Institution: University of Nottingham

Unit of Assessment: UoA1

Title of case study: Reducing treatment uncertainties for childhood eczema

1. Summary of the impact

Research in the Centre of Evidence Based Dermatology at the University of Nottingham has improved the lives of children with eczema throughout the world. This has been achieved by improving the evidence base for clinical care through identifying treatments that work and those that do not, thus reducing the burden of disease for patients and reducing costs for patients and the NHS. Clinical care has been improved, economic benefits have been realised and Government policy informed.

2. Underpinning research

The Centre of Evidence Based Dermatology at the University of Nottingham is internationally recognised for the way it has developed evidence-based treatment pathways for children with eczema by first systematically reviewing all existing evidence to identify research gaps, prioritising those gaps with patients, and then addressing them through national randomised controlled trials. Led by Professors Hywel Williams and Kim Thomas (since 1994 and 1999 respectively), the eczema theme is underpinned by relevant international epidemiological and outcome measure research, and disseminated to a community of over 700 research users and its own patient support group.

Epidemiology: The International Study of Asthma and Allergies in Childhood (ISAAC), for which Williams was eczema lead from 1994 to 2013, has shown that childhood eczema affects up to 20% of children worldwide [1] and its prevalence is increasing, raising awareness of the global importance of the disease. ISAAC holds the Guinness World Record for the largest epidemiological study that has ever been conducted http://www.guinnessworldrecords.com/records-3000/largest-epidemiological-study

Systematic reviews: In 2000, Williams conducted an over-arching systematic review of eczema treatments [2], which included 272 trials in 47 treatment categories. The review was updated in 2013 and a further 259 trials were identified. This body of over 500 eczema trials has helped us to identify treatments that work (such as twice-weekly topical corticosteroids and ultraviolet light), treatments that do not work (such as evening primrose oil) and treatments where further research is desperately needed (such as the evaluation of commonly used treatments including bath emollients and antimicrobials). The review also identified for the first time that once daily application of topical steroids was as effective as more frequent application. We have extracted key information from the 500+ published trials (including trial design, treatments compared, and health outcomes collected), and summarised this in a freely accessible online database (GREAT Database http://www.greatdatabase.org.uk/) designed to prevent unnecessary international duplication of effort in searching and appraising eczema trials for the development of systematic reviews and guidelines. Our eczema review led us to publish five detailed Cochrane reviews and an overview of eczema prevention systematic reviews.

Clinical Trials: Williams and Thomas have conducted **five** randomised controlled trials on the prevention or treatment of eczema since 2002 (and a further three are ongoing) that focus on questions of importance to patients and health professionals. Here, we highlight three that have contributed to changes in clinical practice or to cost savings for families and the NHS:
(i) *Nurse-led clinics and patient education* [3] - this was the first randomised controlled trial to evaluate the role of nurse-led educational clinics alongside dermatology consultations in the management of patients with chronic skin disease including eczema. It showed that patients receiving a consultation with the dermatology nurse had enhanced understanding of the disease and were better able to apply treatments appropriately.

(ii) *Optimal ways of using topical corticosteroids* [4] – this trial was groundbreaking because it studied overall control of disease over a period of months, rather than the usual eczema trial of

6 weeks duration. The study showed that short bursts of stronger corticosteroids were as good as longer term use of milder preparations, and its novel design set down a marker for longer term trials on flare prevention in eczema.

(iii) *Water softeners for eczema treatment* [5] - this trial showed that installing an ion-exchange water softener in the home of eczema patients did not result in improvements in eczema control. Although water softeners are not prescribed via the NHS, our NIHR-funded trial was important as parents often ask about the role of hard water in exacerbating eczema and also whether purchasing a water softener would help.

Diagnostic criteria and outcomes research: In 1993/1994, Williams led the development and validation of international diagnostic criteria for eczema used in ISAAC [1] and other international studies for the following 20 years. Williams and Dr Carolyn Charman (also University of Nottingham) developed a Patient Reported Outcome Measure (PROM) for eczema in 2004 [6] and harmonised the 21 named scales for measuring eczema in clinical trials into one core set with Thomas and an international group of dermatologists, regulators, industry and patients in 2012.

Public engagement in research: In 2011, Thomas and Williams ran a James Lind Alliance research Priority Setting Partnership on eczema, involving 341 patients and 152 clinicians. This used consensus methodology to identify 14 priority topics for future research. Williams (and other clinical colleagues from the award-winning special eczema clinic at Nottingham) also helped to establish the Nottingham Support Group for Carers of Children with Eczema in 2005 (http://www.nottinghameczema.org.uk/). This patient support group works with our Centre to ensure accurate and up to date patient information on eczema.

3. References to the research

1. Asher MI, Bjorksten B, Lai CKW, Strachan DP, Weiland SK, **Williams HC** and the ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phase Three multicountry cross-sectional survey. *Lancet* 2006:368:733-743. http://dx.doi.org/10.1016/S0140-6736(06)69283-0

2. Hoare C, Li Wan Po A, **Williams HC.** Systematic review of treatments for atopic eczema, *Health Technol Assess* 2000; 4(37):1-191. (cited 333 times) http://dx.doi.org/10.3310/hta4370 (PDF available on request.)

3. Gradwell C, **Thomas KS**, English JSC, **Williams HC** An RCT of nurse follow-up clinics: do they help patients and do they free up consultants' time? *Br J Dermatol* 2002; 147: 513-517. http://dx.doi.org/10.1046/j.1365-2133.2002.04901.x

4. **Thomas KS**, Armstrong S, Avery A, Li Wan Po A, O'Neill C, **Williams HC**. Randomised controlled trial of short bursts of a potent topical corticosteroid versus more prolonged use of a mild preparation, for children with mild or moderate atopic eczema. *BMJ* 2002; 324:768-775. http://dx.doi.org/10.1136/bmj.324.7340.768

5. **Thomas KS**, Dean T, O'Leary C, Sach TH, Koller K, Frost A, **Williams HC** and the SWET Trial Team. A randomised controlled trial of ion-exchange water softeners for the treatment of eczema in children. *PLOS Medicine* 2011; 8 (2): e1000395 http://dx.doi.org/10.1371/journal.pmed.1000395

6. Charman CR, Venn AJ, **Williams HC**. The **P**atient-**O**rientated **E**czema **M**easure (POEM) – development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol* 2004;140:1513-1519. http://dx.doi.org/10.1001/archderm.140.12.1513

Attribution and income: Grants to Williams and Thomas that underpinned the above research included: Department of Health, Meta-analysis of Epogam Trials, 1995-6, £10k; NHS R&D Trent Region, Outcome measures for atopic eczema, 1998-2001, £105k and Trial of topical corticosteroids in eczema, 2000-2, £123k; NIHR HTA Programme, Systematic review of eczema

treatments, 1999-2000, £50k and RCT of water softeners for atopic eczema, 2006-10, £905k; NIHR Applied Research Programme Grant, Setting priorities and reducing uncertainties in the prevention and treatment of people with skin diseases, 2008-13, £1,930,000; BUPA Foundation, International Study of Asthma and Allergies in Childhood, 2008-11, £179k.

4. Details of the impact

Epidemiology and diagnostic criteria tools: Our International Study of Asthma and Allergies in Childhood (ISAAC: 1.96 million children, 306 research centres in 105 countries, 53 languages, >500 publications) has increased global awareness of the importance of eczema as a significant childhood disease to policy makers by demonstrating that it is increasing and common in developing as well as developed countries. The work influenced the formation of a National Child & Youth Eczema Clinical Network funded by the Ministry of Health and Paediatric Society of New Zealand in 2012 [a]. This has provided information and training in patient education and eczema management to nurse specialists, general practitioners and paediatricians, and has developed a system for monitoring services to inform continuous quality improvement.The diagnostic criteria for eczema that we developed for ISAAC and other epidemiological studies were found to be the best validated and widely used criteria worldwide in an independent systematic review in 2008 [b]. They continue to be the most widely used diagnostic criteria for eczema for epidemiological studies [PLoS One.2012;7(7):e39803].

Systematic reviews influencing clinical practice: Our systematic review of eczema treatments was the major evidence source for the UK NICE guidance on eczema in children 2007, recommendations of which were taken up from 2008 onwards as in the NICE update in 2011 [c], SIGN guidance on eczema of all ages in 2011 [d], and international eczema guidelines for dermatologists, paediatricians and general practitioners in South Africa, Europe, New Zealand and Japan [e]. The Japanese guidance required a full translation into Japanese. As a result of another key finding from our review, picked up by our BMJ change page [*Br Med J* 2007;334:1272] and 2011 SIGN Guidance [d], it was recommended that doctors prescribe once-daily topical steroids rather than more frequent application. This benefits patients and their carers by reducing the treatment palaver for busy parents, and reducing the risk of side-effects like skin thinning. It also benefits the NHS by reducing treatment costs from £3.25million to £2.44million (2012 prices) [f].

Clinical Trials – introducing cost-effective treatments and discarding ineffective ones: Following on from our pioneering research into nurse-led clinics, dermatologists in the UK, Germany and the Netherlands set up similar clinics from 2005 to 2012, which have been shown to be cost saving. NICE Guidance including an analysis of the cost-effectiveness of nurse-led educational interventions for eczema in children concluded that it “appears to be both effective and good value for money for children with atopic eczema in secondary care” [c], which has been borne out by a subsequent analysis of a large trial of nurse education conducted in the Netherlands in 2010 [Br J Dermatol 2011;165:600-611].

Our topical corticosteroids trial has been cited 111 times and was used to inform the NICE guidance updated in 2011 [c]. It was the first trial to evaluate disease flares in eczema research and has led to a series of trials of “proactive” (twice weekly) therapy which has reduced eczema flares in children and adults by around 50% [g].

Our trial of water softeners provided clear guidance, showing for the first time that *these do not work* for children with eczema. If our work prevented just 10% of the estimated 400,000 UK families with a child with moderate to severe eczema buying a device over the 3-year period 2011-2013, this would save around £4 million (based on an average cost of £750 per unit, plus salt and servicing costs).

Outcomes research: Patient Reported Outcome Measures (PROMs) are recommended by the Department of Health as critical aspects of measuring clinical care outcomes. Our eczema-specific PROM, called the Patient-Reported Eczema Measure (POEM), one of three eczema severity scales that have been appropriately validated and recommended for use, is recommended as a tool for capturing treatment response in consultations with eczema patients by NICE [c] and Map of

Medicine [h]. POEM is being used in clinical practice to assess the severity of eczema and monitor treatment outcomes. Quotes describing its impact include 'especially good as makes assessment less subjective' and 'very useful resources in a busy clinical setting' [i]. Beneficiaries have included paediatric dermatology teams at Nottingham, Birmingham, Dewsbury, Oxford, Gloucester and London, and US care organizations including the Boston Children's Hospital and Mayo clinic [i].

Public engagement in research: Our James Lind Alliance research priority setting partnership has benefitted NHS funders including the NIHR Efficiency and Mechanism Evaluation (EME) Programme who, in 2013, issued a special call on skin diseases [http://www.nets.nihr.ac.uk/funding/eme-commissioned/briefs/13-50-com-brief.pdf]. The Nottingham Support Group for Carers of Children with Eczema (http://www.nottinghameczema.org.uk), which we established in partnership with patients, has developed twenty two information sources for patients' benefit covering all aspects of eczema, and has won several awards. Our University now hosts this website, the value and impact of which is evidenced by numerous quotes from patients, carers and healthcare professionals [j]. Our engagement with the public has benefitted outstanding patient volunteers such as Amanda Roberts [j] who became part of the NICE 2007 and RCPCH 2011 guidelines groups. Amanda runs a Twitter account on the group's eczema work (@eczemasupport), and has over 4,200 followers.

5. Sources to corroborate the impact

a. Email correspondence from Mollie Wilson, Chief Executive Officer, Paediatric Society of New Zealand.

b. Brenninkmeijer EE, Schram ME, Leeflang MM, Bos JD, Spuls PI. Diagnostic criteria for atopic dermatitis: a systematic review. Br J Dermatol. 2008;158:754-765. http://dx.doi.org/10.1111/j.1365-2133.2007.08412.x

c. NICE Guidelines on Management of AE in children (2007): CG57 http://www.nice.org.uk/nicemedia/pdf/CG057FullGuideline.pdf (Although published in Dec 2007, this guidance has not been updated since. The findings which relied on our systematic review (2000) are still relevant and not deemed to require revision despite consideration in 2011. http://www.nice.org.uk/nicemedia/live/11901/55943/55943.pdf This policy document forms the major sole source for many other evidence-based guidelines and patient information resources.

d. Management of atopic eczema in primary care (Number 125, March 2011) http://www.sign.ac.uk/pdf/sign125.pdf

e. Saeki H, Furue M, Furukawa F, et al. Guidelines for management of atopic dermatitis. *J Dermatol*. 2009;36:563-577. (PDF available on request.) http://dx.doi.org/10.1111/j.1346-8138.2009.00706.x

f. Economic analysis by Professor R Elliott, Lord Trent Professor of Medicines and Health, The University of Nottingham.

g. Schmitt J, von Kobyletzki L, Svensson A, Apfelbacher C. Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: systematic review and meta-analysis of randomized controlled trials. Br J Dermatol. 2011;164:415-428. http://dx.doi.org/10.1111/j.1365-2133.2010.10030.x

h. Map of Medicine eczema care pathway (published Nov 2012): http://healthguides.mapofmedicine.com/choices/map/eczema1.html

i. Table of quotes demonstrating impacts of POEM (see pdf).

j. Letter from Amanda Roberts, Carer.