Institution: University of Cambridge		
Unit of Assessment: UOA1		
Title of case study: Improving the outcome of patients with vasculitis: reducing treatment toxicity and developing new treatments.		
Period when the underpinning research was undertaken: August 2003 – Present		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
David Jayne	Professor of Clinical Autoimmunity	2001 – present
Ken Smith	Professor of Medicine	1996 – present
Period when the claimed impact occurred: January 2014 – Present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact (indicative maximum 100 words)

Anti-neutrophil cytoplasm antibody associated vasculitis (AAV) is a group of rare but aggressive diseases that cause inflammation of blood vessels, with the restricted blood flow leading to severe organ damage. Currently, 115,000 people are suffering from AAV across Europe and the USA, with at least 7,500 new cases diagnosed each year. Research led by the University of Cambridge has optimised existing therapies and introduced new treatments of AAV, directly improving the survival, health and well-being of patients. This improvement in therapies has produced more rapid and prolonged disease remission and reduced treatment-associated toxicities; thereby increasing patients' quality of life and five-year survival. Insights from this research have been incorporated into guidelines, NHS policy and healthcare provision for patients, and produced annual health-cost savings of GBP45,000,000.

2. Underpinning research (indicative maximum 500 words)

The destruction and inflammation of blood vessels caused by the autoimmune disease AAV, reduces blood flow to vital organs resulting in severe damage, including renal failure and pulmonary haemorrhage. As an autoimmune disease, conventional treatment of AAV includes immunosuppression combined with high-dose steroid administration, but this fails in 40% of patients and 50% suffer devastating side effects.

Jayne and Cambridge-based colleagues have led the development of research methodology and 10 international randomised clinical trials in AAV, resulting in the evidence-based optimisation of existing treatments and introduction of new therapies. This global effort was facilitated by the European Vasculitis Society (EUVAS), founded by Jayne in 2011, and its subsequent growth into a world-wide network.

Developing safer conventional treatment approaches

Cyclophosphamide is an effective immunosuppressant that was used widely to treat AAV; however, the drug is highly toxic and can cause bleeding from the bladder, infertility and various cancers. These side effects often necessitate reducing or stopping cyclophosphamide treatment, causing AAV to return in up to half of patients. Therefore, Cambridge University researchers have led randomised clinical trials aimed at identifying effective and safer alternatives to cyclophosphamide [1–3]. The **CYCAZAREM** trial (2000) of azathioprine and subsequent **NORAM** trial (1995-2000) of methotrexate [2] showed that cyclophosphamide can be replaced with less toxic therapies whilst maintaining remission.

Jayne and colleagues also led studies aimed at improving outcomes for those patients with the most severe disease. AAV patients who present with renal failure have an increased risk of developing end stage renal failure and death despite immunosuppressive therapy. The Cambridge-led **MEPEX** study (1995-2002) recruited 137 patients across 25 centres and showed that plasma exchange could safely increase the rate of renal recovery when compared with high-dose steroids [3].

To spare patients some of the serious side effects of steroid therapy, the Cambridge-led **PEXIVAS**

study (2010-2016) recruited 704 patients with AAV from 112 sites across four continents and validated both the efficacy and safety of rapidly reducing the steroid dosage, decreasing serious infection complications in patients by 20% [4].

Developing treatment to prevent relapse and reduce co-morbidities

Perhaps most significantly, between 2010 and 2016 Jayne and colleagues led the European trials of **rituximab** therapy of AAV. Rituximab is a therapeutic antibody which reduces inflammation by targeting B cells. The **RITUXVAS** study showed rituximab to be as effective as cyclophosphamide at inducing remission with similar toxicity to azathioprine and methotrexate [5]. And, the **RITAZAEM** trial showed that two-year, fixed-interval rituximab dosing is more effective than azathioprine at preventing disease relapse following treatment [5]. Together with colleagues in the EUVAS, in a study of 323 patients, Jayne also showed that cancer risk in patients treated with rituximab was similar to that of the general population and significantly less than that of cyclophosphamide-treated patients [6].

Introduction of newer vasculitis therapies

Jayne led the **CLEAR** (2011-2016) randomised, placebo-controlled trial that showed avacopan, a new complement C5a receptor inhibitor, induces faster remission with fewer side effects than treatment with high-dose steroids, thereby resulting in an increased quality of life and avoidance of steroid related harm [7]. In 2020 Jayne reported similar positive results of avacopan in an international Phase III trial of 330 patients (**ADVOCATE,** 2017-2019) which has led to licensing submissions [8]. The **MIRRA** study (2014-2016) demonstrated that using mepolizumab to treat the vasculitis Eosinophilic granulomatosis with polyangiitis (EGPA), increased remission duration, permitted steroid reduction and reduced relapse rates. [9].

3. References to the research (indicative maximum of six references)

Evidence of research quality: *Research published in peer-review journals. Research was supported by competitively won grants.

[1] ***Jayne, DR**, Rasmussen, N., *et al*. (2003). A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med*, *349*(1), 36-44.

[2] *De Groot K, Rasmussen N, *et al*…**Jayne DR**. (2005). Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*, *52*(8), 2461-9.

[3] ***Jayne, DR**., Gaskin, G, *et al*. (2007). Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol*, *18*(7), 2180-2188.

[4] *Walsh M., Merkel P., *et al* … **Jayne DR** (2020). Plasma Exchange and Glucocorticoids for Severe ANCA-Associated Vasculitis. *New England J Medicine,* 382, 622-631.

[5] *Smith, R. M., Jones, R. B., *et al*… **Smith, KGC**, **Jayne DR.** (2012). Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*, *64*(11), 3760-3769.

[6] *van Daalen EE, Rizzo R, *et al*…, **Jayne DR**, Bajema IM, Rahmattulla C. (2016). Effect of rituximab on malignancy risk in patients with ANCA-associated vasculitis. *Ann Rheum Dis*, *76*(6), 1064-1069.

[7] ***Jayne DRW**, Bruchfeld J *et al*… CLEAR Study Group. Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis (2017). *J Am Soc Nephrol; 28*(9), 2756-2767.

[8] ***Merkel PA, **Jayne DR,** Wang C, Hillson J, Bekker P. Evaluation of the Safety and Efficacy of Avacopan, a C5a Receptor Inhibitor, in Patients With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis Treated Concomitantly With Rituximab or Cyclophosphamide/ Azathioprine: Protocol for a Randomized, Double-Blind, Active-Controlled, Phase 3 Trial. *JMIR Res Protoc*. 2020 Apr 7;9(4):e16664.

[9] *Wechsler, ME. Akuthota P, **Jayne DR** *et al*. (2017) Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. *N Engl J Med*, **376**, 1921-1932.

Key competitively awarded funding:
Plasma exchange and glucocorticoids in anti-neutrophil cytoplasm antibody associated systemic vasculitis: a randomized controlled trial. PEXIVAS. National Institute for Health Research. GBP1,666,240 2009 – 2018. PI: Jane, D
RITAZAREM trial. Arthritis Research UK. GBP822,950. 2012 – 2016, PI; Jane, D.

4. Details of the impact (indicative maximum 750 words)

Impact on the health and wellbeing of people

Lives saved through earlier diagnosis: Symptoms of vasculitis are easily confused with other illnesses, so the disease can go unrecognised for a long time. Decades of Cambridge University research has contributed to earlier diagnosis of patients by increasing awareness of AAV and training physicians with interest in this disease. The improvement of quality of services for patients in the UK, 1,000 of whom receive treatment from the Cambridge Vasculitis Service, has enhanced wellbeing and saved lives. As such, Vasculitis UK notes, *"the loss or reduction of this service [Cambridge-based research and treatment] would represent the loss of a valuable resource and leave a huge gap in provision of care nationally for patients suffering from systemic vasculitis"* [A].

Lives saved by optimising treatment strategies: Infection related to high-dose steroid use is the major cause of treatment-related death, owing to organ damage and hospital readmission among patients with AAV. Cambridge-led trials, spanning two decades, have tested and led to the use of alternative, less toxic maintenance treatments [1-3]. The results of the Cambridge led PEXIVAS Study in 2020 [4] led to an immediate change in practice, with physicians reducing steroid dose more rapidly across the NHS. This has reduced hospital readmissions by 20% and has become the new standard of care for patients with AAV [B]. The optimisation of these conventional AAV therapies has seen first year fatality rates fall from 50% in 2007 to under 25% in 2020 [4,B].

Access to novel therapies: In March 2013, Cambridge-led research was pivotal to the licensing of rituximab by the European Medicines Agency (EMA). In 2018 new patient use of rituximab was 36% [C]. Use continues to grow as 63% of patients treated in Cambridge were using rituximab in 2020 [C]. In 2019, the EMA announced that mepolizumab is under investigation for the treatment of the specific AAV disease EGPA [D]. As a result, this offers the first licensed therapy to the approximately 3,000 patients with EGPA in the UK [C]. In the same year, the FDA licensed mepolizumab as the first drug in the US to treat EGPA [10; D]. Furthermore, the avacopan programme has led to licensing applications and the availability of this novel treatment on a compassionate basis [9].

Impact on practitioners and the delivery of professional services

Establishment of national policy and guidelines: The January 2015 NHS Clinical Commissioning Policy, *Rituximab for the treatment of AAV in adults* [E], was directly informed and shaped by Cambridge-led research [6]. The Policy ensures the equitable and cost-effective use of rituximab as a treatment for AAV, both as a remission-induction and maintenance agent.

Cambridge researchers also contributed significantly to the writing of the 2014 National Institute for Health and Care Excellence (NICE) accredited British *Guideline for the management of adults with AAV* [E], and the first international *Recommendations for the management of ANCA-associated vasculitis* (2016, European League Against Rheumatism [EULAR]) [E]. Cambridge-led research into rituximab has produced the first recommendations specifically formulated for B cell targeted therapies in autoimmune rheumatic diseases. The 2018 recommendations aid healthcare professionals with clinical decision-making in order to minimise infection risks for patients with drug induced immune deficiency [E].

NICE also drew on Cambridge research [6] to shape its March 2014 Guideline, *Rituximab in combination with glucocorticoids for treating AAV* (TA308) [F]. As a direct consequence, clinicians are now able to implement best practice efficiently within treatment centres where patients and clinicians benefit from a unified practice across the UK, reducing significantly the risk of low quality, 'postcode lottery' management experiences that have been typical among rare diseases.

Networks, training and development: Cambridge researchers have been instrumental in establishing both national and international research and training networks for healthcare professionals caring for patients with AAV. Jayne was the founder of EUVAS in 2011 and remains its President. EUVAS has over 200 members across Europe and Australasia, facilitating international collaboration and sharing best practice. The success of EUVAS has led to the founding of similar clinical trial networks across the globe. The Chair of the NHS England Clinical Reference Group for Specialised Rheumatology, and President of the British Society for Rheumatology, notes that through Jayne's *"international leadership of clinical trials as President of EUVAS, his work has created the evidence base that has directly 'paved the way' for revolutionary new treatments for people living with Vasculitis"* [G].

Additionally, Cambridge researchers run a number of training courses for clinicians, including the annual EUVAS Course for senior trainees, consultants and allied health professionals. Established in 2017, the Course has been well-attended each year (720 attendees to date), and has received positive feedback: in its first year 92% of attendees stated they would implement their learning in clinical practice [H].

The national vasculitis registry, UKIVAS, was established in 2012 with input from Cambridge researchers, and Cambridge is the highest recruiter to the registry (over 950 patients at present). UKIVAS ensures that clinicians, providers and commissioners working in the field of vasculitis have robust and meaningful data to inform decision-making for vasculitis services and patients.

Regional Vasculitis Service: The Vasculitis and Lupus Service at Addenbrooke's Hospital is a nationally eminent treatment centre for sufferers of AAV. Under the directorship of Jayne, the Service provides optimal AAV treatment based on Cambridge-led research. Between 2015 and 2019, the service hosted ~4,500 outpatient appointments per year for ~1,000 patients [I].

Impacts on understanding, learning and participation

Patient engagement: Jayne is a Medical Advisor to Vasculitis UK, the UK's leading vasculitis charity. In this role, Jayne uses his expertise to support and inform patients about their disease and therapies. Jayne contributed to the Fertility and Vasculitis section of the Vasculitis UK *Route Map* [J], published in 2014, which serves as a guide to living with vasculitis. In acknowledging Cambridge's pivotal role in patient and clinician education and engagement through its world-leading service, Vasculitis UK stated: "*the [Cambridge] clinic has become the UK's institution of ultimate recourse for unusual & complex cases with secondary & tertiary referrals from around the UK."* [B].

Impact on commerce and the economy

Healthcare savings for the NHS: By decreasing relapse and improving the management of patients with AAV, Cambridge research has significantly reduced the financial burden on the NHS. Approximately 50% of AAV patients relapse within the five years of treatment, which is particularly costly to the NHS, through hospitalisation, additional treatment, and immunosuppression-associated infection. Significant costs can accrue at relapse from further organ damage, particularly renal damage leading to costly renal replacement therapy [K]. Indeed, the estimated cost savings for the NHS resulting directly from Cambridge-led introduction of rituximab therapy alone are GBP45,000,000 per year (2018/2019) [K]. In the US, healthcare savings are estimated at USD41,400 per major relapse [K].

Cambridge research demonstrating that two 1g infusions of rituximab is as effective as four infusions of 375mg/m^2 at weekly intervals has also produced cost savings to the NHS in terms of reduced clinical activity (50%) and drug costs (40%) [F]. Rituximab also generates more quality-adjusted life years (QALY) than cyclophosphamide; noted by the NICE Evidence Review group to produce an incremental cost-effectiveness ratio of GBP6,006 per QALY gained [F].

Impact on industry and production: Cambridge research has been a major contributor to the licensing of novel treatments for AAV. Since its FDA licensing of mepolizumab for the treatment

of EGPA, GlaxoSmithKline (GSK) has reported a 23% increase in sales of mepolizumab in the USA [L].

Chemocentryx Inc has recently invested USD100,000,000 to develop the novel therapy, avacopan. Jayne is providing scientific advice based on novel work from Cambridge [7]. The drug is now in a Phase III trial and is on a pathway to licensing with the EMA, with the FDA recently accepting the New Drug Application (NDA) for avacopan [C and L; 8].

5. Sources to corroborate the impact (indicative maximum of 10 references)

Impact on the health and wellbeing of people

[A] Lives saved through earlier diagnosis: Testimonial from Vasculitis UK

[B] Lives saved by optimising treatment strategies: Salmela A, *et al*. Prognostic Factors for Survival and Relapse in ANCA-Associated Vasculitis with Renal Involvement: A Clinical Long-Term Follow-Up Study. Int J Nephrol. 2018;63:69-81.

[C] Access to novel therapies: (i) Pearce FA, *et al.* Outcomes and compliance with standards of care in anti-neutrophil cytoplasmic antibody–associated vasculitis—insights from a large multiregion audit. Rheumatology Advances in Practice 2018;0:1–7.;(p3) (ii) Fifth Cumulative Report for RIVAS Study (fig 2, p3); (iii) ChemoCentryx announcement

[D] Access to novel therapies: (i) EMA investigation of mepolizumab for the treatment of EGPA citing study published in [9](p.13); (ii) FDA press release licensing of mepolizumab for the treatment of EGPA (iii) revised prescribing information for mepolizumab citing study published in [9], June 2019 (p.7)

Impact on practitioners and the delivery of professional services

[E] UK and European key guidelines for the treatment of AAV: (i) NHS Clinical Commissioning Policy for Vasculitis (p.10 healthcare savings, p.12 Cambridge studies into rituximab); (ii) British Guideline for the management of adults with AAV; (iii) EULAR Recommendations for the management of AAV; (iv) Recommendations for the management of secondary hypogammaglobulinaemia due to B cell targeted therapies in autoimmune rheumatic diseases

[F] Establishment of national policy and guidelines: NICE Guideline on rituximab: (pp. 9-10 discusses RITUXVAS Study, p. 8 discusses cost savings and p.16 highlights QALYs)

[G] Networks, training and development: Testimonial from National Clinical Lead for Rheumatology

[H] Networks, training and development: Feedback from 2017 EUVAS Course (pp.6-8)

[I] Regional Vasculitis Service: Appointments per annum

Impact on understanding, learning and participation

[J] Patient engagement: Vasculitis UK Route Map (pp.74-5)

Impact on commerce and the economy

[K] Healthcare savings for the NHS: NHS cuts medicine costs news article; Costs of major relapse in AAV. Raimundo K, *et al*. Clinical and Economic Burden of Antineutrophil Cytoplasmic Antibody-associated Vasculitis in the US. J Rheumatol. 2015;42:2383-2391.

[L] Impact on industry and production: GSK annual sales for 2019 (p. 46)