Institution: The University of Manchester

Unit of Assessment: 2 (Public Health, Health Services and Primary Care)

Title of case study: Biologics registers for immune-mediated inflammatory diseases: enhancing access to novel therapies and balancing drug safety concerns versus effectiveness

Period when the underpinning research was undertaken: October 2000 – July 2020

Details of staff conducting the underpinning research from the submitting unit:

Name:	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Kimme Hyrich	Professor of Epidemiology	2006 – present
Ian Bruce	Professor of Rheumatology Senior Lecturer / Reader Honorary Clinical Lecturer	2009 – present 2003 – 2009 2000 – 2003
Chris Griffiths	Professor of Dermatology	2000 – present
Richard Warren	Clinical Chair Clinical Senior Lecturer Clinical Lecturer MRC Fellow	2016 – present 2010 – 2016 2008 – 2010 2005 – 2008
Deborah Symmons	Emeritus Professor Professor of Rheumatology & Musculoskeletal Epidemiology	2017 – present 2000 – 2017
Darren Ashcroft	Professor of Pharmacoepidemiology	2002 – present
Will Dixon	Chair in Digital Epidemiology Clinical Senior Lecturer Lecturer Honorary Lecturer Clinical Research Fellow	2016 – present 2010 – 2016 2009 – 2010 2008 – 2009 2004 – 2008
Mark Lunt	Reader	2008 – present
Zenas Yiu	Clinical Lecturer Honorary Clinical Research Fellow Clinical Research Fellow Honorary Research Fellow	2019 – present 2018 – 2019 2015 – 2018 2013 – 2015
Louise Mercer	Honorary Research Fellow Clinical Research Fellow	2013 – present 2008 – 2012

Period when the claimed impact occurred: August 2013 – July 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Immune-mediated inflammatory diseases (IMIDs), affecting 3% of the UK population, are often life-ruining. New targeted biologic therapies are very expensive, and their safety and 'real-world' effectiveness were largely unknown at the point of drug approval. The University of Manchester (UoM) led a series of national registry studies in rheumatoid arthritis (RA), psoriasis and systemic lupus erythematosus (SLE), representing ~50,000 patients, the largest such studies ever conducted worldwide. These translational pharmacoepidemiological investigations have greatly enhanced patients' outcomes by influencing national and international treatment guidelines and have enhanced access for more than 1,000 people to these high-cost drugs through a unique National Institute for Health and Care Excellence (NICE) access scheme.

2. Underpinning research

IMIDs, including RA, psoriasis, and SLE, are chronic and debilitating conditions. Since the early 2000s, a new type of medication called biologic therapies has become available, transforming the outcomes for patients with IMIDs. Biologics are intravenous or injectable medications that target specific points in a person's immune system. They are highly effective but suppress patients' immune systems, potentially raising their susceptibilities to adverse outcomes such as serious infection and cancer. At point of first regulatory approval, there were only limited short-term trial data on which to base clinicians' decision-making. Such evidence does not reflect the populations that are actually treated in routine clinical settings. Biologics are very expensive, resulting in NICE imposing controlled access to ensure cost-effective utilisation. For some medications and conditions, trial data were so limited that the drugs would never attain the level of evidence for effectiveness required by NICE. Due to non-approval, many patients were denied access to these treatments, and so real-world evidence with comparative outcomes and long-term follow-up was urgently needed.

To close this gap in the evidence base, multi-disciplinary collaborative teams of rheumatologists, dermatologists, pharmacoepidemiologists, digital epidemiologists and biostatisticians at the UoM developed a series of world-leading biologics registers. These studies, all based on a common design and administered centrally at the UoM, have established 'real-world' effectiveness and safety data for clinicians and for patients who receive these drugs. Each register was initiated following the first approval of biologic therapies specific to each disease: 1) RA: British Society for Rheumatology Biologics Register (BSRBR-RA) 2001, >30,000 patients; 2) Psoriasis: British Association of Dermatologists' Biologic Interventions Register (BADBIR) 2006, >19,000 patients; 3) SLE: British Isles Lupus Assessment Group Biologics Register (BILAG BR) 2010, >1,500 patients. Together they represent the largest prospective collection of IMID data in the world (>50,000 patients in the UK and Ireland). These studies aim to address treatment response and persistence, occurrence of serious events such as infections and longer-term outcomes such as the latent induction of cancer.

The key research findings leading to impact between 2013 and 2020 include:

1. **RA**: Etanercept, Adalimumab and Infliximab treatment (anti-TNF (tumour necrosis factor) biologics) are not associated with elevated cancer risk compared to standard therapies [1],[2],[3], with the latter investigation pooling data across 11 biologics registers from 9 countries. This evidence dispelled widespread fear among patients, physicians and drug regulators that had been present since these drugs were first licensed.
2. **Psoriasis**: Ustekinumab (anti-IL (Interleukin) -2/23 biologic) is more effective in the long-term than either Etanercept or Adalimumab (2009 UK National Guideline recommended first choice biologics) [4] but with similar rates of infection [5], thus supporting its superiority as the first-line biologic choice.
3. **SLE**: The feasibility of establishing a register for this rare disease has been demonstrated as well as real-world effectiveness and safety of Rituximab (anti-CD20 biologic) [6]. This evidence has been utilised by NICE and by the pharmaceutical industry for enabling the introduction of Belimumab in England.

3. References to the research

References 1-3 were published in the *Annals of Rheumatic Diseases*, one of the world's top Rheumatology speciality journals; references 4 and 5 were published in a leading journal in Dermatology, the *Journal of Investigative Dermatology*. In aggregate, these six outputs have been cited 477 times (Web of Science (WoS)), 7 November 2020).

1. **Mercer LK**, **Lunt M**, Low AL, **Dixon WG**, Watson KD, **Symmons DP**, **Hyrich KL**, BSRBR Control Centre Consortium; Risk of solid cancer in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Annals of Rheumatic Diseases* 2015;

74(6):1087-93. doi: 10.1136/annrheumdis-2013-204851. (84 citations, WoS, 7 November 2020).

2. **Mercer LK**, Green AC, Galloway JB, Davies R, **Lunt M**, **Dixon WG**, Watson KD; British Society for Rheumatology Biologics Register Control Centre Consortium, **Symmons DP, Hyrich KL**; British Society for Rheumatology Biologics Register. The influence of anti-TNF therapy upon incidence of keratinocyte skin cancer in patients with rheumatoid arthritis: longitudinal results from the British Society for Rheumatology Biologics Register. *Annals of Rheumatic Diseases* 2012; 71(6):869-74. doi: 10.1136/annrheumdis-2011-200622.(77 citations, WoS, 7 November 2020).
3. **Mercer LK**, Askling J, Raaschou P, **Dixon WG**, Dreyer L, Hetland ML, Strangfeld A, Zink A, Mariette X, Finckh A, Canhao H, Iannone F, Zavada J, Morel J, Gottenberg JE, **Hyrich KL**, Listing J. Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers. *Annals of Rheumatic Diseases* 2017 76(2):386-391. doi: 10.1136/annrheumdis-2016-209285. (73 citations, WoS, 7 November 2020).
4. **Warren RB**, Smith CH, **Yiu ZZN**, **Ashcroft DM**, Barker JNWN, Burden AD, **Lunt M**, McElhone K, Ormerod AD, Owen CM, Reynolds NJ, **Griffiths CEM**. Differential drug survival of biologic therapies for the treatment of psoriasis: a prospective observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *Journal of Investigative Dermatology* 2015; 135(11):2632-40. doi: 10.1038/jid.2015.208. (190 citations, WoS, 7 November 2020).
5. **Yiu ZZN**, Smith CH, **Ashcroft DM**, **Lunt M**, Walton S, Murphy R, Reynolds NJ, Ormerod AD, **Griffiths CEM, Warren RB**; BADBIR Study Group. Risk of serious infection in patients with psoriasis receiving biologic therapies: a prospective cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *Journal of Investigative Dermatology* 2018; 138(3):534-41. doi: 10.1016/j.jid.2017.10.005. (34 citations, WoS, 7 November 2020).
6. McCarthy EM, Sutton E, Nesbit S, White J, Parker B, Jayne D, Griffiths B, Isenberg DA, Rahman A, Gordon C, D'Cruz DP, Rhodes B, Lanyon P, Vital EM, Yee CS, Edwards CJ, Teh LS, Akil M, McHugh NJ, Zoma A, **Bruce IN**. Short-term efficacy and safety of rituximab therapy in refractory systemic lupus erythematosus: results from the British Isles Lupus Assessment Group Biologics Register. *Rheumatology* 2018; 57(3):470-9. doi: 10.1093/rheumatology/kex395. (19 citations, WoS, 7 November 2020).

4. Details of the impact

Context and Pathways to Impact

UoM research has produced clear evidence that has had significant impact on the management and outcomes of patients with three different IMIDs. To achieve impact, from the outset the registers have taken a multi-stakeholder approach to ensure that evidence is rapidly translated into impact, utilising communication, and engagement of a number of partners including National Health Service (NHS) doctors, nurses and pharmacists, regulators such as the European Medicines Agency (EMA), professional associations that generate treatment guidelines (e.g. the British Association of Dermatologists), payers (under the auspices of NICE), the pharmaceutical industry, and patient charities (e.g. the National Rheumatoid Arthritis Society). Our research has informed prescribing guidelines that have changed how and when these drugs should/can be prescribed, and our collaborations have led to marketing authorisation and approvals of new drugs in Europe.

Reach and significance of the impact

1. RA: The first significant impact during the REF 2021 period is new evidence that provides reassurance to doctors and patients that anti-TNF biologics do not increase cancer risk. When first licensed, there was significant concern about cancer, and this was a key reason for establishing the BSRBR-RA register. All anti-TNF biologics carry a 'black box

warning' for potentially elevated cancer risk. The finding of no increased cancer risk has now been incorporated into the 2019 British Society for Rheumatology prescribing guidelines (downloaded 21,041 times since publication): "*patients should be advised that there is no conclusive evidence for an increased risk of solid tumours or lymphoproliferative disease linked with biologic therapy… (grade 1A, SOA 99%)… recent studies from BSRBR-RA … failed to show a significant association between anti-TNF use in RA and overall malignancy"* [A]. This has proven to be hugely reassuring for patients, many of whom have received these therapies for years. The National Rheumatoid Arthritis Society's Chief Executive said, *"The University of Manchester has worked with us to share this message, including reviewing the information we hold on our website…This reassuring information has made it possible for patients across the UK to make more informed choices about their therapies"* [B]. Publications on malignancy are also cited and discussed in the point of care resource 'UpToDate', allowing physicians to use these data in 'real time' in the clinic [C] - accessed 54,643 times 2014-2019).

The second significant impact is the European licensing of Tofacitinib (Xeljanz©), a new treatment for RA. Authorisation of this drug was initially declined by the EMA due to safety concerns. Analysis of the BSRBR-RA study was included in Pfizer's further regulatory submission to the EMA. Pfizer stated UoM researchers "*provided critical scientific leadership and fostered collaboration with other European biologic DMARD registers…to generate expected background rates of safety events*". Pfizer confirmed, "*These data assisted Pfizer in their submissions to the EMA*" [D]. This analysis, which presented rates of key safety events in biologic-treated patients such as infection, cancer and heart attacks, was viewed by the EMA as robust and they relied on these results for reaching several conclusions in their risk-benefit assessment [E]. The drug was licensed across Europe on 22 March 2017. The BSRBR-RA is now included in Pfizer's ongoing post-marketing Risk Management Plan (RMP) for Tofacitinib as a Post-Authorization Safety Study. Over 200 patients in the BSRBR-RA have now received Tofacitinib. In addition to Pfizer, the BSRBR-RA has now contributed data to 20 different drug RMPs.

2. Psoriasis: Research output has directly influenced and changed the recommended first choice biologic in the UK. The finding that Ustekinumab had better treatment persistence, with no increase in infection rates, repositioned this drug as a first-line agent in the 2017 British prescribing guidelines (most downloaded *British Journal of Dermatology* manuscript in 2017/18: 14,526 times) [F] meaning patients are now prescribed the most effective and safe biologic. The impact was evidenced through a marked rise in the proportion of patients who were prescribed Ustekinumab as a first-line biologic, as recorded in the national BADBIR register (from 23% in 2014 to 39% in 2017) [G].

3. SLE: Critically, UoM research has made it possible for two new drugs, previously declined, to be prescribed via the NHS. Establishing the BILAG-BR has directly influenced both the approval of an unlicensed biologic (Rituximab) and establishment of a NICE Managed Access Agreement (MAA), making a licensed biologic (Belimumab) available across England & Wales. The BILAG-BR demonstrated the feasibility of establishing a biologic registry for a rare disease and supported an interim NHS England policy [H] to allow use of Rituximab (unique for an unlicensed drug) for refractory SLE. Subsequent evidence indicating efficacy of Rituximab from BILAG-BR underpinned the formal policy change [I]. Belimumab was licenced in 2011 but was initially rejected by NICE. Using its innovative pharmacoepidemiological registry infrastructure, UoM was able to support establishing an MAA between GlaxoSmithKline (GSK) Pharma, Lupus UK, NHS England and the University to enable NICE approval and access to Belimumab for patients [J]. This MAA places UoM research at the centre of this decision. Provision of real-world data from the BILAG-BR has meant that these vital drugs are available for patients with this rare IMID. To date, 1,050 patients (900 Rituximab and 150 Belimumab) have been prescribed these previously inaccessible effective medications.

The data held within the three registers has also leveraged GBP24,000,000 investment from MRC and NIHR. This investment funds four stratified medicine consortia as we work towards better targeting of therapies for IMID: RA - MATURA (MAximising Therapeutic Utility

for Rheumatoid Arthritis; Psoriasis - PSORT (Psoriasis Stratification to Optimise Relevant Therapy); SLE - MASTERPLANS (MAximizing Sle ThERapeutic PotentiaL by Application of Novel and Stratified approaches) and juvenile arthritis - CLUSTER (Childhood arthritis and associated uveitis: stratification through endotypes and mechanism).

5. Sources to corroborate the impact

A. The British Society for Rheumatology Biologic DMARD Safety Guidelines in Inflammatory arthritis. Holroyd CR, Seth R, Bukhari M, et al. *Rheumatology*, Volume 58, Issue 2, February 2019, Pages e3–e42, doi:10.1093/rheumatology/key208 *National guidelines that cite UoM research findings indicating no evidence for elevated cancer risk (21,041 hits at 30/09/20)*.

B. Letter from the Chief Executive of National Rheumatoid Arthritis Society, 9 October 2020, *stating the invaluable role that the BSRBR-RA has played in providing current and relevant evidence for patients.*

C. 'Up-to-date' Topic – 'Tumor necrosis factor-alpha inhibitors: risk of malignancy' - *Educational material for clinicians authored by Hyrich about general lack of association between anti-TNF biologics and cancer, frequently cites BSRBR-RA data and a*ccessed >54,000 times, 2014-2019.

D. Letter from two Senior Directors, Global Medical Epidemiology, Pfizer Inc., 1 October 2020. *Outlining the critical role the rheumatoid arthritis register (BSRBR-RA) played in Pfizer gaining approval for Tofacitinib*.

E. Tofacitinib European Public Assessment Report, 26 January 2017. *This document outlines the role the BSRBR-RA played in the risk-benefit assessment of Tofacitinib. The role of data use (under auspices of EU registries) outlined on page 133 (Mortality), p137 (Malignancy) and p138 (Cardiovascular disease). The role of the BSRBR-RA in the RMP stated on p.143 and Information for Notice to Healthcare Professionals about registration in the BSRBR-RA on p156. EMA positive decision stated on p154.*

F. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. Smith CH, Jabbar-Lopez ZK, Yiu ZZ, et al. British Journal of Dermatology 2017; 177(3):628-36. doi:10.1111/bjd.15665. *These guidelines recommended Ustekinumab as first-line therapy - most downloaded British Journal Dermatology paper in 2017 and 2018, cited 106 times in Scopus on 07 October 2020, co-authored by Warren.*

G. UK Registration Data for Ustekinumab in BADBIR *showing increase in Ustekinumab registrations between 2014 and 2017.*

H. NHS England Interim Clinical Commissioning Policy Statement: Rituximab for the treatment of Systemic Lupus Erythematosus in adults. (A13/PS/a: August 2013), *gives information on how clinicians can access Rituximab for patients with SLE, including mandatory registration in the UoM BILAG register.*

I. NHS England Clinical Commissioning Policy Rituximab for refractory Systemic Lupus Erythematosus (SLE) in adults and post-pubescent children [200402P] published 9 July 2020 - *Final policy indicating that Rituximab is an approved treatment under NHS England for patients with SLE. The contribution of UoM research (reference [6], McCarthy et al.) in contributing to this positive decision for Rituximab is highlighted throughout and it is recommended that all patients starting RTX continue to be enrolled in the BILAG-BR.*

J. NHS England (NICE) Belimumab for treating active autoantibody-positive systemic lupus erythematosus. Technology appraisal for SLE, 22 June 2016. *Provides information on how clinicians can access Belimumab for patients with SLE, including mandatory registration in the UoM BILAG register*.