Institution: University of Bristol		
Unit of Assessment: 1) Clinical Medicine		
Title of case study: Targeted therapy in juvenile idiopathic arthritis-associated uveitis has reduced visual impairment and changed practice globally		
Period when the underpinning research was undertaken: 2004 - 2019		
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:**
Andrew Dick Athimalaipet Ramanan	Professor of Ophthalmology Honorary Professor	03/2000 - present 02/2010 - present
Period when the claimed impact occurred: 2015 – 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Research conducted at the University of Bristol (UoB) led directly to the introduction of adalimumab around the world for treatment of children with uveitis. Previously there were no licensed or approved therapies for children with uveitis. The SYCAMORE study demonstrated overwhelming efficacy of adalimumab (anti-TNF agent) in children with sight threatening eye disease (uveitis). Presentation of initial results led to unprecedented next day approval by NHS England and adalimumab has since been approved for use in 76 countries, as well as the European Medicines Agency and the US Federal Drugs Agency. It is estimated over 33,400 children in the US, Europe and Canada alone, have benefited from the treatment to April 2020.

2. Underpinning research

UoB research led by Prof Andrew Dick published the original description of the benefit of neutralisation of tumour necrosis factor (TNF) in mouse models of the rare eye inflammation condition, uveitis, and elucidated the detrimental mechanisms of action of TNF in models of uveitis [1]. Following the discovery that this pivotal cytokine was instrumental in tissue destruction during uveitis, the research group developed a translational pathway to demonstrate clinical benefit, using a p55 TNF receptor fusion protein in humans. Translating through, the study generated a proof of concept, illustrating that 70% of refractory adult non-infectious uveitis patients achieved remission [2].

Following pre-clinical and clinical early phase translation, other groups also showed potential of clinical benefit in cohort studies of anti-TNF therapies in uveitis in adults and children. In adults, Prof Dick was Co-Investigator and UK lead for three clinical trials investigating the fully human anti-TNF monoclonal antibody, adalimumab. Developed and funded by the US based biopharmaceutical company Abbvie (formerly Abbott), they investigated the efficacy and safety of adalimumab in active (VISUAL I) and inactive (VISUAL II) uveitis, followed by an evaluation of extended treatment (VISUAL III) [e.g. 3].

From 2005, a combined clinic led by Prof Dick and Prof Ramanan was initiated to provide better clinical care for children. The need for a prospective RCT of anti-TNF in children with juvenile idiopathic arthritis uveitis (JIA-U) was identified as the most important unmet research priority across UK and North America.

The SYCAMORE (SafetY and Cost-effectiveness of Adalimumab in Combination with MethOtRExate) trial for JIA-U, funded by National Institute for Health Research (NIHR) and Arthritis Research UK (ARUK) [i] and sponsored by University Hospitals Bristol (UH Bristol) NHS Foundation Trust, ran between 2011 and 2017. The trial was a randomised, parallel-group, double-blind, multicentre study, to compare adalimumab versus a placebo, in children receiving a stable dose of methotrexate for active JIA-U [4, 5]. The study target size was 114 participants aged between 2 and 18 with JIA-U. By early 2015, 90 participants had been recruited; however, an interim data analysis showed that adalimumab was overwhelmingly more effective than the placebo. In April 2015, the Trial Steering Committee recommended recruitment to the trial should cease and that participants in the active arm (adalimumab) should continue to be followed up. The trial then ran to completion in an open-label phase containing only participants continuing treatment with adalimumab. Results from the double-blind phase [4], were supported by integrated analysis of both double-blind, and open-label phase data [5], revealing that adalimumab significantly controlled inflammation and reduced the rate of treatment failure.

The SYCAMORE study was also the first to undertake prospective cost-effectiveness using patient health utilisation data [6]. The results highlighted that a price reduction of 84% would be necessary for adalimumab to be cost-effective compared with methotrexate alone in the United Kingdom setting.

3. References to the research

[1] **Dick AD**, Forrester JV, Liversidge J, Cope AP (2004). The role of tumour necrosis factor (TNF-alpha) in experimental autoimmune uveoretinitis (EAU). *Progress in Retinol and Eye Research,* 23 (6): 617-37. DOI:10.1016/j.preteyeres.2004.06.005

[2] Murphy CC, Greiner K, Plskova J, Duncan L, Frost A, Isaacs JD, Rebello P, Waldmann H, Hale G, Forrester JV, **Dick AD.** (2004). Neutralizing Tumor Necrosis Factor Activity Leads to Remission in Patients With Refractory Noninfectious Posterior Uveitis. *Archives of Ophthalmology,* 122 (6), 845–851. DOI:10.1001/archopht.122.6.845

[3] Suhler EB, Adán A, Brézin AP, Fortin E, Goto H, Jaffe GJ, Kaburaki T, Kramer M, Lim LL, Muccioli C, Nguyen QD, Calster JV, Cimino L, Kron M, Song AP, Liu J, Pathai S, Camez A, Schlaen A, Velthoven MEJ, van Vitale AT, Zierhut M, Tari S, **Dick AD.** (2018). Safety and Efficacy of Adalimumab in Patients with Noninfectious Uveitis in an Ongoing Open-Label Study: VISUAL III. Ophthalmology 125, 1075–1087. DOI:10.1016/j.ophtha.2017.12.039

[4] **Ramanan AV, Dick AD,** Jones AP, McKay A, Williamson PR, Compeyrot-Lacassagne S, Hardwick B, Hickey H, Hughes D, Woo P, Benton D, Edelsten C, Beresford MW. (2017). Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis. *New England Journal of Medicine*, 376, 1637–1646. DOI:10.1056/NEJMoa1614160

[5] **Ramanan AV, Dick AD,** Jones AP, Hughes DA, McKay A, Rosala-Hallas A, Williamson PR, Hardwick B, Hickey H, Rainford N, Hickey G, Kolamunnage-Dona R, Culeddu G, Plumpton C, Wood E, Compeyrot-Lacassagne S, Woo P, Edelsten C, Beresford MW (2019). Adalimumab in combination with methotrexate for refractory uveitis associated with juvenile idiopathic arthritis: a RCT. *Health Technology Assessment,* 23 (15): 1-140. DOI:10.3310/hta23150

[6] Hughes DA, Culeddu G, Plumpton CO, Wood E, **Dick AD,** Jones AP, McKay A, Williamson PR, Lacassagne SC, Hardwick B, Hickey H, Woo P, Beresford MW, **Ramanan AV.** (2019). Cost-Effectiveness Analysis of Adalimumab for the Treatment of Uveitis Associated with Juvenile Idiopathic Arthritis. *Ophthalmology*, 126, 415–424. DOI:10.1016/j.ophtha.2018.09.043

Grant Information:

[i] **Ramanan A,** Beresford M (Co-I, University of Liverpool). Phase III randomised controlled trial of the clinical effectiveness, safety and cost effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE), NIHR Health Technology Assessment and Arthritis Research UK (ARUK), 2011 – 2017, GBP1,472,523

4. Details of the impact

Juvenile idiopathic arthritis (JIA) affects 1 in 1000 children with about a third of these children developing inflammation in the eye (Uveitis), which can be sight-threatening. JIA associated uveitis (JIA-U) leads to significant visual impairment in more than half the children with this condition.

Prior to the SYCAMORE trial [4, 5] there were no licensed or approved therapies for children with uveitis. In 2015, the study was unmasked early by the Independent Data Safety Monitoring Committee [4, 5] due to overwhelming efficacy and to avoid exposing more children to placebo. These initial results were first presented by Prof Ramanan to the American College of Rheumatology Annual Meeting on 10th November 2015 [Aii]. In an unprecedented response, the day after presentation of results, interim access to this expensive medicine was approved by NHS England, with direct reference to the SYCAMORE trial [Ai (11th November 2015), H].

Approval of Adalimumab Globally

This is one of the first investigator-initiated studies in a rare disease that has led to a pharmaceutical company, Abbvie, who supplied the investigational medicinal product adalimumab (Humira) for SYCAMORE, negotiating a data sharing agreement with University Hospital Bristol (UH Bristol) to access data for licensing and market authorisation. Following this agreement, Abbvie submitted the data (citing the SYCAMORE study) to the European Medicines Agency (EMA) leading to approval in 2017 [Bi]. Approval from the US Food and Drug Administration (FDA) followed this in 2018 [Bii], and Health Canada in 2019 [Biii]. To date, SYCAMORE has led to approval of adalimumab in JIA-U in more than 76 countries [C]. Both EMA and FDA have approved adalimumab for wider indication than the trial population, which led to substantially more children benefiting from this drug (estimated over 30,000 in North America and Europe). 10,000 children in the US have benefitted from treatment with adalimumab [C] (~ 0.003% of US population). Using estimates of population (Europe: 740 million, Canada: 40 million), we estimated 23,400 children in Europe and Canada alone will have benefitted.

Changes to International Health Guidelines

The SYCAMORE trial has also led to new guidelines for management of children with uveitis across Europe, the US and internationally. Findings from the trial [4] were cited in a 2018 consensus statement by a European initiative, the Single Hub and Access point for paediatric Rheumatology (SHARE), providing recommendations for the management of JIA-U [D]. The consensus specifically noted that the SYCAMORE study improved the quality of the evidence from level 3 to level 1, relating to Recommendation 1:5 *'In case of methotrexate inefficacy or intolerance, adding or switching to biological treatment is recommended'* [D]. In 2019, an update to the German Ophthalmological Society guideline for anti-inflammatory treatment of JIA-U [E] cited the SYCAMORE trial [4] among evidence for the use of Adalimumab, concluding that it was the preferred anti-TNF therapy for JIA-U [E]. The American College of Rheumatology Guideline

(2019) also recommends adalimumab or infliximab, over alternative anti-TNF therapies and cited evidence from the SYCAMORE study [4], describing it as the only *'well-conducted RCT on the use of adalimumab and methotrexate in children'* [F].

In 2018, an international consensus report from the Fundamentals of Care for UveitiS (FOCUS) initiative, recommended adalimumab (grade A recommendation) for treatment of non-infectious uveitis in adults, and cited SYCAMORE [4] as evidence for the benefit in juvenile patients [G]. The guidance for treatment of adults also draws heavily on evidence from the VISUAL trials led in the UK by Prof Dick [e.g. 3]. The VISUAL trials also played a fundamental role in the recommendation of the use of adalimumab for the treatment of non-infectious uveitis in adults by the NHS (2017).

Benefits to Health and Well-being

The SYCAMORE trial demonstrated clear short-term therapeutic benefit, including excellent visual acuity results [4, 5]. A 5-year follow-up of the SYCAMORE trial highlighted a longer-term role for adalimumab in the treatment of refractory JIA-U [I]. Dick and Ramanan are the Bristol lead investigators for a current US-funded trial (ADJUST), investigating the length of time treatment with adalimumab continues to be effective in children.

In 2007, Prof Dick and Prof Ramanan hosted a meeting in Bristol to bring together for the first time the Rheumatologists and Ophthalmologists managing paediatric uveitis, and gain consensus for the development of a paediatric programme for trials in paediatric uveitis. This generated public and patient support through engagement with the patient-led charity Olivia's Vision, who provide information, support and advice for anyone affected by uveitis. Prof Dick and Prof Ramanan both act as expert members of the medical advisory board for the charity [J].

Health Economics

The SYCAMORE study was the first study to undertake prospective cost-effectiveness using patient health utilisation data and provided a clear demonstration of the importance and benefits of this approach [6, H]. The results highlighted that a price reduction of 84% would be necessary for adalimumab to be cost-effective compared with methotrexate alone in the United Kingdom setting [6]. Adalimumab is now off patent, and the study has provided information for the change in drug cost, permitting accessibility to treatment across England and Wales [H]. The Pharmacy Lead, Specialised Commissioning for NHS England noted that *'This HE study will have helped benchmark pricing for adalimumab biosimilar and for other manufacturers when setting pricing for new therapies in this indication'* [H].

5. Sources to corroborate the impact

[A] i) NHS England (11th November 2015). NHS England publishes clinical commissioning policy on adalimumab for children with uveitis
ii) American College of Rheumatology (10th November 2015). Meeting Abstracts: Abstract Number: 3L Ramanan *et al.* A Randomised Controlled Trial of the Clinical Effectiveness, Safety and Cost-Effectiveness of Adalimumab in Combination with Methotrexate for the Treatment of Juvenile Idiopathic Arthritis Associated Uveitis

[B] i) European Medicines Agency (2017). Assessment report: Humira
ii) US Food & Drug Administration (2018). BLA 125057/S408
iii) Eyewire news (2019). AbbVie's Humira (Adalimumab) Approved by Health Canada to Treat Pediatric Patients with Chronic Noninfectious Anterior Uveitis

[C] AbbVie (2020). Humira peds uveitis approvals as of 24 February 2020

[D] Constantin T, Foeldvari I, Anton J, de Boer J, Czitrom-Guillaume S, Edelsten C, Gepstein R, Heiligenhaus A, Pilkington CA, Simonini G, Uziel Y, Vastert SJ, Wulffraat NM, Haasnoot A-M, Walscheid K, Pálinkás A, Pattani R, Györgyi Z, Kozma R, Boom V, Ponyi A, Ravelli A, **Ramanan AV.** (2018). Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative. *Annals of the Rheumatic Diseases,* 77, 1107–1117. DOI:10.1136/annrheumdis-2018-213131

[E] Heiligenhaus *et al.* (2019). Update of the evidence based, interdisciplinary guideline for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. *Seminars in Arthritis and Rheumatism*, 49, 43–55. DOI:10.1016/j.semarthrit.2018.11.004

[F] Angeles-Han *et al.* (2019). 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis–Associated Uveitis. *Arthritis Care & Research,* 71, 703–716. DOI:10.1002/acr.23871

[G] **Dick AD**, Rosenbaum JT, Al-Dhibi HA, Belfort R Jr, Brézin AP, Chee SP, Davis JL, **Ramanan AV**, Sonoda KH, Carreño E, Nascimento H, Salah S, Salek S, Siak J, Steeples L. (2018). Fundamentals of Care for Uveitis International Consensus Group. (2018). Guidance on Noncorticosteroid Systemic Immunomodulatory Therapy in Noninfectious Uveitis: Fundamentals Of Care for UveitiS (FOCUS) Initiative. *Ophthalmology,* 125, 757–773. DOI:10.1016/j.ophtha.2017.11.017

[H] NHS England (2020) – Supporting letter – Pharmacy Lead, Specialised Commissioning

[I] Horton S, Jones AP, Guly CM, Hardwick B, Beresford MW, Lee RW, **Dick AD, Ramanan AV.** (2019). Adalimumab in Juvenile Idiopathic Arthritis–Associated Uveitis: 5-Year Follow-up of the Bristol Participants of the SYCAMORE Trial. *American Journal of Ophthalmology*, 207, 170–174. DOI:10.1016/j.ajo.2019.06.007

[J] Olivia's Vision (2020). Medical Board