Institution: Cardiff University

Unit of Assessment: Clinical Medicine (1)

Title of case study: Improving clinical care in people with the inflammatory skin condition hidradenitis suppurativa

Period when the underpinning research was undertaken: 2014 – 2018

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:
John Ingram	Clinical Reader	01/01/2014 – present
Vincent Piguet	Clinical Professor	01/08/2010 – 31/07/2017

Period when the claimed impact occurred: 2014 – 2020

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

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

Hidradenitis suppurativa (HS) is a painful inflammatory skin disease associated with abscesses and skin lesions around apocrine sweat glands (e.g., armpits, breasts, groin). Cardiff research supported work by the National Institute of Health and Care Excellence (NICE) which resulted in the approval of the biological drug adalimumab as the first licensed treatment for HS. The research also enabled development of the first UK guidelines for HS, now transforming clinical management of patients with the disease, and facilitated the first UK public funding call for research into HS.

2. Underpinning research (indicative maximum 500 words)

Hidradenitis suppurativa (HS) is a distressing, chronic skin disease characterised by multiple abscesses and lesions in flexural areas, including the armpits, breasts and groin. The abscesses are painful, exude pus and produce scarring. Despite the detrimental impact of these skin lesions on patient health and wellbeing, there has been little research on the disease. Cardiff University researchers, Ingram and Piguet, undertook new research aimed at: (a) understanding the prevalence of HS; (b) identifying effective treatments for the disease; and (c) standardising outcome measures to enhance comparison between randomised clinical trials.

2.1 HS prevalence

Cardiff researchers used data from 15 million patient records in the UK primary care Clinical Practice Research Datalink (CPRD) to create and validate algorithms designed to better identify patients not yet diagnosed with HS, but where there was recorded evidence of multiple skin boils. The researchers found that HS prevalence in the UK was actually 1%, where previous estimates had suggested a prevalence as low as 0.1%. The study also found that HS was associated with depression, and that patients had a higher prevalence of cardiovascular risk factors such as hyperlipidaemia and type 2 diabetes **[3.1]**. This important study revealed the true extent of HS prevalence in the UK, as well as substantial other health risks to patients associated with the disease.

2.2 Identifying best treatment options

In 2015, Ingram led a Cochrane systematic review on interventions for HS, undertaking a synthesis of randomised controlled trial evidence on HS management **[3.2]**. The Cochrane review found that adalimumab, an anti-tumour necrosis factor alpha monoclonal antibody therapy, was an effective treatment for HS, with patients reporting reductions in pain and improvements in their quality-of-life (as measured by the Dermatology Life Quality Index). The review recommended adalimumab for treatment of HS in moderate to severe cases. The review also highlighted a lack of evidence in favour of other treatments (e.g., the vitamin A derivative, isotretinoin).

2.3 Re-framing research priorities and standardising outcome measures for HS patients

In 2013, Ingram chaired a HS Priority Setting Partnership (PSP) with the remit to establish a new research agenda focused on identifying novel HS treatments. The PSP was a collaboration between the HS Trust patient support group and dermatologists with significant HS experience, supported by the James Lind Alliance **[3.3]**. The PSP identified key knowledge gaps in HS research, including around benefits associated with biological drug therapies and surgical intervention, as well as approaches to providing optimal pain relief.

A second systematic review was undertaken by the Cardiff team. This identified considerable differences in the methods being used to assess HS clinically, with particular variation in outcome measures (with effectively 30 different types identified across 12 randomised trials in the review) **[3.4]**. The variable use of outcome measures limited effective meta-analysis and comparison between clinical trials, preventing evidence-based decisions on the best treatments for improved patient care.

As a consequence, Ingram co-founded HISTORIC, the HS Core Outcomes Set International Collaboration. HISTORIC involves HS patients and healthcare professionals from 19 countries across 4 continents. The group sought to overcome the heterogeneity of outcome measures identified by the earlier research, focusing on identifying new outcome measures which could form the basis of future research programmes and trials. Consensus decision-making focused on six core outcome domains: pain, physical signs, HS specific quality of life, global assessment, disease progression and symptoms **[3.5]**.

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

[3.1] Ingram JR, Jenkins-Jones S, Knipe DW, Morgan CLI, **Cannings-John R**, **Piguet V**. Population-based Clinical Practice Research Datalink study using algorithm modelling to identify the true burden of hidradenitis suppurativa. *Br J Dermatol* 2018; 178: 917-924. http://dx.doi.org/10.1111/bjd.16101

[3.2] Ingram JR, Woo P, Chua SL, Ormerod AD, Desai N, Kai AC, et al. Interventions for hidradenitis suppurativa. *Cochrane Database of Systematic Reviews* (10), CD010081; 2015. http://dx.doi.org/10.1002/14651858. CD010081.pub2

[3.3] Ingram JR, Abbott R, Ghazavi M, Alexandroff AB, McPhee M, Burton T, Clarke T. The Hidradenitis Suppurativa Priority Setting Partnership. *Br J Dermatol* 2014; 171: 1422-7. http://dx.doi.org/10.1111/bjd.13163

[3.4] Ingram JR, Hadjieconomou S, **Piguet V**. Development of core outcome sets in hidradenitis suppurativa: a systematic review of outcome measure instruments to inform the process. *Br J Dermatol* 2016; 175: 263-72. http://dx.doi.org/10.1111/bjd.14475

[3.5] Thorlacius L, **Ingram JR,** Villumsen B, Esmann S, Kirby JS, Gottlieb AB, Merola JF, Dellavalle R, Nielsen SM, Christensen R, Garg A, Jemec GBE; Hidradenitis SuppuraTiva cORe outcomes set International Collaboration (HISTORIC). A core domain set for hidradenitis suppurativa trial outcomes: an international Delphi process. *Br J Dermatol* 2018; 179: 642-50. http://dx.doi.org/10.1111/bjd.16672

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

Cardiff research on hidradenitis suppurativa (HS) informed National Institute for Health and Care Excellence (NICE) guidance, establishing adalimumab as a treatment of choice for HS. It also led to new British Association of Dermatologists' guidelines, with new HS screening protocols and recommended treatment (adalimumab) for HS patients, whilst additionally setting the direction of a new research programme addressing clinical gaps in knowledge around HS.

4.1 New treatment approaches for HS

a. NICE approval for use of adalimumab in treatment of HS

Cardiff's 2015 Cochrane review **[3.2]**, which evidenced adalimumab's efficacy for treatment of moderate and severe HS patients, informed the work of a NICE team as they undertook a

Single Technology Appraisal (TA392) for the use of adalimumab as a treatment of HS. Ingram represented the British Association of Dermatologists (BAD), with Ingram's evidence and research being cited over 25 times in the NICE Committee Papers **[5.1]**. Ingram was also a member of the Evidence Review Group commissioned by NICE which determined that adalimumab was cost effective for HS **[5.2]**.

In 2016, NICE approved the use of adalimumab as the first biological drug intervention for HS in the UK **[5.3]**. A patient representative from the Hidradenitis Suppurativa Trust commented on NICE's decision: "*When we were told last July that Adalimumab was licensed for HS, it was like a ray of sunlight. It means that those who were stage 2 and 3 could go to their GP and name a medication that could help*" **[5.1]**. Prior to the NICE Technology Appraisal, clinicians were required to submit a funding request for each patient they wished to treat with adalimumab. This was a complex process with low rates of take-up by clinicians, resulting in few patients benefiting from the treatment. As Philip Hampton, Joint Lead for the Newcastle HS service, confirms: "*The NICE approval of adalimumab for the treatment of HS was a pivotal moment in the care of HS patients*" **[5.4]**. This change led to a 3-fold increase in prescribing of adalimumab for HS (see section 4.2 for details of change on clinical practice).

b. Recognition of HS as a prevalent and serious condition by UK Department of Work and Pensions

Following the NICE approval, the UK Department of Work and Pensions formally recognised HS as a disability, enabling those affected by HS to apply for Personal Independence Payments and other benefits based on their diagnosis. To ensure translation of this change into practice, in 2015 the Department of Work and Pensions produced a training module to guide occupational physicians in their assessment of HS patients. This training was further updated in 2019 **[5.5]**. The training module cites Ingram and Piguet's study on HS prevalence **[3.2]** and British Association of Dermatologist's guidelines, which were developed by the Cardiff team (see section 4.1c) **[5.6]**, the latter being named as a key resource for physicians in the training package.

c. British Association of Dermatologists (BAD) Guidelines

While the NICE appraisal was ongoing, Ingram chaired (with Piguet a key contributor) the British Association of Dermatologists' (BAD) Guideline Development Group on HS. This group produced the first UK clinical guidelines for HS in 2018 **[5.6]**.

The guidelines adhere to GRADE methodological standards, with BAD's guidelines development process accredited by NICE. Based on Cardiff's research demonstrating increased risk of depression and death from cardiovascular disease **[3.2]**, a core recommendation in the guidelines was that HS patients be screened for depression and cardiovascular disease risk factors: [Recommendation 4]*: "Screen people with HS for associated comorbidities including depression, anxiety and cardiovascular risk factors (diabetes, hypertension, hyperlipidaemia and central obesity)*" **[5.6,** p.3**]**.

Aligned to Cardiff's research, in patients with moderate to severe HS, who were found to be "*unresponsive to conventional systemic therapy*", adalimumab was recommended as the frontline biological drug therapy for this patient group [Recommendation 13] **[5.6,** p.3**]**.

In January 2016 Ingram was also asked by BAD to update their Patient Information Leaflet (PIL), taking into account new research outcomes. The updated PIL includes Cardiff research, for example, the recommendation to provide adalimumab as a treatment option. The leaflet also focuses on mental health 'self-care' options (e.g., stress management and joining a support group), as recommended by the research **[5.7]**. Provision of the new PIL to all diagnosed patients is recommended in the BAD HS guidelines **[5.6]**.

Ingram was also author of two chapters on HS in UpToDate, a medical information repository. UpToDate is used by more than 1.3 million clinicians in 187 countries, including 90% of academic medical centres in USA. In 2018 alone, his Medical Treatment of HS chapter was viewed 214,000 times, with his HS Aetiopathogenesis chapter viewed 86,000 times **[5.8]**.

4.2 Driving clinical practice change

The Cardiff team conducted baseline and follow-up surveys of dermatological practice (2014 **[5.9]** and 2019 **[5.10]** respectively). These were designed to assess the effects of NICE's approval of adalimumab and the introduction of the BAD HS guidelines on frontline patient care. The survey found that dermatologists had positively amended their practice as follows **[5.10]**:

- For moderate to severe HS cases, 83% of dermatologists were now prescribing adalimumab compared to only 27% in 2014;
- Use of the vitamin A derivative isotretinoin (not recommended by the Cochrane review **[3.2]**) fell by nearly a half from 62% to 35%;

The impact of the NICE approval on clinical practice is described by Philip Hampton (Newcastle): "*as we identify patients at an earlier stage in their disease, we are seeing better responses with more patients going into remission and managing to resume a normal life. With previous limited treatment options, this was an extremely rare outcome*" **[5.4]**.

He further confirms that the NICE approval and the BAD guidelines led to a transformation of care for HS patients: "*Together, the approval of adalimumab and the BAD guidelines have hugely improved how clinicians approach managing and treating HS in their patients. I have also had the opportunity to see the improvements these changes have led to for HS patients. Improvements in diagnosis and a clear framework for treatment give patients greater confidence that the debilitating effects of their condition are recognised and can be managed. For many patients that I see, treatment with adalimumab brings alleviation of painful and distressing symptoms that have an extremely detrimental effect on quality of life*" **[5.4]**.

4.3 Setting a new research agenda and evaluating new treatments for HS

Through leadership of the HS Priority Setting Partnership the Cardiff researchers were instrumental in influencing allocation of public funds to HS research for the first time in the UK. The new funding was made available by the commissioning of a Health Technology Assessment (HTA) funding call, by the National Institute of Health Research, in 2018. HTA supports research and innovations of direct benefit to patients, clinical practice and policy makers, which must be immediately effective within the existing NHS care pathway. The research priorities identified by the HS PSP (chaired by Ingram) **[3.3]**, and the research outcomes from Ingram's 2015 Cochrane Review **[3.2]**, were directly cited in the HTA briefing document **[5.11]** and provided the basis for the new £600K funding call.

4.4 Summary

Cardiff research resulted in NICE approval for adalimumab as a critical, and highly effective treatment for HS. New guidelines and recommendations altered clinical practice, evidenced by clear changes in dermatological treatment over the REF period, as well as improved patient access to disability payments and monitoring for associated health conditions. The research also supported establishment of a new funding scheme for health innovations for HS.

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

[5.1] Final appraisal determination document, committee papers and impact report.

[5.2] Tappenden P, Carroll C, Stevens JW, Rawdin A, Grimm S, Clowes M, Kaltenthaler E, Ingram JR, Collier F, Ghazavi M. Adalimumab for treating moderate-to-severe hidradenitis suppurativa: An Evidence Review Group perspective of a NICE Single Technology Appraisal. *Pharmacoeconomics* 2017; 35: 805-815.

[5.3] NICE TA392 adalimumab for HS

[5.4] Letter corroborating use of adalimumab and the BAD guidelines in clinical care

[5.5] UK DWP training module 523a CMEP

[5.6] Ingram JR, Collier F, Brown D, Burton T, Burton J, Chin MF, Desai N, Goodacre TEE, Piguet V, Pink AE, Exton LS, Mohd Mustapa MF. British Association of Dermatologists

guidelines for the management of hidradenitis suppurativa (acne inversa) 2018. *Br J Dermatol* 2019; 180: 1009-1017. http://dx.doi.org/10.1111/bjd.17537

[5.7] BAD HS Patient Information Leaflet

[5.8] UpToDate Chapter viewing figures

[5.9] Ingram JR, McPhee M. Management of hidradenitis suppurativa: a UK survey of current practice. *Br J Dermatol* 2015; 173: 1070-1072.

[5.10] Hasan SB, Ingram JR. What has changed in the UK management of hidradenitis suppurativa from 2014 to 2019? *Br J Dermatol*. 2020 November; 183(5): 973-975. doi: 10.1111/bjd.19302. Epub 16 July 2020

[5.11] HTA Commissioning Brief Background information