Institution: University of Liverpool		
Unit of Assessment: UOA 1		
Title of case study: Global access to a sight-saving therapy for children with arthritis-associated uveitis		
Period when the underpinning research was undertaken: 2009-2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): **Professor Michael William Beresford**	**Role(s) (e.g. job title):** **Brough Chair, Professor of Child Health; Honorary Consultant Paediatric Rheumatologist**	**Period(s) employed by submitting HEI:** **2005 onwards**
Period when the claimed impact occurred: From 2013 onwards		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Juvenile idiopathic arthritis (JIA) affects approximately 10,000 UK children with 1,000 new cases per year. JIA-associated uveitis, occurring in 38% of patients, can cause partial or complete sight loss. Standard treatments have significant side effects: 50% of children may be unresponsive. Working closely with patient representatives, the SYCAMORE Trial tested the drug adalimumab for addressing unresponsive cases.

The significant positive effect of adalimumab led to rapid changes in NHS Clinical Commissioning Policy, commercial licensing and approval across 65 countries. In England alone, >480 children failing all other available treatments for non-infectious uveitis have received this sight-saving therapy since 2015. Globally, approximately 50,000 children now have access to adalimumab for this indication.

2. Underpinning research

JIA, the most common rheumatic disease in children, affects approximately 10,000 UK children with 1,000 new cases diagnosed each year. Up to 38% of children with JIA develop uveitis as a co-morbidity. Uveitis is inflammation of the uvea (i.e. iris, ciliary body and choroid) with chronic uveitis causing ocular complications, including glaucoma and cataracts, which together can lead to permanent vision loss. Up to 50% of children affected exhibit refractory disease, unresponsive to standard therapies (corticosteroids and methotrexate, both themselves having significant associated side-effects). Corticosteroids, the first-line treatment for uveitis, should be limited because the risk of cataract increases with >3 corticosteroid drops per day. Children with uveitis have impaired quality of life, worrying about becoming blind, with additional strain from the burden of examinations and treatment regimens.

Professor Beresford (UoLiverpool) developed the UK's Paediatric Rheumatology Clinic Study Group (CSG) in 2007, forming a unique partnership between the NIHR Medicines for Children Research Network and Arthritis Research Campaign (ARC, now Versus Arthritis), with a remit to identify and tackle the major clinical priorities in paediatric rheumatic disorders in the UK and further afield [3.1]. JIA-associated uveitis was identified as a top priority, both in the UK and internationally, due to the disease's sight-threatening nature. The CSG's first Strategic Research Strategy (published on the ARC website in 2008, with Professor Beresford as Chair and lead author) developed and specifically prioritised a trial of anti-TNFα therapy in children failing methotrexate for JIA-associated uveitis, reinforced again in 2011 with the CSG's revised Research Strategy.

These efforts coalesced in a successful application to the Health Technology Assessment/ARC for funding (GBP1,500,000) to deliver SYCAMORE, an investigator-led, publicly-funded study commenced in 2011 with Co-Chief Investigators, Professors Beresford (UoL) and Ramanan (UoBristol) [3.2]. The trial was coordinated by Liverpool Clinical Trials Unit and sponsored by University Hospitals Bristol NHS Foundation Trust. The SYCAMORE Trial investigated the effectiveness of adalimumab (trade name Humira) in the treatment of JIA-associated uveitis. Adalimumab is an anti-TNFα biologic recommended for treatment of JIA. The study was halted 18 months early due to the very significant positive effect of adalimumab on disease remission. The study was published in the New England Journal of Medicine (NEJM) in 2017 [3.3] and NIHR Health Technology Assessment in 2019 [3.4], with Professor Beresford as Senior Author. Along with the wider impact of the trial, it was the first formal health economic evaluation of a biologic therapy in children with JIA-uveitis in the context of a clinical trial [3.5].

The success of SYCAMORE enabled Professors Beresford and Ramanan to secure funding from Arthritis Research UK for the APTITUDE Trial of tocilizumab in JIA-uveitis patients failing adalimumab/methotrexate as Co-Chief Investigators, published in Lancet Rheumatology with Professor Beresford as Senior Author [3.6]. The accomplishments of UoL and its national and international partners in paediatric rheumatology, including UoBristol, led Professor Beresford to be successfully awarded as Director, the UK's first and only 'Experimental Arthritis Treatment Centre for Children' (EATC4Children, 2014-24). SYCAMORE, APTITUDE, and a succession of follow-on investigator-led and industry-sponsored studies forms part of the JIA-uveitis work stream of the EATC4Children.

3. References to the research

[3.1] Thornton J, **Beresford MW**, Clayton P. Improving evidence base for treatment of JIA: the challenge and opportunity facing the MCRN/arc Paediatric Rheumatology Clinical Studies Group. Rheumatology 2008;47(5):563-566. https://doi.org/10.1093/rheumatology/ken055

[3.2] Ramanan AV, Dick AD, Benton D, Compeyrot-Lacassagne S, Dawoud D, Hardwick B, Hickey H, Hughes D, Jones A, Woo P, Edelsten C, **Beresford MW**, on behalf of The SYCAMORE Trial Management Group. 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 (SYCAMORE Trial). Trials. 2014;15(14): doi:10.1186/1745-6215-15-14

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[3.4] 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**. Adalimumab in combination with methotrexate for refractory uveitis associated with juvenile idiopathic arthritis: a RCT. Health Technol. Assess. 2019. doi:10.3310/hta23150

[3.5] Hughes DA, Culeddu G, Plumpton C, Wood E, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot Lacassagne S, Hardwick B, Hickey H, Woo P, **Beresford MW,** Ramanan AV **Beresford** and Ramanan: joint senior authors). Cost-effectiveness analysis of adalimumab for the treatment of uveitis associated with Juvenile Idiopathic Arthritis. Ophthalmology. 2018 Oct 15. pii: S0161-6420(18)31146-1. doi: 10.1016/j.ophtha.2018.09.043. [Epub ahead of print]. PMID: 30336181

[3.6] Ramanan AV, Dick AD, Guly C, McKay A, Jones AP, Hardwick B, Lee R, Smyth M, Jaki T, **Beresford MW**, on behalf of the APTITUDE Trial Management Group. Tocilizumab in patients with anti-TNFα refractory juvenile idiopathic arthritis-associated uveitis (APTITUDE Trial): a multicentre, single arm, phase 2 trial. Lancet Rheumatol. 2020 Feb 7;2(3):e135-e141. doi: 10.1016/S2665-9913(20)30008-4. eCollection 2020 Mar. PMID: 32280950

4. Details of the impact

The EATC4Children, under Professor Beresford's leadership, has been instrumental in tackling sight-threatening JIA-associated uveitis in cases that were unresponsive to standard treatment, demonstrating the efficacy of the drug adalimumab through the SYCAMORE trial and enabling access to adalimumab for children across the globe.

Versus Arthritis describe the experience of one of many suffers that have benefitted, when other treatments were not working: **'*…for Lily, walking was too painful, and her sight was at risk when she was recruited to the SYCAMORE trial. Responding brilliantly to the treatment, she subsequently is 'busy dancing, doing gymnastics, playing netball and spending time with her friends.'*** [5.1]

Professor Beresford founded the UK's Paediatric Rheumatology Clinic Study Group (CSG) in 2007, prioritising in its research strategy, sight-threatening JIA-associated uveitis. Under Professor Beresford's leadership, the CSG established a proactive UK-wide Patient and Family Public Involvement and Engagement group (PPIE). Contributing directly to the CSG's research strategy, PPIE directly contributed to SYCAMORE's trial protocol development and the required final placebo-controlled study design, and all aspects of co-ordination and delivery. Recruiting centre clinicians note that families accepted and understood the importance and significance of the placebo design during trial recruitment: ***"The trial meant a lot to the children and the families who took part; I had not expected them to accept the placebo and understand why it was important."*** [5.2]. This trial design ultimately contributed to the success and such a decisive outcome and impact of the trial.

Changing policy and practice

SYCAMORE was the world's first randomised control trial in JIA-associated uveitis and led to rapid changes in drug commissioning policy; following the release of preliminary trial data in 2015, the NHS revised its Clinical Commissioning Policy of National Guidelines to provide access to adalimumab for children with severe refractory uveitis that same year [5.3]. Subsequently, the SYCAMORE trial was used specifically for commercial licensing across Europe and North America through the European Medicines Agency (2017), the Food and Drug Administration (2018) and Health Canada (2019) [5.3]. This resulted in approval of adalimumab for the indication of non-infectious uveitis (JIA- and non-JIA-associated) across 65 countries and international access to this sight-saving therapy [5.1]. The international SHARE Initiative, endorsed by the worldwide Paediatric Rheumatology European Society, advocated for adalimumab use based on SYCAMORE in its recommendations for treatment of JIA-associated uveitis [5.4].

Benefits for patients

Adalimumab is prescribed in cases that are unresponsive to standard treatment and data from NHS England reports 315 children have been prescribed adalimumab for JIA-associated uveitis since the Commissioning Policy in November 2015 [5.5]. Another 166 children received the drug for non-JIA-associated non-infectious anterior uveitis, highlighting an additional patient population benefiting from SYCAMORE. All these children may have lost their sight without this intervention. Globally, based on the prevalence of JIA-uveitis, some 50,000 children now have access to adalimumab for this indication. In 2017, Professors Beresford and Ramanan were awarded the University of Bristol Health and Wellbeing Impact Award (2017) for their seminal work in facilitating international access to adalimumab for children with uveitis [5.6].

Public and patient engagement

The SYCAMORE Trial has been widely disseminated to the public. BBC Radio 4's "Inside Health' featured it in 2017 [5.7]. Olivia's Vision, the UK's leading uveitis charity, responding to the NICE Multiple Technology Appraisal for treatment of non-infectious uveitis, explicitly referenced the importance of SYCAMORE [5.8]. Arthritis Research UK's CEO highlighted SYCAMORE as one of the charity's biggest achievements over the last 30 years describing it as "*a great example of the growing legacy of the TNF story, and how other biologic treatments can and are being used to effectively treat conditions*" [5.9]. These examples highlight the importance of SYCAMORE for major charities and the patients they represent.

International drug licencing driving cultural change and economic impact

This publicly-funded trial was the first of its kind to secure a licensing contract with a commercial company, AbbVie, resulting in a submission to regulatory bodies. SYCAMORE established a UK-wide network of centres with joint paediatric rheumatology/ophthalmology multi-disciplinary clinics enhancing clinical care and enabling research. This UK-wide paediatric uveitis "trial culture" did not exist before SYCAMORE but led to successful delivery of APTITUDE. The EATC4Children has subsequently secured a pipeline of investigator-led and commercial trials that continues to benefit children with sight-threatening uveitis. It enabled additional academic and commercial partnerships including the MRC/Versus Arthritis-funded Stratified Medicine 'CLUSTER' Consortium [5.10] in which UoL are leading, along with UoB, the uveitis and industry workstreams in collaboration with five major pharmaceutical partners: AbbVie, UCB, GSK, Pfizer and Sobi. This has enabled continued close collaboration with children and their families, tackling together the challenge of determining the very best way of treating children with sight-threatening uveitis.

5. Sources to corroborate the impact

[5.1] https://www.versusarthritis.org/news/2019/august/a-spotlight-on-the-sycamore-trial-developing-treatments-for-young-people-with-arthritis/
(Versus Arthritis website: SYCAMORE trial resulted in adalimumab becoming available for patients in 65 countries worldwide)

[5.2] Clinician Survey Sycamore Study Site Results

[5.3] Global Commissioning Policy:

i. NHS England News_interim clinical commissioning policy_adalimumab_11th Nov 2015: https://www.england.nhs.uk/2015/11/adalimumab-child/
ii. European Medicine Agency_2017_ EMA Assessment Report Humira EMEA/H/C/000481/II/0163
iii. Food and Drug Administration 2018_ https://www.empr.com/home/news/humira-approved-for-the-treatment-of-pediatric-uveitis/
iv. Health Canada_2019 https://www.newswire.ca/news-releases/abbvie-s-humira-r-adalimumab-approved-by-health-canada-to-treat-pediatric-patients-with-chronic-non-infectious-anterior-uveitis-846451617.html

[5.4] SHARE initiative publication: T. Constantin, I. Foeldvari, J. Anton, J. De Boer, S. Czitrom-Guillaume, C. Edelsten, R. Gepstein, A. Heiligenhaus, C. A. Pilkington, G. Simonini, Y. Uziel, S. J. Vastert, N. M. Wulffraat, A. M. Haasnoot, K. Walscheid, A. Pálinkás, R. Pattani, Z. Györgyi, R. Kozma, V. Boom, A. Ponyi, A. Ravelli, A. V. Ramanan, Ann. Rheum. Dis. 2018, DOI 10.1136/annrheumdis-2018-213131.

[5.5] NHS England data from Blueteq system and pre-policy individual funding request (IFR) data

[5.6] UoB News: Trial co-leads facilitating world-wide access to sight saving medicine: http://www.bristol.ac.uk/news/2017/november/vci-awards.html

[5.7] BBC Radio 4_Inside Health 03.10.2017: https://www.bbc.co.uk/programmes/b096hczd

[5.8] NICE MTA summary form: https://www.nice.org.uk/guidance/ta460/documents/scope-consultation-comments-and-responses

[5.9] Association of Medical Research Charities Arthritis Research UK article_ biggest achievement(s) over the last 30 years: https://www.amrc.org.uk/blog/interview-celebrating-30-years-of-amrc-with-arthritis-research-uk

[5.10] CLUSTER Consortium: https://www.clusterconsortium.org.uk/co-investigators/