt a lot about pathogenesis of RA and the exciting new approach to treating RA by restoring the balance in autonomic nervous system. It certainly was a proud moment for both doctors and their families and I was thrilled to participate in the ceremony at this prestigious location.

The whole experience taught me a lot about the Dutch model of clinical research conducted with vigour and enthusiasm. I was inspired by the cohesive team and their thirst to unravel the mysteries of immune mediated inflammatory arthritis with patient at the heart of their endeavours. I liked the diversity of PhDs pool and the joint working of several disciplines as a well-oiled machine. I plan to share my wonderful experience with trainees and colleagues at home and how we can implement the learning to improve practice.

**Mayo clinic**

My host was Dr Timothy Niewold, Associate Professor & Research Chair for Division of Rheumatology and Department of Immunology. He leads a highly successful team of clinical and translational research. US News and World Report consistently rank the department amongst top three rheumatology units in the country.
The Mayo Clinic is a non-profit organization committed to clinical practice, education and research, providing expert, whole-person care to everyone who needs healing. It has three main campuses in addition to the Mayo Clinic Health Systems which has dozens of locations in several US states and abroad. It employs 64,000 staff and welcomes over one million patients every year. The Education and Research funding approaches one billion dollars with over 10,000 human research studies running at any given time.

The Division of Rheumatology has 18 consultants with many more fellows and trainees. The first chair of Rheumatology at Mayo Clinic, Dr. Philip S. Hench, started the tradition of research that still motivates the division today. His efforts led to the discovery of the beneficial effect of cortisone in rheumatoid arthritis, an observation that led to his sharing the Nobel Prize in 1950.

Day 1

The weather on Labour Day morning was grey and dull which instantly made me feel at home. Dr. Niewold welcomed me into his cozy office and my thoughts strayed to my office in the UK which I share with at least two great colleagues and looks similar to Star Trek Enterprise. After initial introductions, we walked through a maze of shiny marble-tiled tall glass buildings to a futuristic staff office with sophisticated coffee vending facilities. Again I could only think of Costa at our hospital’s main foyer where baristas warmly welcome a long queue of patients and staff every morning.
My first meeting was at Rheumatology Study Unit with clinical trials coordinators chaired by Dr Niewold. It is held first Monday of every month to review trial updates and address issues that affect the study unit. All the studies running in the department as well as upcoming trials were discussed. It was refreshing to see open communication with contribution from all trial coordinators. I was surprised to know that all four staff members had varied backgrounds and none had nurse training. This is in contrast to the UK model where most, if not all, trial coordinators are research nurse specialists. The benefits would be relatively lower cost and better use of research resources however more reliance on investigators for study queries.

I had a long chat with the lead and learnt about study resources for such a career and how it allowed pooling of generic research skill sets. The Association of Clinical Research Professionals (ARCP) provides nationwide certification and thus anyone could pursue a career in clinical research.

Secondly, another major role of trials coordinator is to budget a forthcoming study. Financial modeling is more complex owing to private entity setup compared to the NHS and hence requires careful consideration. Job plans for such roles are quite detailed taking study setup and budgeting needs into account. It certainly provided me food for thought!

We then proceeded to the Division’s research meeting again held once a month. This allows the research chair, well equipped with study updates from the trial coordinators, to share thoughts with individual primary investigators (PIs) and provide administrative updates to the Division. Strong and open communication among the team was again the key feature of the meeting.
The highlight of this meeting was the Study Protocol review. All requests from prospective PIs to adopt a study on the portfolio is undertaken formally. Protocol is passed to two consultants with different sub-speciality interest. They would review it in detail and after the putative PI has presented, the reviewers would probe it further before the quorate Division takes a formal vote whilst the presenter(s) step out of the room. This allowed learning for colleagues, inclusion of ideas to streamline the study setup and an opportunity to all for their views. Certainly something I feel that needs to be a part of healthy and flourishing research facility.

Day 2

I was privileged to spend time in Dr Niewold’s laboratory on my second day of the visit. Dr. Niewold’s lab is mapping the genetic factors that cause autoimmune diseases, and exploring the ways in which genetic variations alter the human immune response to result in disease. In lupus, he has established a large body of work demonstrating ways in which the normal immune response against viruses has been pathologically and persistently activated, resulting in autoimmune disease. His current work focuses on type I interferon in autoimmune diseases.
I was given the opportunity to discuss basic science techniques with the team. Having been away from a lab since my Physiology experiment days at medical school, I was glad to see that one does not have to suck the reagent into a pipette anymore! Instead there were multi channel pipettes at work. I was also impressed to see the high sensitivity flow cytometer and Fluidigm® for high-sample-throughput SNP genotyping and other endpoint PCR applications. Being a clinical researcher, it was great to see bench science and how it allows for smooth bench to bedside transition with Dr Niewold at the helm of translational medicine.

I met with Jessica Dorschener, senior research technologist, who runs the laboratory and helps visiting fellows and PhD students complete research projects. She spends most of her time analysing human blood samples for lupus studies. However I was surprised to know that, in the evening, she goes by the name of ‘Jessicutioner’ - a blocker and jammer on the MedCity Mafia roller derby team. Her derby uniform number, 702, is a tribute to a strain of bacteria she studied during graduate school as part of her thesis work. The name of the strain ended in 7002. Roller Derby is the fastest growing sport in the US. London Roller girls are fourth in the world. Not something I thought I would learn in an advanced lupus research laboratory!

Lunch was served in an adjacent building where there was certain focus on ‘healthy living’. Grilled fish and vegetables were the key ingredients. I was also impressed with the automated dish washing where one could leave the tray on a conveyor belt at exit.
My thoughts wandered to the six feet high trolleys in our hospital restaurant where I would unsuccessfully attempt to stack my tray ultimately spilling the contents on the floor.

In addition to the healthy food options, there are several facilities including a ‘wellness’ centre for staff at the Mayo. One feels that the organisation values its staff and provides opportunities for, not just professional, but personal development as well.

Second day ended with attendance at research laboratory meeting where all lab staff, basic science researchers and international fellows meet once a week with Dr Niewold. This allows cross-fertilization of ideas and updates on each project’s progress. The lab collaborates with premier organisations around the world such as Karolinska institute. During my visit, a fellow from China was returning and another post doctoral fellow had joined.

I listened to participants presenting their project’s progress with discussion culminating in recent or upcoming publications and future ideas. It certainly provided a stimulating environment for learning and sharing best practice. I also learnt regarding a successful case submission of rheumatic manifestation of immune checkpoint inhibitors employed to treat various cancers. Dr Uma Thanarajasingam has now developed special interest in this rapidly growing field and aims to pursue the subject. I felt that somehow such stimulating discussions around the table could mould a research career for the future.
I had a great opportunity to observe connective tissue disease clinic where four new patients would be seen between Dr Niewold and his fellow over four hours. That allowed over an hour for a new patient and usually 30-40 minutes for follow up thus enabling specialist education with patient care. The patients had travelled from afar and hence had every opportunity to discuss their condition, treatment plan and future strategy in a true shared decision making model. Hence Mayo clinic has one of the best patient experience examples in the world. This starkly contrasts with my clinic where I have at best 30 and 15 min respectively for new and follow up appointments with growing pressure to see more in less time in the NHS. I was also impressed to hear that Mayo clinic operates less than full capacity work policy so patients can be slotted at a day’s notice! I wish patients on my six-month waiting list would have that option as well. It certainly taught me that if an organisation could work this model with 1.3 million appointments yearly then NHS certainly could learn from that.

Patient comfort and confidentiality was also practically at the core of the consultation. Outside each clinic room, a different colour light indicator operates clearly indicating which team member is inside and whether they have a patient with them. That way, they would remain undisturbed. On the other hand, the interruptions I notice in my clinic when someone walks in saying ‘Sorry, I didn’t realise you were in there!’ calls for a similar system. I certainly intend to discuss implementing a similar process where the patient feels comfortable and knows that privacy is maintained at all times.

I was impressed with the agility of the IT system. The warm up time from login to accessing electronic health records was five seconds! Similarly the doctor would only undertake the consultation and all administrative needs will be fulfilled at the front desk including printing blood requests, organising visits and any other help patient may need. This allows the clinician to maximise their time with the patient and make every contact count.

I was also interested to note that each clinic encounter resulted in the consultant being responsible for the billing of the case appropriately. Every test organised and the time taken to review the patient dictates the reimbursements for each case. This also helps with audit trail and avoids misuse of the system. This is probably a fairer system than the one we pursue in the NHS where there is at times undue focus on new to follow up ratio with standard tariffs irrespective of the complexity of the case.

Day 4

My final day incorporated a meeting with Department of Medicine Clinical Trials Unit (DOM CTU). I met with Dr Ivana Croghan, Professor of Medicine and Scientific Director, and Tamara Evans who is the unit manager. Dr Croghan and Ms Evans have been at the Mayo clinic for over twenty years with vast experience of research conducted at the Mayo. Dr Croghan’s background is epidemiology and she has been leading the CTU for several years. They shared their paper published in *Contemporary Clinical Trials* in 2015. This encapsulates their years of work in developing CTU to advance research in an academic institution.

CTU aims to encourage research among clinicians in the 12 divisions of the DOM. It can help at all stages including trial concept and design, grant application process, setting up a study and running the project with help from its ten clinical trials coordinator. Activity,
publications and grant awards monitor success of the unit. Benefits include a pool of research resources with generically trained coordinators who can help individual investigators. I felt that there were similarities with clinical research networks in the UK. However, the remit of CTU is wider and the currency of success evaluation is not limited to recruitment numbers but rather research output of each department. This certainly allows more clinicians to contribute without always worrying about recruitment figures.

It was interesting to hear that even for federally funded studies, approvals were required at each local Institutional Review Board (IRB) though it’s now changing. Certainly the UK is ahead with Research and Ethics Committee (REC) evaluation structure and the more recent HRA approval endeavour.

The day culminated with a visit of the facility and a trip to Trial unit pharmacy and phlebotomy services. It was a great end to a highly rewarding learning experience for me. There were many pearls of wisdom that I picked and hope to employ that learning in enhancing research at my organisation.
Future aims

I intend to share my learning with the colleagues and trainees locally and regionally. I also plan to discuss the report with local CRN and the Trust to see how we can improve research activities in the region.

I aim to develop a clinical trials unit hopefully collaborating on projects of mutual interest with both centres and continue the research journey together.