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SUPPORTING PATIENT CARE AND RESEARCH IN RHEUMATIC DISEASES

CLINICAL RESEARCH ON E6 - Dr Deepak Jadon – STUDIES OF INFLAMMATORY ARTHRITIS

Dr Deepak Jadon is a consultant rheumatologist and Director of the Rheumatology Research Unit (RRU) at Addenbrooke's Hospital. His clinical and research interests relate to inflammatory arthritides such as psoriatic arthritis (PsA), ankylosing spondylitis (AS) and rheumatoid arthritis (RA).

We currently have approaching 20 active clinical studies and several due to start over the coming year. We have a balanced portfolio of academic and non-academic (often clinical trials of new medications) research. The team comprises of a senior administrator (Mrs Katherine Hodges), research nurse manager (Sister Sam Wright), four research nurses, a research practitioner and several research fellows (senior doctors undertaking a period of research, as described below).

Dr Mark Sapsford conducted a study in 2017-18, recruiting 106 patients with PsA to his research study (**CLUE-PsA**) that investigated the burden of enthesitis (inflammation where tendons, ligaments and joint capsules insert into bone) as measured by ultrasound versus clinical examination. The results of the study have now been published and can be read here: https://journals.sagepub.com/doi/10.1177/1759720X211003812?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed&

Dr Jobie Evans completed recruiting 200 patients to his 2-year study (**ProSpA-CD**) investigating how MRI scans of the abdomen in patients with Crohn's disease can be used to screen for patients with spondyloarthritis (inflammation of the spine). Dr Evans is currently analysing the results and has published a literature review on this topic, that can be read here:
https://journals.sagepub.com/doi/10.1177/1759720X21996973?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

Dr Joseph Hutton was successful in being awarded a 3-year Medical Research Council PhD Fellowship. His **TAPPsA** study will investigate newly diagnosed patients with PsA in terms of synovial biopsy (sample of joint lining), blood cells from whole blood samples, and tracking certain types of white cells (macrophages) in patients with PsA.

Dr Hannah Jethwa continues her 2-year study (**Spectrum-PsA**) investigating how blood tests may be added to a questionnaire (PEST) to improve the detection of arthritis (PsA) amongst patients with skin psoriasis in the dermatology clinic.

Dr Beverly Ng visited the RRU in 2020-21 from Sydney (Australia) as the RRU Research Fellow supporting several research trials. In particular, she conducted her PhD research whilst with us, studying the **stool microbiome** (flora) in patients with PsA and how it changes from diagnosis, before and after using disease modifying agents (DAMRDs).

Dr Azhar Abbas has recently joined us from Dublin (Ireland) for one year and is the fellow dedicated to the clinical trials on the RRU. In PsA he is recruiting to the **MONITOR-PsA** study, which is an inception (from first diagnosis) cohort study of patients with PsA running for 5 years and recruiting 500 patients across Cambridge, Oxford and Bath. We have recruited 58 patients to date in Cambridge and over 200 across all sites. Dr Abbas will also be

recruiting the nested clinical trial, **SPEED-PsA** study**,** where patients with PsA will be randomised to receive adalimumab anti-TNF therapy immediately after diagnosis. We will also be continuing our follow-up of patients recruited to the British Society of Rheumatology **PsA Registry,** assessing the safety of biologic treatments in clinical practice.

For patients with **osteoarthritis of the knee**, we are recruiting to an interventional clinical trial of a novel biologic therapy led by the pharmaceutical company GlaxoSmithKline (GSK).

For patients with RA we continue to follow-up patients recruited to the British Society of Rheumatology **RA Registry** assessing the safety of biologic treatments in clinical practice. We have completed the **IMRABIOME** study assessing the microbiome of patients with RA (Dr Andra Negoescu, consultant, is leading the study in Cambridge).

Professor Kenneth Poole (Professor of Metabolic Bone Disease at the University of Cambridge) is leading two clinical studies relating to osteoporosis and osteogenesis imperfecta (**ToPAZ** and **Asteroid** studies), as well as other academic studies in his university department.

Dr Gavin Clunie (Consultant) is leading on a large study assessing **X-linked hypophosphataemia**.

If you are interested in taking part in any of the research studies mentioned above, please visit the **new CARE website** (https://cambridge-arthritis.org.uk) and **please do not hesitate to contact the research team.**

STUDIES IN AUTOIMMUE CONNECTIVE TISSUE DISEASES (CTD) – Dr Natasha Jordan

Since the last CARE Newsletter, a number of studies under Dr Jordan's supervision have completed recruitment including the **BEAT Lupus trial**. BEAT Lupus was a multicentre, UK phase II, randomised, double blind, placebo controlled trial investigating the safety and efficacy of belimumab after B-cell depletion therapy in patients with active systemic lupus erythematosus (SLE) resistant to conventional therapy. We successfully recruited our target of three patients for this study and results will be published in the near future.

Recruitment has also now been completed in the **CARE lupus study**, a multicentre, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of cenerimod in SLE patients. We are eagerly anticipating the results of the study.

Dr Jordan and the research team have also completed recruitment to two studies of idiopathic inflammatory myopathy (IIM). Dr Hector Chinoy, University of Manchester, led both studies. The studies were **MYOPROSP**; a prospective cohort study with the aim of identifying the best approach to the diagnosis and treatment of patients with myositis. The second study was **UKMYONET**, a study collecting clinical information and performing genetic and antibody studies on patients' blood samples. Results of these studies are awaited.

A further clinical trial in SLE recently opened at our site, the **SLEek study** which is an international multicentre trial investigating the safety and efficacy of ABBV-105 and Upadacitinib in moderately to severely active SLE patients. Work on this study is ongoing.

Another study currently running at the RCRU is the **GCA Consortium**, a study led by Professor Ann Morgan, University of Leeds. This study aims to establish a database which will permit clinical characterisation of giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) patients with a view to developing a better understanding of these diseases. The research team will also carry out genetic studies on this patient cohort, investigating the contribution of relevant genes to the susceptibility to GCA/PMR and the risk of complications and response to therapy.

We are also taking part in the **United Kingdom primary Sjögren's syndrome registry (UKPSSR)**. This study is being led by Professor Wan Fai Ng, Newcastle University. The aim of the UKPSSR is to establish a cohort of well-characterised primary Sjögren's syndrome (pSS) patients and matched healthy controls, together with samples of DNA, RNA, serum and immune cells from these subjects in order to facilitate clinical trials, genetic and epidemiological studies in this disease area. Further clinical trials in lupus are planned to open later this year and in 2022.

PAIN RESEARCH - Dr Nicholas Shenker

Dr Shenker continues to be an active member of CamPAIN contributing to the research studies across the campus. Thank you to all the CARE members who contribute to the ongoing studies. We collaborate with various basic scientists across the Cambridge biomedical campus. Dr Flavia Mancini is a lead scientist for some of these studies and should you be interested in contributing in such studies, then please visit the following website: Www.noxlab.org/community

People with Complex Regional Pain Syndromes have contributed to several studies including having their genetic coded sequenced (exome sequencing) and their pain responses studies with EEG working with Professor Geoff Woods, Dr Tristan Beckinschtein, Dr Samia Shaikh, Dr Mike Lee, Maria Niedernhuber. Papers showing changes in the pain response have been published and Maria continues to work in this field. Currently, she is hoping to recruit 100 people with the diagnosis of CRPS and provide them with a headset to study the electrical activity from their brains (EEG) to wear whilst they are at home, including when they are asleep. This work is in collaboration with a group in Switzerland and a technology firm that provides the home headsets. The work hopes to be able to compare people's experiences with their brain waves, hoping to understand more about what electrical activity in the brain 'looks like' when the person experiences pain.

Unfortunately, the Gait Lab has had to close in Addenbrooke's as Accident and Emergency expanded massively during the COVID crisis. Nevertheless, new technology has allowed Dr Tom Stone to put this into the back a lorry (?!) and we hope to be able to continue our studies using this when it is up and ready.

Finally, a complicated but exciting study for those patients who suffer with rheumatoid arthritis. In collaboration with Glasgow, who are leading this study, we would like to perform brain scans and watch the movement of white blood cells (macrophages) through the brain using SPECT in people with RA who are awaiting anti-TNF treatment. This study will give either anti-TNF (adalimumab) or placebo for 8 weeks whilst people are awaiting to start their anti-TNF therapy and take a myriad of assessments and imaging (2 days worth!) before and after. This is a 'state of the

art' study using technology that has never been used in the world (7T MRI combined with macrophage trafficking). Needless to say, it has a large team of scientists at both institutions contributing to this work. We are all interested in what it may show and perhaps it will support Professor Ed Bullmore's hypotheses outlined in his book 'The Inflamed Mind'.

CLINICAL TRIALS AND STUDIES - Dr Frances Hall

A randomised double-blind controlled trial comparing Rituximab against intravenous Cyclophosphamide in Connective Tissue Disease (CTD) associated Intersitial Lung Disease (ILD) (RECITAL). (Dr Hall - PI)
Three patients were recruited from Cambridge. The study has now closed and has been analysed. The results are embargoed pending publication.

Safety of Abatacept in Rheumatoid Arthritis-associated Interstitial Lung Disease: A Feasibility Trial (APRIL) (Dr Hall - CI)
The APRIL study was suspended 19/3/20 due to the Covid-19 pandemic. It was deemed unsafe to continue to recruit patients with ILD to a trial of an immunosuppressive medication which required them to attend study visits. A total of 23 patients had been recruited; 10 had completed the study. The data has been fully collected and cleaned and is awaiting entry into the clinical trials database and analysis. These steps have been delayed because the data managers and statisticians have been fully-engaged with Covid-related studies. We anticipate that this step will be completed in the first quarter of 2022.

A Phase II Randomised Controlled Study of Oral Prednisolone in Early Diffuse Cutaneous Systemic Sclerosis (Dr Hall – PI)
Three patients were recruited from Cambridge. This trial ended 6/7/21 and is currently being analysed.

A Phase II, randomized, multi-center, placebo-controlled, double-blind study to investigate the safety of GS-248, and efficacy on Raynaud's phenomenon (RP) and peripheral vascular blood flow, in subjects with systemic sclerosis (SSc) (Dr Hall PI) - One patient has been recruited to date

mulTi-Arm Therapeutic study in pre-Icu patients admitted with Covid -19 – Repurposed Drugs (TACTIC-R) (Dr Hall – CI)

Since the severe disease manifestations of Covid-19 were mainly inflammatory, this raised the prospect that immunosuppression might be an effective therapy. TACTIC-R is a platform clinical trial designed to test immunomodulatory agents, licenced for use in other diseases, for efficacy in Covid-19. Two immunmodulators were selected:
Baricitinib – JAK2 inhibitor (inhibitor of multiple cytokine pathways) licenced for use in rheumatoid arthritis
Ravulizumab – monoclonal Ab which inhibits complement C5 activation; licenced for use in paroxysmal nocturnal haemoglobinuria and haemolytic uraemic syndrome.

Enrolment into TACTIC—R started on 8th May 2020 and completed 7th May/2021. Patients were recruited across 22 sites in the United Kingdom. Trial participants were recruited from adult patients hospitalised with COVID-19, who had disease severity above a threshold determined by use of a risk score derived by summing one point for each of the following features on admission: male gender, non-white ethnicity, diabetes mellitus, hypertension, neutrophils > 8.0 x 10^9/L, age > 40 years, C-reactive protein > 40 mg/L and radiographic severity score >3. Patients were considered eligible if the risk score was ≥ 4 or if the risk score is ≥ 3 with a radiographic score >3.

417 patients were randomized (open-label) in a 1:1:1 ratio between arms: standard of care (SoC) only, SoC plus Ravulizumab, or Soc plus Baricitinib. All patients received UK standard of care for patients admitted with Covid-19. This included prophylaxis for venous thromboembolic disease, Remdesivir (from 26th May 2020), Dexamethasone (from 3rd September 2020) 6mg daily for 7-10 days in patients with severe or critical COVID-19 and Tocilizumab (from 15/Jan/2021) in patients who are receiving (or have completed) a course of dexamethasone and have a C-reactive protein of at least 75 mg/L and either have an oxygen saturation of <92% on room air or require supplemental oxygen, or who have commenced respiratory support within 24-48h].

The primary endpoint was the time to incidence (up to and including Day 14) of any of the following events, whichever came first:

- Death
- Invasive mechanical ventilation
- ECMO
- Cardiovascular organ support (balloon pump or inotropes)
- Renal failure (estimated creatinine clearance (by Cockcroft-Gault formula) <15 ml /min), haemofiltration or dialysis.

Secondary endpoints were:

- Change in clinical status as assessed on 7-point ordinal scale compared to baseline
- Time to discharge from hospital
- Time to each of the individual endpoints of the composite primary outcome measure
- Proportion of participants with adverse events of special interest in each treatment arm
- Time to $Sp0_2$ >94% on room air
- Time to first negative SARS-CoV2 PCR
- Duration of oxygen therapy (days)
- Duration of hospitalisation (days)
- All cause mortality at day 28

Time to clinical improvement (defined as >2 point improvement from day 1 on 7-point ordinal scale)

In May 2021, the Data Monitoring Committee advised that recruitment cease for futility. There were no significant safety signals. The trial has been analysed and has not shown significant benefit of either baricitinib or ravulizumab. Manuscripts are being drafted.

Figure 1: TACTIC-R Recruitment Curve

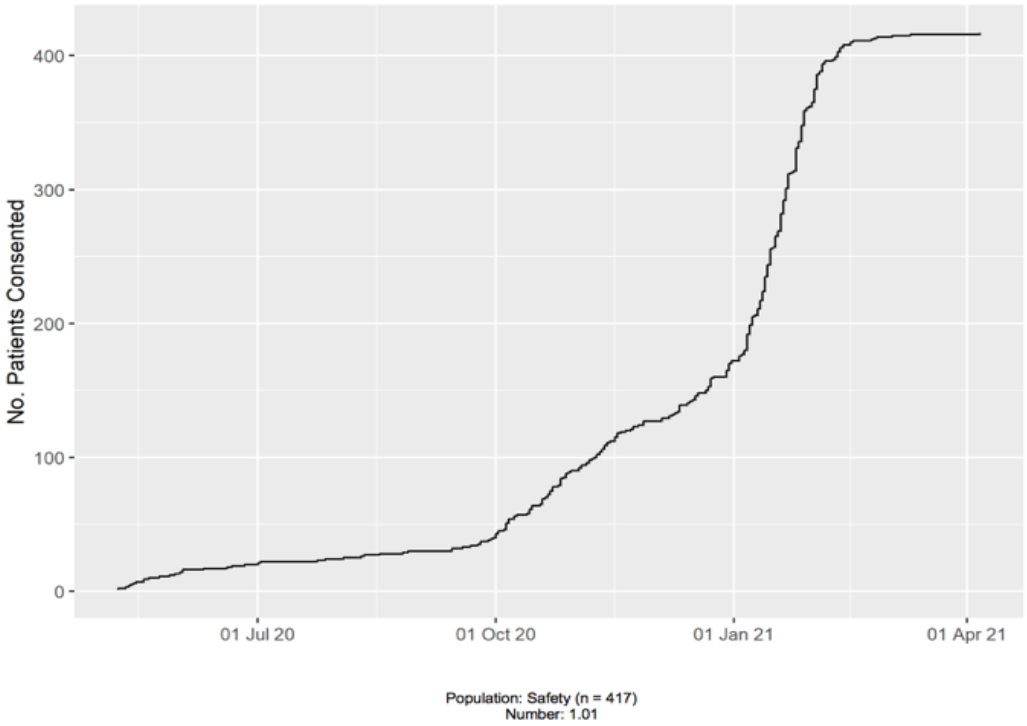


Figure 2: TACTIC-R CONSORT Diagram

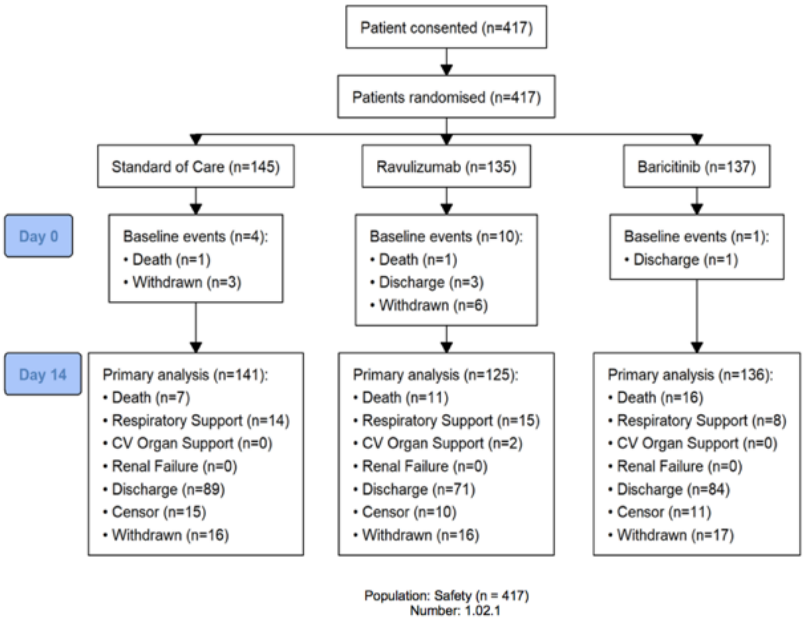
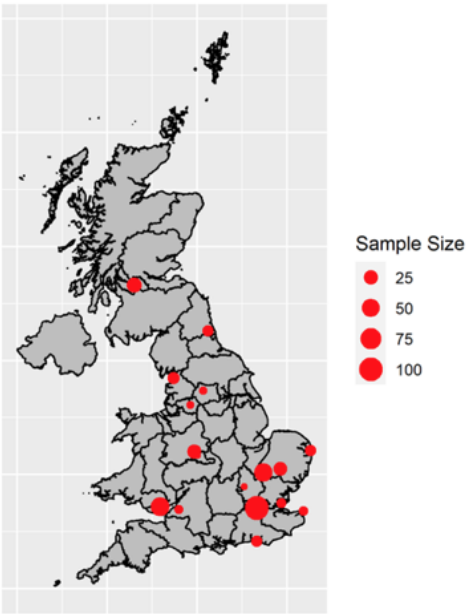


Figure 3: TACTIC-R Recruitment Map



"Censor" are patients who didn't experience a primary event and daily data was collected up to and including day 14, right-censoring was applied on day 14.
"Withdrawn" are patients who withdrew consent, stopped trial treatment or were lost to follow up prior to day 14. Data collection for these patients stopped early, at which point they were right-censored.

ORTHOPAEDIC RESEARCH – Professor Andrew McCaskie

Andrew McCaskie moved to Cambridge in 2013 to take up the Professorship in Orthopaedic Surgery, becoming Head of the Department of Surgery in 2017. He led the bid to establish the Arthritis Research UK Tissue Engineering Centre and became the Director. The Centre brings together many institutions across the UK (University of Cambridge, Newcastle University, the University of Aberdeen, Keele University/the Robert Jones and Agnes Hunt Hospital NHS Foundation Trust in Oswestry, the University of York and the University of Birmingham) bringing together clinicians, engineers and biologists from research and clinical groups to develop regenerative therapies for people with Osteoarthritis. Funded by a core grant of £2.4 million in the first five years and renewed in 2016 (£1.9M) the centre was subsequently renamed; Versus Arthritis; Tissue Engineering and Regenerative Therapies Centre.

Professor McCaskie led the Smart Step programme (£1.1M) as part of Stage II UK Regenerative Medicine Platform and is a co-investigator in the recently established UK Regenerative Medicine Platform Hub; Engineered cell environment (£5.1M). His clinical interest is lower limb, particularly hip disease in young patients and he aims to link research to the clinic, for example clinical trials (cell therapy trial for knee arthritis - ADIPOA2 EU €5.9M). He is one of the three editors of Bailey and Love's Short Practice of Surgery 27th Edition and is the Director of the Academic Foundation Programme in Cambridge, establishing the transplant and regeneration theme. He Chairs the Cell Therapy Oversight Committee and represents Addenbrooke's in the Midlands and Wales Advanced Therapy Treatment Centre'.

TAILPIECE – Hill Gaston, Chair of CARE and Emeritus Professor of Rheumatology.

I hope that the preceding accounts convince you that there is an enormous amount of research activity at CUH across the wide field of topics that are important in rheumatology. Although the COVID pandemic imposed some limitations on research which was planned, it has not all been bad news: rheumatologists have used their expertise in clinical trials and the use of "biological" treatments, to contribute to the urgent problem of life-threatening SARS2. Likewise, the new condition of "long COVID" is an opportunity to shed light on the chronic fatigue and pain that complicate many inflammatory conditions. The pandemic highlighted the crucial importance of rapid and well-organized research trials to discover useful treatments for a novel disease and to understand it better. Ideally, every patient with a condition should be recruited into a trial to determine which treatments improve outcomes. The UK managed to lead the world in carrying out some of the most important early trials, using NHS infrastructure. We must not lose sight of the lessons learned from this experience, and make sure we investigate rheumatic diseases and their treatment with the same urgency and efficiency. **In all this, your support for CARE is critical and much appreciated. Thanks!**

Donations - 'THANK YOU' to all those who are still holding CARE collecting boxes and to those who have donated though the CARE website or our Just Giving page. Over the last 12 months, we have received **£787.41.**

Visit our fundraising page to request information or to donate now

CARE is a registered Charity, number 802862, and exists to support patient care and research in rheumatic diseases in the region around Cambridge. It shares offices with the Rheumatology Clinical Research Unit.