Institution: University of York

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

Title of case study: Biologic agents for plaque psoriasis and psoriatic arthritis: enabling patient benefit and efficient use of NHS resources

Period when the underpinning research was undertaken: 2006 - 2017

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:
Laura Bojke	Professor	1999 – present
Mark Corbett	Research Fellow	2008 – present
Susan Griffin	Professor	2002 – present
Ann Mason	Senior Research Fellow	1998 – present
Stephen Palmer	Professor	1994 – present
Mark Rodgers	Research Fellow	2001 – present
Claire Rothery	Senior Research Fellow	2006 – present
Pedro Saramago Gonçalves	Research Fellow	2012 – present
Mark Sculpher	Professor	1997 – present
Marta Soares	Senior Research Fellow	2007 – present
Simon Walker	Senior Research Fellow	2006 – present
Beth Woods	Senior Research Fellow	2014 – present
Nerys Woolacott	Reader	2000 – 2017 (emerita)

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

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

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

York evidence syntheses and economic evaluations of biologic agents for psoriatic arthritis (PsA) and plaque psoriasis (PS) underpin 15 national guidance statements issued by the National Institute for Health and Care Excellence (NICE) since 2014. These resulted in 11 new biologic agents being recommended for use in the NHS. Subsequent prescription has alleviated pain, improved mobility, functional status and quality of life for patients with PS and PsA, generating an estimated 4,100 additional quality-adjusted life years (QALYs) for the UK population 2014 – 20. Impact has arisen directly from York's underpinning health technology assessments (HTAs), and from further use of the economic decision models that these developed, in subsequent evaluations. York research has therefore driven national policy defining which biologic agents are available to treat PsA and PS within the NHS, and for whom. It has also informed national and international clinical guidelines.

2. Underpinning research (indicative maximum 500 words)

The York Technology Assessment Review Programme (led by Stewart, Palmer, Dias and Rothery) directly supports national decision-making, carrying out HTA across a broad range of health conditions for NICE. This includes a substantive body of research in PsA and PS, including 13 HTA evaluations (9 since 2014) of biologic agents and oral small molecule inhibitors for PS or PsA patients who have not responded to conventional disease-modifying antirheumatic drugs (carried out by Bojke, Duarte, Mason, Palmer, Rothery, Saramago Goncalves, Sculpher, Soares, Woolacott).

Worldwide over 100 million people are affected by psoriasis, a chronic inflammatory disease of the skin and joints (World Health Organisation, 2016). Patients often suffer from social stigmatisation as well as from cardiovascular, metabolic and psychiatric comorbidities leading to significantly reduced health-related quality of life. Up to 30% of people with psoriasis develop PsA, which causes pain and swelling of the joints and, if left untreated, can cause irreversible joint damage. Establishing which agents are most effective and cost effective in alleviating symptoms and improving quality of life, is important for patients and for health care systems.

Five underpinning multiple technology appraisals (MTAs) were undertaken; each comprised a synthesis of clinical effectiveness data from multiple clinical trials using network meta-analysis (NMA), an assessment of epidemiological evidence and development of cutting edge *de novo* decision models to estimate cost effectiveness. York researchers led these HTAs with

collaborative input from expert clinicians and, for one project **[C]**, from colleagues in the NICE Decision Support Unit (DSU).

Initial MTAs (2006) produced the first-generation "York Psoriasis Model" **[A]** and "York PsA Model" **[B]**, and were the first NICE appraisals to include NMA. These were further developed with increasing sophistication in subsequent MTAs **[C][D][E]** (2011-2017) to incorporate new evidence and innovative methods. The MTAs and intervening appraisals of single agents (based on the York models) assessed effectiveness, safety and cost effectiveness of successive new biologics as they were licenced.

The second-generation York PsA model (2011) **[C]** was the first to apply a hierarchical ordered logit model to synthesise multinomial data from several trials. This allowed the relationships between disease severity scores reported in different ways to be incorporated in the model, whilst maintaining original trial randomisation, so that all relevant evidence could be used. We found that etanercept, infliximab and adalimumab all improved joint condition and functional status at short-term follow-up, with some evidence of benefit for skin disease. All had a similar probability of being cost-effective for patients with PsA and moderate-to-severe psoriasis; etanercept was identified as most likely to be cost-effective for those with PsA and mild-to-moderate psoriasis. The most recent York PsA model (2017) **[D]** incorporated treatment sequencing in a fully incremental framework, stratifying patients by prior biologic experience and severity of concomitant psoriasis. This improved on previous models because it enables treatment decisions to be more tailored to individual patient needs over the course of their disease, and facilitates access to a series of further biologic treatments if response to a specific treatment attenuates over time. Results for biologic naïve subpopulations indicated that both certolizumab pegol and secukinumab were effective after 3 months' therapy (although relative effectiveness was uncertain) and were a cost-effective use of NHS resources in subpopulations defined by prior treatments and psoriasis severity.

A revised psoriasis model (2017) was developed for an MTA evaluation of adalimumab, etanercept and ustekinumab in children and young people **[E]**. As paediatric data were limited, a wider network incorporating evidence from adult trials permitted indirect comparison of the three biologics, meaning that NICE was able to make more informed judgements about comparative effectiveness and value for money. The NMA (adjusting for differences in population and placebo response rates) found ustekinumab to be most effective, followed by adalimumab, etanercept and methotrexate.

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

A. (2006) **Woolacott N**, Hawkins N, **Mason A**, Kainth A, Khadjesari Z, Vergel YB, Misso K, Light K, Chalmers R, **Sculpher M**, Riemsma R. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. Health Technology Assessment 10(46) pp.1-233, i-iv. DOI**:** 10.3310/hta10460**.***

B. (2006) **Woolacott N**, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, Light K, Asseburg C, **Palmer S**, Claxton K, Bruce I, **Sculpher M**, Riemsma R. Etanercept and infliximab for the treatment of psoriatic arthritis; a systematic review and economic evaluation. Health Technology Assessment. 10(31) pp.1-258. DOI: 10.3310/hta10310 *

C. (2011) **Rodgers M**, Epstein D, **Bojke L**, Yang H, Craig D, Fonseca T, Myers L, Bruce I, Chalmers R, Bujkiewicz S, Lai M, Cooper N, Abrams K, Spiegelhalter D, Sutton A, **Sculpher M, Woolacott N**. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technology Assessment. 15(10) pp.i-xxi, 1-329. DOI: 10.3310/hta15100 ***+**

D. (2017) **Corbett M**, Chehadah F, Biswas M, Thirimon M, **Palmer S, Soares M**, Walton M, Harden M, Ho P, **Woolacott N, Bojke L**. Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease-modifying antirheumatic drugs: a systematic review and economic evaluation. Health Technology Assessment 21(56) DOI: 10.3310/hta21560 ***

E. (2017) **Duarte A**, Mebrahtu T, **Saramago Goncalves P**, Harden M, Murphy R, **Palmer S, Woolacott N, Rodgers M, Rothery C**. Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people: systematic review and economic evaluation.

Health Technology Assessment 21(64). DOI: 10.3310/hta21640 *

*peer reviewed publication; + REF 2014 output. All funded by a peer reviewed research programme. Each HTA report also has associated journal publications.

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

(1) Impact on NICE guidance/national policy:
York HTAs and economic decision models for PS and PsA have supported national decision-making and NHS prescribing policy since 2006, continuing through the REF period. Decision models are the fulcrum of NICE technology appraisal committee deliberative process and produce estimates of value in a standardised cost per QALY 'currency' that allows comparison across healthcare interventions. Decisions have rapid and direct impact because NHS England is legally obliged to provide funding for drugs and treatments recommended by NICE within 90 days, and the right to access these is enshrined in the NHS constitution.

"Decision models are central to NICE process and national decision-making as they provide the framework for synthesising available evidence and generating estimates of clinical and cost effectiveness in a format relevant to the NICE committee's decision-making process. The decision models that the York team developed for psoriasis and psoriatic arthritis within multiple technology appraisals (MTAs) therefore directly informed and supported NICE committee decisions about use of the agents considered in those MTAS". **NICE Deputy CEO [1]**

In addition to the specific NICE evaluations for which they were developed **[A-E]**, the York models provided the backbone for subsequent NICE single technology appraisals (STAs). STAs comprise independent evaluations of single therapeutic agents based on academic critique and evaluation of pharmaceutical company submissions to NICE. Both company submissions and academic appraisals have utilised the York models.

"The models developed within the MTAs were then applied and used as a basis for new models in subsequent STAs, which resulted in a series of biologic agents being made available to NHS patients with psoriasis and psoriatic arthritis during the period 2014 to 2020." **NICE Deputy CEO [1]**

Specifically, since 2014 the York PsA model **[C]** formed the basis of company models submitted for ustekinumab [TA313] and apremilast [TA433]; the more recent York PsA model **[D]** for ustekinumab [TA340], ixekizumab [TA537] and tofacitinib [TA543]. The original York PS model **[A]** provided the basis for secukinumab [TA350], apremilast [TA419], ixekizumab [TA442], dimethyl fumarate [TA475], brodalumab [TA511], certoluzumab pegol [TA574], and tildrakizumab [TA575]. In addition two fast track appraisals of guselkumab [TA575] and risankizumab [TA596] drew on efficiency and cost assumptions from previous appraisals. All agents were approved for use in the NHS.**[2]**

Thus, since 2014,York research has informed 15 separate national guidance statements on psoriasis and PsA: two directly from underpinning York MTAs **[D][E]**, seven from York STAs plus six STAs/ fast-track assessments completed by others. Together these led to 11 biologic agents being made available within the NHS, as were two small molecule drugs (dimethyl fumarate and apremilast), evaluated using the same model.

"*I can therefore confirm that your research has supported national decision-making that has had direct impact within the NHS".* **NICE Deputy CEO [1]**

(2) Impact on UK clinical practice guidelines
As well as underpinning NICE guidance, the York models informed the NICE overarching clinical guideline for the assessment and management of PS (2012, updated 2017), the Scottish Intercollegiate Guidelines Network guideline for the diagnosis and management of PS and PsA (2010) and the British Association of Dermatologists guidelines for biologic therapy for psoriasis (2015, updated 2020). All remain current and have cited/referred to the underpinning York HTA reports, associated NICE guidance or the "York models". **[3]**

(3) Impact on prescribing

The impact of York research acting through mandatory NICE guidance and clinical guidelines is corroborated by national prescribing data available from NHS digital, analysis of which illustrates that prescribing patterns of approved drugs for autoimmune disease (data are not available by specific condition) align with positive recommendations from NICE **[4]**. An example is given in the figure below.

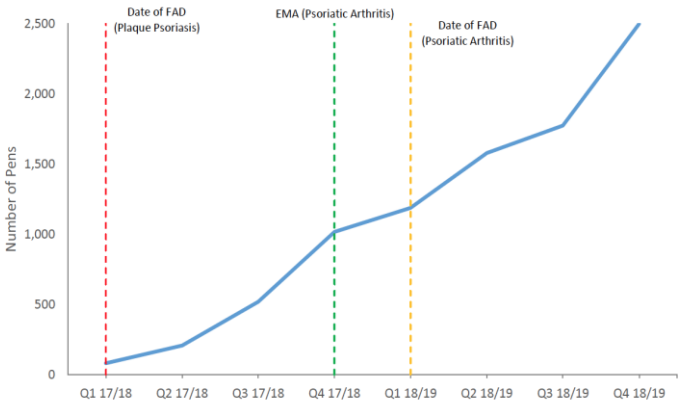

Figure 1. Ixekizumab prescription in England and Wales (2017-2018) showing dates of issue of NICE Final appraisal documents (FAD; 1st and 3rd vertical lines) and European Medicines Agency (EMA) licencing (middle vertical line), illustrating rise in prescriptions following the issue of each FAD.

(4) Impact on patients' lives

Psoriasis and PsA are debilitating chronic conditions that have a serious adverse impact on patient health and wellbeing. The 11 new biologic agents approved during the REF period provide patients who fail on conventional therapy with access to life-enhancing treatment, improving their symptoms and quality of life, whilst ensuring value for the NHS.

"In my experience as an expert patient at NICE technical appraisals of biologic agents for the treatment of psoriasis and psoriatic arthritis, evidence from the University of York HTAs and the York models has been both informative and essential in the understanding of the range of benefit which has provided choice to patients, but also has guided and provided healthcare professionals with confidence, certainty and knowledge to help in their discussions with patient about care plans and pathways. This has also aided patients to see that treatments are of benefit and increased the choice available. It is clear that without the thorough and consistent evaluations carried out at York to inform national decision making, the advancement of care for people with psoriasis and psoriatic arthritis would not have been as comprehensive and would not have provided the life-changing benefit that many patients are currently experiencing."
Chief Executive Psoriasis and Psoriatic Arthritis Alliance (PAPAA) [5]

(5) Estimated population benefit to the UK

It is estimated that 21,000 PS and 6,500 PsA patients who fail conventional therapy are eligible to receive biologic agents annually. Using an average of the quality adjusted life years (QALYs) in NICE committee preferred modelled scenarios quantifies the impact of the underpinning research on UK population health as generating an estimated gain of approximately 692 QALYs for psoriasis and 3,408 QALYs for psoriatic arthritis 2014 - 2020. This derives mostly from improved quality of life rather than extended survival **[6].**

(6) Wider impact on NICE evaluations by example in NICE technical guidance

The York psoriasis model provides a detailed example (with code) in the NICE DSU technical document on generalised linear modelling frameworks for network meta-analysis. This forms the guidance that all NICE technology appraisal teams are encouraged to follow, including materials produced and submitted by pharmaceutical companies (York is part of the DSU). Thus, our research on PS indirectly supports the production of all submissions to NICE, committee decisions and national guidance across a broad range of clinical topics **[7]**.

"The inclusion of York's psoriasis model as one of the key models and as a worked example with ready to use code, highlights its importance to NICE technology appraisals thereby indirectly supporting the production of NICE submissions which underpin committee decisions and NICE guidance." **NICE DSU Director [7]**

(7) International impact through international guidelines
Evaluations and economic models developed by the York team have also had wider international impact beyond the expectation of the original research and been used in clinical guidelines in several countries. These include the Dutch Society of Dermatology and Venereology (2011), Italian Society for Rheumatology (2009) and guidelines issued by the Japanese Dermatological Association and the Japanese Ministry of Health (2018), all of which remain current. York models have also been used as the basis of HTAs conducted in other jurisdictions including the USA, thereby generating indirect impact and population health gain in those jurisdictions. All have cited/referred to the underpinning York HTA reports, the associated NICE guidance or the "York models". **[8]**

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

1. NICE Deputy CEO and Director of the Centre for Health Technology Evaluation Letter confirming the role that the York TAR team and York models have played in generating national guidance for treatment of PS and PsA.
2. Impact through national NICE guidance issued since 2014.
Collated NICE guidance documentation for appraisals described in section 4.
3. Impact on national clinical guidelines: Document with marked up extracts and web links to national guidelines highlighting where York HTA reports or associated NICE guidance are cited.
4. Impact on prescribing: Document with graphical display of data available publicly from NHS digital (scorecard of NICE technology appraisals) illustrating patterns of prescribing in relation to issue of NICE guidance.
5. Impact for patients:
Letter from the Chief executive of PAPAA, outlining the debilitating nature of PS and PsA and the importance of York's role in providing reliable research evidence that facilitated introduction of new biologic agents in the NHS, and how this has improved patients' lives.
6. Impact on population health and wellbeing:
Document explaining how population health gain expressed as QALYs was estimated.
7. Use as exemplars in NICE Decision Support Unit Technical documents:
NICE DSU technical support document 2: A generalised linear modelling framework for pairwise and NMA of RCTs (last updated 2016) and supporting letter from the DSU Director outlining the value of the York model as an exemplar.
8. Impact on international clinical guidelines and guidance:
Document with marked up extracts and web links to international guidelines/guidance highlighting where York HTA reports or associated NICE guidance are cited.