Institution: University of Birmingham

Unit of Assessment: UoA 1, Clinical Medicine

Title of case study: Improving outcomes for people with rheumatoid arthritis by facilitating and optimising early treatment regimens

Period when the underpinning research was undertaken: 2000–2020

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:
Karim Raza	Professor of Rheumatology	2000–present
Dr Andrew Filer	Reader in Rheumatology	2000–present
Christopher D. Buckley	Professor of Rheumatology	2000–present

Period when the claimed impact occurred: January 2014–December 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

We have dramatically improved management of rheumatoid arthritis (RA) by facilitating early treatment. Specifically:

(i) **Public health policy and guidelines have changed** and rapid access to care is now a national priority.

(ii) **Patient outcomes have improved** as a result of earlier identification and reduced treatment times.

(iii) **New patient care practices have been introduced**, including the development of new diagnostic approaches and new clinical interventions.

(iv) **Public and policy-makers' awareness** of the health risks associated with RA **have been raised**.

2. Underpinning research

Rheumatoid arthritis (RA) affects 1 in 100 people worldwide. Chronic inflammation of the joints drives the destruction of cartilage and bone leading to joint damage, disability, loss of employment and social contacts. Systemic complications, including accelerated heart disease, lead to a 10-year reduction of life expectancy. Direct annual NHS costs are around £560 million, with an additional annual cost of £1.8 billion due to work-related disability.

Since 2000, we have undertaken 2 major programmes of work that have:

- 2.1 Identified the determinants of late presentation into secondary care and defined the clinical benefit of early treatment; and
- 2.2 Developed minimally invasive ultrasound assessment and biopsy, and autoantibody measurement in order to stratify patient outcome.

2.1 Pathways to early treatment

We have shown that:

- The **early treament of RA** (within the first 3 months of symptom onset) significantly improves clinical outcomes with less joint damage and an increased chance of achieving disease remission [R1].
- **Most patients have not been treated within this window** because of delays at the level of: (i) the patient seeing the GP, (ii) the GP referring the patient to a rheumatologist, (iii) the rheumatologist seeing the patient after referral [R2, R3].

- **Delay on the part of patients is a key reason for delay** in the UK and Europe [R2, R3]. Furthermore, we have identified the reasons underlying this delay [S1].

These findings informed the 2009 National Audit Office report on "Services for people with RA" [S2], which highlighted the need to improve access to care and the provision of early treatment in RA.

2.2 Predicting long-term outcome at time of acute presentation

Only about 25% of patients who present to rheumatologists with a new onset of peripheral arthritis in the first 3 months of symptom onset go on to develop RA. In fact, almost 50% have a self-limiting disease. It is thus critical to be able to **predict which patients coming to an early arthritis clinic will develop RA** to allow treatment to be targeted appropriately. We have shown that:

- The **autoantibodies** rheumatoid factor and anti-CCP antibody are predictive biomarkers for RA development [R4].
- These can be usefully incorporated into a **predictive algorithm** which allows early targeting of treatment that we have validated internationally [S3].
- Additional variables, identified by **ultrasound assessment** of the synovium, can further enhance the prediction of RA [R5].

Recognising that access to synovial tissue may help further improve prediction of RA development in patients with early arthritis and inform therapeutic decision-making, we have:

- Developed a safe and patient-acceptable approach to the acquisition of synovial tissue using a **minimally invasive ultrasound guided technique** [R6].

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

R1. van der Linden MP, le Cessie S, **Raza K**, van der Woude D, Knevel R, Huizinga TWJ, van der Helm-van Mil AHM. Long-term impact of delay in assessment of early arthritis patients. *Arthritis Rheum*. 2010;62:3537-46. **doi: 10.1002/art.27692** *(cited 407 times; journal impact factor 9.586)*

R2. Raza K, Stack R, Kumar K, **Filer A**, Detert J, Bastian H, Burmester GR, Sidiropoulos P, Kteniadaki E, Repa A, Saxne T, Turesson C, Mann H, Vencovsky J, Catrina A, Chatzidionysiou A, Hensvold A, Rantapaa-Dahlqvist S, Binder A, Machold K, Kwiakowska,B., Ciurea A, Tamborrini G, Kyburz D, **Buckley CD**. Delays in assessment of patients with rheumatoid arthritis: variations across Europe. *Ann Rheum Dis* 2011; 70 :1822-1825 **doi:10.1136/ard.2011.151902** *(cited 136 times; journal impact factor 16.102)*

R3. Kumar K, Daley E, Carruthers DM, Situnayake D, Gordon C, Grindulis K, **Buckley CD**, Khattak F, **Raza K**. Delay in presentation to primary care physicians is the main reason why patients with rheumatoid arthritis are seen late by rheumatologists. *Rheumatology 2007;* 46 (9):1438-1440. **doi:10.1093/rheumatology/kem130** *(cited 147 times; journal impact factor 5.606)*

R4. Raza K, Breese M, Nightingale P, Kumar K, Potter T, Carruthers DM, Situnayake D, Gordon C, **Buckley CD**, Salmon M *et al*. Predictive value of antibodies to cyclic citrullinated Peptide in patients with very early inflammatory arthritis. *J Rheumatol* 2005, **32**(2):231-238. **PMID: 15693082** *(cited 235 times journal impact factor 3.350)*

R5. Filer A, de Pablo P, Allen G, Nightingale P, Jordan A, Jobanputra P, Bowman S, **Buckley CD, Raza K**. Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. *Ann Rheum Dis* 2011, 70(3):500-507. **doi: 10.1136/ard.2010.131573** *(cited 236 times; journal impact factor 16.102)*

R6. Kelly S, Humby F, **Filer A**, Ng N, Di Cicco M, Hands RE, Rocher V, Bombardieri M, D'Agostino MA, McInnes IB, **Buckley CD**, Taylor PC, Pitzalis C. Ultrasound-guided synovial biopsy: a safe, well-tolerated and reliable technique for obtaining high-quality synovial tissue from both large and small joints in early arthritis patients) Ann Rheum Dis. 2015 Mar;74(3):611-7. **doi: 10.1136/annrheumdis-2013-204603**. Epub 2013 Dec 13. PMID: 24336336 *(cited 130 times; journal impact factor 16.102)*

4. Details of the impact

1. Public health policy and guidelines have changed for patients with RA

We have directly influenced the 2018 update to the **National Institute for Health and Care Excellence (NICE)'s Quality Standard 33 for the treatment of RA** [S4]. Quality Standard 33 clearly identifies the importance of rapid GP referral and rapid assessment in secondary care in the RA care pathway and directly cites our work [R3]. In order to promote adherence to Quality Standard 33, **The Best Practice Tariff for Early Inflammatory Arthritis** was introduced by NHS England in 2018, requiring patients to be seen within 3 weeks of referral.

This change came about through a number of stages, all of which drew on our work [R1–R3]. For example, delays in the assessment of patients with early arthritis was a topic for the National Healthcare Quality Improvement Partnership (HQIP) audit 2014–2016 and remains in the second HQIP National Early Inflammatory Arthritis Audit (NEIAA) 2017–2020 [S5.i, ii, iii]. Raza was a member of the British Society for Rheumatology HQIP advisory group and directly influenced the development of the national audit. **Including the issue of delay in access to care in the HQIP audit has ensured that the need for early diagnosis and treatment is nationally prominent and acted upon.**

2. Patient outcomes for RA patients have improved by the reduction of treatment times

As a result of guideline changes, we have **reduced delays in treatment for patients with RA** significantly between 2013 and 2020 [S5.i, ii, iii)]: the October 2019 National Early Arthritis Audit Report confirmed that "although referral from primary care is frequently delayed, performance has improved significantly since the last phase of this audit [in 2014]" and that "since the start of the last phase of this audit in 2014, there have been significant reductions in treatment delay" [S5.ii]. The January 2021 National Early Arthritis Audit Report showed that delays in referral, assessment and treatment times continue to improve [S5.iii]. As a consequence of this, **a greater proportion of patients with RA have been treated within the therapeutic window of opportunity**. This will have reduced the proportion of patients with significant joint damage and increased the proportion achieving remission [R1]. Furthermore, the National Audit Office report 2009 (citing R4 and additional work by the team [S1]) has confirmed that increasing the percentage of patients treated within the 3-month window of opportunity from 10% to 20% will increase quality of life by 4% over 5 years and have financial benefit, resulting in productivity gains of £31 million over 5 years [S2].

3. Changed clinical practice for patients with RA

3.a. We have **changed practice through the development of autoantibody and imaging approaches** to support early diagnosis and treatment [R4, R5].
The importance of our underpinning research on autoantibody testing [R4] is highlighted by an editorial in the *Journal of Rheumatology*, which states "Their findings clearly show the practicality and importance of serologic testing for both serum rheumatoid factor (RF) and anti-CCP antibodies in making an accurate diagnosis in those with persistent symptoms of RA. These findings serve as a challenge to the rheumatologist to amend the manner in which early arthritis patients are currently diagnosed and treated" [S6.i]. We have shown that autoantibodies (rheumatoid factor and anti-CCP antibody) are predictive biomarkers for RA development and should be used widely to test for RA. As a result, **anti-CCP antibody testing is now routinely performed as standard of care across the UK and Europe**: a survey by The Benchmarking Partnership of a representative sample of immunology labs showed that in 2005, the year of publication of R4, 245 anti-CCP tests were performed with 27.6% of Immunology laboratories offering this service. By 2013, the number of tests conducted was 2,896; currently the number of tests has plateaued at 4,301 with **100% of Immunology laboratories now offering the test** [S6.ii].

Our research on imaging assessment of synovitis [R5] and tenosynovitis has also informed the development of international (e.g. European League Against Rheumatism 2013) guidelines on the management of RA/early arthritis [S7.i]. As a result of our work, **musculoskeletal**

ultrasound of specific joint regions is now used earlier in the management of patients with early arthritis and is a technique being increasingly learnt by Rheumatology trainees in the UK and Europe [S7.ii–iii].

3.b. We have **changed practice through the development and adoption of a new clinical intervention**.
We have **developed a safe and patient-acceptable approach to the acquisition of synovial tissue using a minimally invasive ultrasound-guided technique [R6]**. The availability and increasing number of studies using ultrasound-guided biopsy procedures, which were developed in their current forms in University of Birmingham and QMUL London, is changing the attitude of both doctors and the public towards investigation and treatment in early arthritis [S8.i]. This has been supported by training programmes for professional training in ultrasound-guided biopsy that we have developed [S8.ii–iii]. This paradigm shift is particularly clear in clinical trials (e.g. PEAC, STRAP and within the Arthritis Therapy Acceleration Programme) and observational studies (e.g. NIH Accelerating Medicines Partnership) that are testing the hypothesis that routine synovial biopsy can determine the most effective therapy for each patient [S8.iv].

4. Improved public and policy-makers awareness of the health risk of RA and the benefit of early treatment nationally and internationally

The development of **national and international public health campaigns** to raise awareness of RA were underpinned by our research [R1–R3]. For example, Raza was a member of the Inflammatory Arthritis expert group which shaped and developed the **NHS England/Public Health England Pilot Public Health Campaign for RA 2015** [S9.i–ii]. Similarly, our research stimulated the development and influenced the content of the **Pan-European EULAR 'Don't delay connect today' campaign 2017** [S9.iii–iv]. **Raised awareness internationally** is evidenced through a move to early treatment and reduced delays to treatment being adopted beyond the UK. For example, following workshops at Birmingham for Rheumatologists from Africa and the Middle East (in 2011, 2012 (x2), 2015, 2016, 2018), early arthritis clinic services have been introduced (including in UAE, Oman, Jordan, Lebanon, Egypt, South Africa). This has resulted in the time from symptom onset to treatment of patients being reduced from 6 months to 3.5 months at participating centres [S10].

Similarly, we have **highlighted the importance of RA as an issue of concern to parliamentarians**. For example, Raza talked at the House of Lords in December 2013 with Ms Ailsa Bosworth (Chief Executive of the National Rheumatoid Arthritis Society) and Mr Peter Kay (National Clinical Director for Musculoskeletal Services) at a meeting titled "How Poor Public Awareness is Hurting Patients" presenting data from R1–R3 [S9.ii].

5. Sources to corroborate the impact

S1. Sheppard J, Kumar K, **Buckley CD**, Shaw KL, **Raza K**. 'I just thought it was normal aches and pains': a qualitative study of decision-making processes in patients with early rheumatoid arthritis. *Rheumatology.(Oxford)* 2008;47:1577-1582. DOI: 10.1093/rheumatology/ken304 Article link
S2. National Audit Office report "Services for people with RA" (2009):

S3. van der Helm-van Mil A, Detert J, le Cessie S, **Filer A**, Bastian H, Burmester GR, Huizinga TWJ, **Raza K**. Moving towards individualized treatment decision making: validation of a prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis. Arthritis Rheum. 2008;58:2241-2247. DOI: 10.1002/art.23681 Article link

S4. National Institute for Health And Care Excellence (NICE) Guideline for Rheumatoid arthritis in over 16s (Quality standard 33).

S5. (i) HQIP National Early Arthritis Audit. HQIP Early Arthritis Audit; **(ii)** National Early Arthritis Audit Report October 2019. National Early Arthritis Audit Report October 2019. **(iii)** National Early Arthritis Audit Report January 2021. National Early Arthritis Audit Report January 2021.

S6. (i) Editorial highlighting the clinical relevance and impact underpinning research reference 4: Cush JJ: Early arthritis clinics: if you build it will they come? J Rheumatol 2005, 32(2):203-207; **(ii)** Data from The Benchmarking Partnership illustrating adoption of anti-CCP testing into UK practice over time.

S7. (i) EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. Ann Rheum Dis. 2013 Jun;72(6):804-14; DOI: 10.1136/annrheumdis-2012-203158. **(ii)** Testimonial, Past-Chair of the EULAR standing committee on musculoskeletal imaging (11/11/2020); **(iii)** European surveys 2010 and 2019 documenting expansion of ultrasound training and clinical use in rheumatology: (a) Current state of musculoskeletal ultrasound training and implementation in Europe: results of a survey of experts and scientific societies. Rheumatology (Oxford). 2010 Dec;49(12):2438-43, DOI: 10.1093/rheumatology/keq243 (b) Implementation and role of modern musculoskeletal imaging in rheumatological practice in member countries of EULAR. RMD Open. 2019 Jun 25;5(2):e000950. DOI:10.1136/ rmdopen-2019-000950

S8. (i) Testimonial, head of NIH NIAMS summarising the critical role of Birmingham in the development of the Ultrasound guided biopsy methodology in the USA (31/03/2020); **(ii)** Online training package enabling training of professionals worldwide in the ultrasound technique: (a) Professional training videos for clinicians, Portal and Forceps ultrasound guided biopsy training video, Fixed length portal with easier insertion; Demonstration of finding lining layer during ultrasound guided biopsy (b) Professional videos for patients explaining the procedure Ultrasound guided biopsy: A patient's view.; **(iii)** EULAR online and face to face courses in Ultrasound guided biopsy, facilitated by A. Filer to extend global reach of training; **(iv)** International adoption of Ultrasound guided biopsy technology into clinical trials; PEAC, STRAP Observational studies NIHR Accelerating Medicine Partnership and as a key enabling technology for the £7 million Kennedy Trust funded Arthritis Therapy Acceleration Programme A-TAP which is developing tissue-based outcomes for clinical trials across IMIDs including RA.

S9. (i). Public Health Campaign for Rheumatoid Arthritis 2015; **(ii)** Testimonial: Chief Executive of the National Rheumatoid Arthritis Society, UK (18/11/2020); **(iii)** EULAR don't delay connect today campaign EULAR don't delay connect today campaign; **(iv)** Testimonial EULAR Past President and current Liaison Officer Public Affairs highlighting how University of Birmingham research has informed the 'EULAR don't delay connect today' campaign (25/06/2020).

S10. Audit data from participants of workshops conducted including delegates from the United Arab Emirates, Bahrain, Kuwait, Qatar, Oman, Jordan, The Lebanon, Egypt, Saudi Arabia, Algeria, Morocco, Tunisia, Nigeria, Kenya, South Africa.