

Impact case study (REF3)

Institution: University of Nottingham		
Unit of Assessment: UoA1		
Title of case study: Generating world-class evidence that has transformed national and international prescribing practices and improved care for people with skin diseases		
Period when the underpinning research was undertaken: 2003 to 2018		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Professor Kim S Thomas	Role(s) (e.g. job title): • Professor of Applied Dermatology Research,	Period(s) employed by: 1996 to current
Professor Hywel C Williams	• Professor of Dermato-Epidemiology,	1994 to current
Dr Joanne R Chalmers	• Senior Research Fellow in Dermatology	2003-2015, 2016 to current
Period when the claimed impact occurred: November 2013 to current		
Is this case study continued from a case study submitted in 2014? No		
1. Summary of the impact University of Nottingham researchers have led six clinical trials across multiple skin diseases that have provided world-class research evidence and transformed clinical practice throughout the NHS and around the world. These six trials have informed 7 national and 34 international guidelines and changed clinical practice in 22 countries across 5 continents. This has resulted in a better quality of life for people with skin disease, reduced deaths and serious side-effects from commonly used treatments, and reduced spending on ineffective and potentially harmful treatments.		
2. Underpinning research Skin disease represents the fourth most common cause of non-fatal burden of disease globally ¹ and accounts for a quarter of GP consultations in England and Wales. Over the last 20 years, researchers from the University of Nottingham have led and delivered multiple national pragmatic trials that have informed clinical decision-making and enabled patient benefit for people with skin disease within the UK and globally. Between 2003 and 2018 researchers at the Centre of Evidence Based Dermatology completed 12 multi-centre, collaborative randomised control trials (RCTs) that provided evidence to inform clinical practice and patient choice. Here we highlight six seminal trials [1-7]. These trials were led by Professor Thomas, Professor Williams and Dr Chalmers at the University of Nottingham, who developed the study questions and trial design, obtained independent funding, and led on delivery, interpretation and dissemination of the research. Other Nottingham collaborators are highlighted in the publication references. CHILDHOOD ECZEMA Eczema affects 1 in 5 school-aged children and has a high patient burden, with intense itching affecting sleep, ability to concentrate at school and psychological well-being. Treatment regimens for people with eczema can be complicated and confusing. Providing better evidence to decide which treatments are effective simplifies choices for patients. The BATHE trial , [Thomas, Williams, 2014-2018] evaluated the commonly prescribed treatment of bath emollients (emollients poured into bath water) in 483 children and showed no benefit from using 'standard eczema care PLUS bath emollients', compared to 'standard eczema care WITHOUT bath emollients' [1]. BATHE is the first RCT to assess the effectiveness of this commonly prescribed treatment. The CLOTHES trial , [Thomas, Williams, 2013-2016] included 300 children and tested whether silk clothing could provide relief of eczema symptoms. The study showed no benefit from using therapeutic silk clothing in addition to standard care [2]. Prior to the CLOTHES trial there had been just three very small RCTs, including a total of 79 participants.		

¹ Karimkhani C, Dellavalle RP, Coffeng LE et al. Global skin disease morbidity and mortality: an update from the Global Burden of Disease Study 2013. JAMA Dermatol 2017; 153:406-12.

SKIN CANCER

Basal cell carcinoma (BCC) is the most common type of human cancer with more than 80,000 cases diagnosed annually in the UK. The **SINS trial [Williams, 2003-2010]** evaluated a new cream treatment (imiquimod) and compared it to surgical removal of BCC in 501 adult patients [3]. Imiquimod is a cream that stimulates the body's immune system to reject BCC cells. Prior to the SINS trial it had only been tested in short-term, industry-sponsored studies. The SINS trial showed that imiquimod provides an effective alternative treatment option for people with BCC lesions at low risk of recurrence.

CELLULITIS

Cellulitis is a common, potentially serious, bacterial skin infection that often results in hospitalisation and reoccurs in up to 50% of cases. Prior to the **PATCH Trial [Thomas, Williams, Chalmers, 2006-2011]**, two small RCTs involving 16 and 40 patients suggested that prophylactic antibiotics might help to prevent cellulitis recurrence. The PATCH trial included 274 participants and was the first large, high-quality trial that showed prophylactic antibiotics can prevent recurrent lower limb cellulitis [4] and is cost-effective [5].

BULLOUS PEMPHIGOID

Pemphigoid is a distressing, itchy blistering skin condition that affects 0.3% of people aged over 80 years with rising prevalence. People with pemphigoid are three times more likely to die within 2 years of diagnosis than people without the condition. Increased mortality and morbidity have been linked to treatment with oral prednisolone, which is effective in controlling blisters but can cause complications such as osteoporosis, diabetes and sepsis. Prior to our trial, one small open label RCT of 18 patients had suggested tetracyclines may be a useful alternative to steroids. **The BLISTER trial [Chalmers, Williams, 2009-2013]** included 253 participants and demonstrated that starting treatment with doxycycline significantly reduced the number of deaths and severe adverse reactions, whilst still providing acceptable disease control, compared with oral prednisolone [6].

PYODERMA GANGRENOSUM

Pyoderma gangrenosum is a rare, painful, mutilating and rapidly spreading skin ulcer that has a severe impact on quality of life and can result in limb amputation. Prior to our study there had been no RCTs evaluating commonly used treatments. **The STOP GAP trial [Williams, Thomas, 2009-2013]** included 121 participants and showed that the two most commonly used oral treatments (prednisolone and ciclosporin) were about the same in terms of effectiveness, but that side-effects differed and so treatments should be tailored to the needs and comorbidities of individual patients [7].

3. References to the research

- [1] Santer M, Ridd MJ, Francis NA, Stuart B, Rumsby K, Chorozioglou M, Becque T, Roberts A, Liddiard L, Nollett C, Hooper J, Prude M, Wood W, **Thomas KS**, Thomas-Jones E, **Williams HC**, Little P. Emollient bath additives for the treatment of childhood eczema (BATHE): multicentre pragmatic parallel group randomised controlled trial of clinical and cost effectiveness. *BMJ*. 2018 May 3;361:k1332. DOI: [10.1136/bmj.k1332](https://doi.org/10.1136/bmj.k1332)
- [2] **Thomas KS**, Bradshaw LE, Sach TH, **Batchelor JM**, Lawton S, Harrison EF, **Haines RH**, Ahmed A, **Williams HC**, Dean T, Burrows NP, Pollock I, **Llewellyn J**, Crang C, Grundy JD, Guinness J, Gribbin A, **Mitchell EJ**, Cowdell F, Brown SJ, **Montgomery AA**; UK Dermatology Clinical Trials Network's CLOTHES Trial Team. Silk garments plus standard care compared with standard care for treating eczema in children: A randomised, controlled, observer-blind, pragmatic trial (CLOTHES Trial). *PLoS Med*. 2017 Apr 11;14(4):e1002280. DOI: [10.1371/journal.pmed.1002280](https://doi.org/10.1371/journal.pmed.1002280)
- [3] **Bath-Hextall F**, **Ozolins M**, **Armstrong SJ**, Colver GB, Perkins W, Miller PS, **Williams HC**; Surgery versus Imiquimod for Nodular Superficial basal cell carcinoma (SINS) study group. Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled trial. *Lancet Oncol*. 2014 Jan;15(1):96-105. DOI: [10.1016/S1470-2045\(13\)70530-8](https://doi.org/10.1016/S1470-2045(13)70530-8)
- [4] **Thomas KS**, Crook AM, Nunn AJ, **Foster KA**, Mason JM, **Chalmers JR**, Nasr IS, Brindle RJ, English J, Meredith SK, Reynolds NJ, de Berker D, Mortimer PS, **Williams HC**; U.K. Dermatology Clinical Trials Network's PATCH I Trial Team. Penicillin to prevent recurrent leg cellulitis. *N Engl J Med*. 2013 May 2;368(18):1695-703.

DOI: [10.1056/NEJMoa1206300](https://doi.org/10.1056/NEJMoa1206300)

- [5] Mason JM, Thomas KS, Crook AM, Foster KA, Chalmers JR, Nunn AJ, Williams HC. Prophylactic antibiotics to prevent cellulitis of the leg: economic analysis of the PATCH I & II trials. PLoS One. 2014 Feb 14;9(2):e82694. DOI: [10.1371/journal.pone.0082694](https://doi.org/10.1371/journal.pone.0082694)
- [6] **Williams HC**, Wojnarowska F, Kirtschig G, Mason J, Godec TR, Schmidt E, **Chalmers JR**, Childs M, Walton S, Harman K, Chapman A, **Whitham D**, Nunn AJ; UK Dermatology Clinical Trials Network BLISTER Study Group. Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial. Lancet. 2017 Apr 22;389(10079):1630-1638. DOI: [10.1016/S0140-6736\(17\)30560-3](https://doi.org/10.1016/S0140-6736(17)30560-3)
- [7] Ormerod AD, **Thomas KS**, Craig FE, **Mitchell E**, Greenlaw N, Norrie J, Mason JM, Walton S, Johnston GA, **Williams HC** Comparison of the two most commonly used treatments for pyoderma gangrenosum: results of the STOP GAP randomised controlled trial. BMJ. 2015 Jun. DOI: [10.1136/bmj.h2958](https://doi.org/10.1136/bmj.h2958)

GRANTS

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Santer M, Little P, **Williams HC, Thomas KS**, Ridd MJ, Francis NA, Stuart B, Chorozioglou M, Roberts A. RCT of Bath Emollients for the treatment of childhood eczema. NIHR Health Technology Assessment (Mar 2014-Aug 2017): GBP959,035

HC Williams, F Bath-Hextall. A randomised controlled trial of excisional surgery versus imiquimod 5% cream for nodular and superficial basal cell carcinoma. Cancer Research UK (2003-2011): GBP314,321 (plus GBP90,950)

HC Williams, KS Thomas, N Cox, N Reynolds, A Crooke, J Mason, S Meredith. Randomised controlled trial of prophylactic antibiotics for the prevention of recurrent cellulitis (erysipelas) of the leg. Action Medical Research (Jul 2006-Oct 2011): GBP116,175

HC Williams, KS Thomas, W Perkins, N Evans, R Patel, C Paule, J Norrie, M Whitton, A Nunn, J Mason, S Crowe, A Ormerod, F Bath-Hextall, J Leonardi-Bee, S Lawton. Setting Priorities and Reducing Uncertainty for people with Skin Disease. NIHR Programme Grant (Sept 2008-Aug 2013): GBP1,930,186

HC Williams, JR Chalmers, A Nunn, G Kirtschig, F Wojnarowska, J Mason A randomised controlled trial to compare the safety and effectiveness of doxycycline with prednisolone for initial treatment of bullous pemphigoid. NIHR Health Technology Assessment (Oct 2008-Mar 2015): GBP859,503

4. Details of the impact

Research to Impact Pathways: Our trials [1-7] have been seminal in changing clinical practice throughout the UK and internationally. The trial results have been incorporated into 7 national (UK) and 34 international guidelines, spanning 5 continents, including key national guidelines such as NICE (BATHE, 2019; PATCH, 2019), NHS England (CLOTHES, 2019), British Association of Dermatologists (STOP GAP, 2019), American Academy of Dermatology (SINS, 2018) and Japanese Dermatological Association (BLISTER, 2019) [A].

Impacts achieved include: i) transformed national and international clinical practice; ii) improved health and well-being of patients (including reduced deaths and serious side-effects); and iii) reduced NHS costs. International reach has been demonstrated through a survey of clinicians in 22 countries from 5 continents (2020), which suggested that adoption of our trial findings has been rapid [B].

ECZEMA - BATHE [1] and CLOTHES [2] trials

Transforming Clinical Practice: Despite being commonly used treatments in the NHS, our trials provided the first high-quality evidence that 'bath emollients' and 'silk garments' **do not** provide tangible clinical benefit for people with eczema. These trials have informed four national and five international guidelines including those of Europe, New Zealand, and Argentina (between 2018 and 2020) [A].

Ongoing prescribing of these products is complicating treatment regimens for patients unnecessarily and incurs unnecessary costs for the NHS. These two trials were used as the *key evidence sources* for an NHS England consultation in **2018**, which concluded by recommending that emollient bath additives and silk garments should no longer be prescribed in primary care for eczema **[2019][C, p16 and p35]**.

Reduced NHS costs: Based on the BATHE trial, an NHS PrescQIPP report (**2019**) concluded that stopping or reducing the prescribing of bath emollients “*by 80% could release savings of up to £4.9 million. This equates to savings of £7,663 per 100,000 patients*” **[D, p3]** Similarly a PrescQIPP report on silk clothing (**2017**), informed by the CLOTHES trial, concluded that “*a potential 30% reduction in prescribing ... could result in a national saving of £385,047. This equates to £630 per 100,000 patients.*” **[E, p3]** Prescribing data for England show a sustained reduction in prescribing **[F, p1]**. For bath emollients there has been a decrease of 44% from a peak of GBP18,123,512 to GBP10,109,182 (**between 2016 and 2019**) **[F, p1]**. For silk clothing, prescription costs have decreased from a peak of GBP1,367,624 to GBP797,086, a decrease of 43% (**between 2016 and 2019**) **[F, p1]**.

SKIN CANCER (Basal cell carcinoma) – SINS Trial [3]

Transforming Clinical Practice: The SINS trial was the first large independent trial to show that, topical imiquimod cream provides a viable and less invasive treatment option than surgery, with excellent cosmetic results for people with BCC at low risk of recurrence. The SINS trial has informed nine international guidelines including those of Europe, USA, Canada and Russia (**between 2014 and 2019**) **[A]**. The trial has informed clinical practice **internationally** “*it [the SINS trial] certainly shifted the way we cared for patients almost immediately. It also influenced a whole body of research, on how patients should be informed about the risks, benefits and options for BCC. We cite your study in our decision tool for patients with BCC and your data directly helps patients make more informed decisions. Your work is truly impactful internationally, and I imagine has influenced the care of thousands (if not hundreds of thousands) of patients in the US*” (survey response, dermatologist in USA, 2020) **[B, p10-11]**.

Improving health and wellbeing of patients: Basal cell carcinoma (BCC) is the most common type of skin cancer. Availability of imiquimod as an effective, non-surgical treatment option is something that patients value, especially for skin cancers on sites such as the face: “*[I] delayed going to the doctor as I dreaded surgery... too many people feel as I did - making their condition harder to tackle because they come to treatment so late... I was ... able to avoid intrusive surgery and the risk of scarring by trying a non-surgical treatment option - a topical cream called Aldara [imiquimod]... now that I have seen how easy it can be to get rid of BCCs, I will seek treatment as soon as I notice anything unusual.*” **[G]**

CELLULITIS - PATCH trial [4, 5]

Transforming clinical practice: Low dose narrow spectrum penicillin prophylaxis remains the only proven strategy for prevention of recurrent cellulitis. Our PATCH trial has informed 16 national and international guidelines including ones covering Europe, USA, Australia, Kazakhstan, Azerbaijan and Korea (**between November 2013 and 2020**) **[A]**. Penicillin prophylaxis has been adopted **internationally**: “*A lot of my colleagues learned your strategy from UpToDate and used it to determine treatment and prophylaxis in actual clinical practice based on your evidence.*” (survey response, dermatologist in Japan, 2020) **[B, p9]**.

Improving health and wellbeing of patients: **Between 2017 and 2018**, there were 88,664 hospital admissions with cellulitis (average bed stay of 5 days, at a cost of GBP2,553 per stay). Our PATCH trials showed that use of prophylactic penicillin as a prevention strategy prevented approximately 30% of cases **[5, p1]**. Assuming a 20% uptake of prophylactic penicillin (with 86% of inpatient cases affecting the limbs and 50% having recurrent cellulitis), an estimated 2,500 cases could be prevented, with a potential estimated cost saving of over GBP6,000,000 per annum **[H]**.

BULLOUS PEMPHIGOID - BLISTER trial [6]

Transforming clinical practice: The BLISTER trial has informed four international guidelines in Europe and Japan (**between 2019 and 2020**) [A]. Surveys have shown that UK dermatologists are now more likely to start pemphigoid treatment with doxycycline in order to reduce serious side-effects and deaths. Surveys conducted prior to the trial (**2015**, n=113) and after the trial (**2018**, n=74) showed that 84% of UK dermatologists felt the results of the BLISTER trial had influenced their management of patients with pemphigoid. Nearly 30% who did not previously use tetracyclines now plan to do so, and for those already using tetracyclines, the trial results increased their confidence in prescribing them [I, p1]. Similar uptake has been seen **internationally**: “*We are routinely now using doxycycline as the first step of treatment of BP.*” (survey response, dermatologist Iran, 2020) [B, p8]. “*This study has changed our practice in Colombia as it [doxycycline] has become the first option before starting systemic corticosteroids for all patients (not only for some) in the majority of in-patient dermatology centres.*” (survey response, dermatologist Colombia, 2020) [B, p7].

Improving health and wellbeing of patients: Changes in practice resulting from this trial has reduced exposure of elderly people with bullous pemphigoid to harmful long-term use of oral prednisolone. Population and trial data conservatively estimate this change could have avoided 170 deaths in the UK (**between 2017 and 2019**), where every quality-adjusted life-year subsequently gained is worth GBP50,000 to NICE, and avoided an additional 255 serious to life-threatening side-effects such as increased infections and reductions in bone density [J, p4].

PYODERMA GANGRENOSUM - STOP GAP trial [7]

Transforming clinical practice: The STOP GAP Trial has informed one national and two international guidelines (between 2019 and 2020). The trial, which recruited from 39 hospitals across the UK, increased awareness of this rare condition amongst clinical disciplines where people with pyoderma gangrenosum present, and encouraged teams from gastroenterology, surgery as well as dermatology to recruit into the trial. Awareness amongst different professional groups is crucial as commonly performed procedures, such as surgical exploration, can cause pyoderma gangrenosum to worsen if not recognised; potentially leading to amputation. As a direct result of the STOP GAP trial, a co-investigator Dr Martin-Clavijo established a specialist clinic that now accepts **national** referrals. His clinic has adopted a proforma based on the trial protocol, which has been critical for obtaining specialized treatment funding for patients. “*I now always aim to give my patients with PG realistic expectations, warning them that ulcers may take months to heal. I also know that 30% of patients have recurrences after healing, so I advise patients accordingly when they are discharged, and I give them direct access to my dedicated PG clinic.*” UK Dermatologist, 2017) [K, p3]. **Internationally:** “*...my clinical practice is influenced by this study... Depending on patients with different clinical conditions, we will consider to use cyclosporine for PG patients with possible severe infection or underlying infection, whereas we will use prednisolone... for PG patients with underlying renal diseases or electrolyte imbalances.*” (survey response, dermatologist in Taiwan, 2020) [B, p10].

Sources to corroborate the impact

- [A] Summary of 41 clinical guidelines with links (2013 – 2020)
- [B] [Scoping the international impact from four independent national dermatology trials](#) (2020), doi:10.1111/ced.14506
- [C] [Items which should not routinely be prescribed in primary care](#) (2019)
- [D] [PresQUIPP Bulletin 244: Bath and shower emollient preparations](#) (2019)
- [E] [PresQUIPP Bulletin 160: Silk and antimicrobial garments](#) (2017)
- [F] Prescribing data downloaded from OpenPrescribing.net, EBM DataLab
- [G] [Cream that 'rubs away' skin cancer \(Daily Mail article\)](#) (2015)
- [H] Economic modelling for PATCH trial
- [I] [Assessing the impact of the BLISTER trial in the U.K](#) (abstract 001) (2019), doi:10.1111/bjd.17749
- [J] Economic modelling for BLISTER Trial
- [K] [Generating new evidence, improving clinical practice and developing capacity](#) (2017), doi:10.1111/bjd.15959