

A multicentre randomized controlled trial of ion-exchange water softeners for the treatment of eczema in children: protocol for the Softened Water Eczema Trial (SWET) (ISRCTN: 71423189)

K.S. Thomas and T.H. Sach* on behalf of the SWET Trial Investigators¹

Centre of Evidence Based Dermatology, University of Nottingham, King's Meadow Campus, Nottingham NG7 2NR, U.K.

*University of East Anglia, Norwich NR4 7TJ, U.K.

Summary

Correspondence

Kim Thomas.

E-mail: kim.thomas@nottingham.ac.uk

Accepted for publication

6 March 2008

Key words

eczema, ion-exchange, randomized controlled trial, water, water hardness

Conflicts of interest

The authors and members of the trial team have no conflicts of interest to declare. While the study is being conducted with the valuable assistance of the trade associations for the water softener industries, the study team has complete control over the design, analysis and reporting of the study.

The views and opinions expressed in this article are those of the authors and do not necessarily reflect those of the National Institute for Health Research Health Technology Assessment Programme.

¹The SWET Trial Investigators are listed in the Appendix.

DOI 10.1111/j.1365-2133.2008.08704.x

Epidemiological evidence linking increased water hardness with increased eczema prevalence was first demonstrated in an ecological study of 4141 randomly selected primary school children in the Nottingham area.¹ The 1-year period prevalence of eczema was 17.3% in the hardest water category and 12.0% in the lowest (odds ratio 1.54, 95% confidence interval 1.19–1.99 after adjustment for confounders). Similar results have been found in Japan.² A number of plausible mechanisms can be forwarded to suggest why hard water could exacerbate eczema. Perhaps the most likely explanation is increased soap usage in hard water areas, the deposits of which can cause skin irritation in individuals with eczema. A direct chemical irritant effect from chlorine or calcium and

Background There is epidemiological evidence linking increased water hardness with increased eczema prevalence. A number of plausible mechanisms can be forwarded to suggest why hard water could exacerbate eczema. The most likely explanation is increased soap usage in hard water areas, the deposits of which can cause skin irritation in individuals with eczema.

Objectives To assess the cost and cost-effectiveness of ion-exchange water softeners for the treatment of eczema in children.

Patients/Methods Three hundred and ten children aged 6 months to 16 years, with moderate to severe eczema. The children must live in hard water areas (≥ 200 mg L⁻¹ of calcium carbonate) and have a home that is suitable for the installation of a water softener. This is a single-blind, parallel-group, randomized controlled trial of 12 weeks duration followed by a 4-week cross-over period.

Results/Analysis Plan Primary outcome: difference in the mean change in disease severity (Six Area, Six Sign Atopic Dermatitis score) at 12 weeks compared with baseline. Secondary outcomes: (i) proportion of time spent moving during the night; (ii) self-reported global changes in eczema severity; (iii) amount of topical treatment used; (iv) Patient Oriented Eczema Measure; (v) number of totally controlled and well controlled weeks; (vi) impact on health-related quality of life for the child (EQ-5D) and the family (Dermatitis Family Impact questionnaire); and (vii) cost-effectiveness. It is planned that recruitment will be completed by the end of 2008 and results will be available towards the end of 2009.

magnesium salts is also possible, as is the indirect effect of enhanced allergen penetration due to a disruption in the skin barrier.

The Health Technology Assessment systematic review of eczema treatments included a chapter on the evidence base for nonpharmacological interventions.³ This failed to identify any trials evaluating the use of water softeners for patients with eczema. The only trials of possible relevance were an inconclusive trial looking at the benefits of salt baths, and another that examined the use of biological vs. nonbiological washing powders. This search was updated in 2006 and no new references were found. As a result of this poor evidence base, the National Institute for Health Research in the U.K. put out a call for

primary research through its Health Technology Assessment programme. The protocol outlined in this paper describes the trial that was commissioned through this process.

The Softened Water Eczema Trial (SWET) study has two main objectives: (i) to assess whether the installation of an ion-exchange water softener can help to relieve the symptoms of eczema in children with moderate to severe eczema, and (ii) if so, to establish the likely cost and cost-effectiveness of the intervention.

Patients and methods

Design

SWET is a single-blind, parallel-group randomized controlled trial of 12 weeks duration, followed by a 4-week cross-over period (Fig. 1). Three hundred and ten children with moderate to severe eczema are being enrolled into the study for a period of 16 weeks. Participants are being enrolled over a period of 18–20 months. Recruitment started in April 2007.

The study will be analysed as a parallel-group study with the primary outcome assessed at 12 weeks. The final 4-week period includes exploratory analyses to explore tertiary outcomes. Specifically, these exploratory analyses provide further information on: (i) the speed of onset of benefit for the delayed treatment group, and (ii) how quickly benefits are lost once treatment is removed in the active treatment group. Further details are available on the trial's website (<http://www.swet-trial.co.uk/>).

Participants

Children aged 6 months to 16 years with eczema can be enrolled into the study. A diagnosis of eczema has been standardized using the U.K. working party's diagnostic criteria for eczema.⁴ The children must live in an area of hard water (minimum of 200 mg L⁻¹ of calcium carbonate) and have a home that is suitable for the installation of a water softener.

Children are excluded if they: (i) plan to be away from home for > 21 days in total during the 16-week study period; (ii) have taken systemic medication (e.g. ciclosporin, methotrexate) or have had ultraviolet treatment for their eczema within the last 3 months; (iii) have taken oral steroids within the last 4 weeks, or who have started a new treatment regimen for eczema within the last 4 weeks; or (iv) already have a water treatment device installed, including ion-exchange softeners, polyphosphate dosing units or physical conditioners.

Recruitment is taking place in both secondary and primary care in five recruiting centres in the U.K. All have predominantly hard water (although water in the Nottingham area is mixed). The five recruiting centres are: (i) Queen's Medical Centre, Nottingham; (ii) Barnet & Chase Farm Hospital, London; (iii) Addenbrooke's Hospital, Cambridge; (iv) The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight; and (v) Leicester Royal Infirmary, Leicester.

Approval has been sought to install units in the homes of Council/Housing Association tenants in order to be as inclusive as possible in recruiting participants into the trial.

Interventions

Ion-exchange water softening units are to be compared with usual care. Ion-exchange water softening units typically reduce the water hardness to practically zero.

All units are installed in the child's main residence and salt is supplied for the duration of the trial. A mains drinking water faucet is provided at the kitchen sink if desired.

The water softeners to be used in this trial have been supplied and paid for by a consortium of representatives from the water treatment industry. Their contribution is being co-ordinated through the U.K. Water Treatment Association. The units are encased in an unbranded box in order to prevent the possibility of commercial advantage to any particular company. Similarly, unbranded salt is being supplied for use during the trial.

Apart from having a unit installed in the home, participants continue with their normal eczema treatment in the usual way and are asked to bathe/wash their clothes according to their usual practice (although instructions are provided to reduce the amount of soap consumption). The units meet all necessary quality standards, and are installed by a trained water engineer according to British Water's code of practice. For a schematic diagram of a typical ion-exchange unit, see Figure 2.

Participants allocated to delayed installation are asked to continue their usual eczema care for 12 weeks, and receive a water softener between weeks 12 and 16 of the trial.

Treatment adherence/loss to follow-up

In order to confirm that the units are working correctly, participants send water samples to the research team once a week. Any samples with a reading of > 20 mg L⁻¹ calcium carbonate are referred back to the engineer for investigation.

	Study period = 16 weeks		
	0 to 12 weeks	12 to 16 weeks	
Group A	Usual eczema care + water softener installed (n = 155)	Unit removed	Option to purchase unit at reduced cost
Group B	Usual eczema care + delayed installation (n = 155)	Unit installed	

Fig 1. Study design.

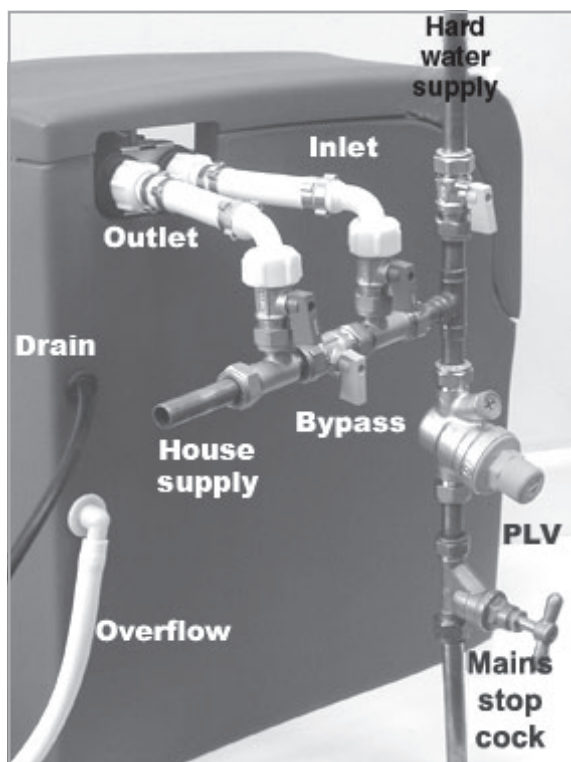


Fig 2. Typical ion-exchange water softening unit. PLV, pressure-limiting valve.

Participants are reminded of the importance of replenishing the salt supply by telephone at 8 weeks and a weekly reminder is included in the child's symptom diary.

If participants are away from the main residence for any reason, this information is recorded in their symptom diaries. Absence from the home will be included in a predictors of response model, and used as a measure of treatment adherence for the (secondary) per protocol analysis.

Based on pilot work and previous experience of eczema trials,⁵ it is anticipated that loss to follow-up will be < 15%. At the end of the study all participants will be offered the chance to purchase the units at a reduced cost (£446.50 inclusive of VAT, installation and warranty; this is approximately half the full retail price for the model provided).

Concomitant therapy

Participants are allowed to use their usual eczema treatments as prescribed. However, children are asked not to start any NEW treatments during the period of the study if medically possible. (See also exclusion criteria).

Starting and stopping treatment

Units are installed in the participants' homes as soon as possible after being randomized to active treatment (ideally within 10 working days).

If participants choose to withdraw from the study, any units that have been installed will be removed as soon as is practicably possible. Participants will be asked to complete an end of study questionnaire at this time and diaries will be collected.

Randomization

Participants are randomized using a web-based randomization service to immediate or delayed installation on a 1 : 1 basis. The randomization is stratified by age, disease severity [baseline Six Area, Six Sign Atopic Dermatitis⁶ (SASSAD) score ≥ 10 to ≤ 20 , or SASSAD score > 20] and recruiting centre. Access to the sequence is confined to the Nottingham Clinical Trials Support Unit Data Manager. The allocation group is indicated to the Trial Manager only after baseline data have been irrevocably entered into the randomization programme. The sequence of treatment allocations will be concealed until interventions have all been assigned and recruitment, data collection and analysis are complete.

The research nurses are blinded to treatment allocation throughout the study period. If any of the nurses feel that this blinding may have been compromised, details are logged centrally with the Trial Manager. Integrity of information bias will be assessed using clinical photographs of a target lesion. These images are taken at each assessment visit and graded remotely by two independent dermatologists, who will not be aware of the study design, or of the assessment visit at which the image was taken.

Primary outcome

The primary outcome is the difference between the softened water and delayed intervention groups with regard to mean change in disease severity (SASSAD) at 12 weeks compared with baseline. SASSAD is an objective severity scale that is completed by the research nurse during follow-up appointments. This scale does not require input from the participant or their family in assessing disease severity.

Secondary outcomes

Secondary outcomes include the following:

- Difference between the groups in the proportion of time spent moving during the night. Movement will be captured for periods of 1 week at weeks 1 and 12, and will be measured using accelerometers (ActiwatchTM). These units are worn by the child in the same way as a wrist watch. This outcome has been included as an objective surrogate for sleep loss and itchiness (two of the defining features of eczema).
- Difference in proportion of children who report either good or excellent improvement in eczema severity at 12 weeks (using a five-point Likert scale).
- Difference in the amount of topical corticosteroid/calcineurin inhibitors used during the 12-week study period (captured by weighing the medication).

- Difference in Patient Oriented Eczema Measure⁷ (POEM). This scale is a well validated tool that has been developed to capture symptoms of importance to patients (rather than objective signs that are used in traditional severity scales, such as SASSAD).
- Difference in the number of totally controlled weeks (TCW) and well controlled weeks (WCW) based on the number of days with eczema symptoms and the number of days that topical treatment is applied. This outcome is based on a recent systematic review looking at ways of assessing long-term control for chronic conditions such as eczema, asthma and rheumatoid arthritis.⁸ The terms TCW and WCW have been adopted for use by researchers in the field of asthma and appear to be a useful and intuitive means of capturing disease activity over time.
- Difference in the mean change in the Dermatitis Family Impact (DFI) questionnaire at 12 weeks.⁹
- Mean change in health-related quality of life at 12 weeks. This will be captured using a generic measure of health utility (the children's version of the EQ-5D for children aged 7 years and over, or the proxy version of the EQ-5D for children aged 3–6 years).¹⁰

Further exploratory analyses

In addition to the main outcomes listed above, further exploratory analyses are planned as follows:

- Difference in mean change in disease severity (SASSAD) at 4 weeks compared with baseline. This outcome is included in order to capture speed of onset of benefit.
- Further within-person analyses will be conducted comparing outcomes collected during the final 4-week period (12–16 weeks) with those collected during the initial 4 weeks of the study (0–4 weeks). Data collected for the active treatment group will provide an indication of the likely carry-over effect of this intervention, which will be useful in planning the design of future trials in this area. Data collected for the delayed treatment group will inform the analysis regarding speed of onset of improvement.
- Predictors of response model, including baseline factors.

Statistical analysis

Analyses have been planned in order to place emphasis on objective outcomes that are less likely to be influenced by the potential bias inherent in a single-blind study. Nevertheless, various additional tools are to be used that reflect more closely the disease process throughout the study period. Some of these are relatively objective indicators of disease activity (such as nocturnal movement and treatment application), while others reflect subjective concepts (such as self-reported symptoms in the POEM), in order to capture the many health-related dimensions affected by eczema.

The planned analyses should answer the following questions:

- Does exposure to softened water for 12 weeks improve the symptoms and severity of eczema, compared with standard care alone?

- Does softened water improve quality of life for patients and their carers?
- Are water softeners a cost-effective treatment for children with eczema?

In addition, tertiary analyses will explore the following parameters:

- How quickly the benefits of softened water become evident.
- How quickly the benefits of softened water are lost once treatment is stopped.
- What baseline factors best predict treatment success.

The main intention-to-treat analysis will be conducted at 12 weeks. An additional per protocol analysis will also be conducted for the primary outcome in order to test the proof of concept.

A subgroup analysis will be conducted based on the presence or absence of mutations on the filaggrin gene (collected using spit samples). Mutations on the filaggrin gene have been associated with dry skin and may therefore be a useful predictor of treatment response.^{11,12}

Sample size

Sample size estimates are based on pilot data (unpublished), and are supported by other published data relating to the use of SASSAD in patients recruited in secondary care.¹³ Based on a minimum clinically relevant difference of 20% in the change in SASSAD score between the two groups, and assuming a mean baseline SASSAD score of 20 with a standard deviation in change scores of 10, a sample size of 310 children will provide 90% power, with a significance level of 5% allowing for an attrition rate of 15%.

Cost-effectiveness

An economic evaluation will be undertaken alongside the clinical trial. The cost analysis will compare the overall and mean cost difference for the intervention vs. usual care, measuring resource use such as primary care contacts, medication prescribed, secondary care contacts and patient costs. Health and family resource use data will be measured using participant diaries. Resource use will be valued using published unit costs for a single price year (e.g. Curtis and Netten,¹⁴ BNF 54¹⁵ and NHS reference costs¹⁶), and patient reported estimates. The costs to the NHS and patient will be reported separately as well as in combination.

The primary measure of effectiveness for the cost-effectiveness analysis is the number of participants who show a $\geq 50\%$ improvement in SASSAD at 12 weeks compared with baseline, which will be used to present the incremental cost per 1% change in the number of participants showing a $\geq 50\%$ improvement in SASSAD. Secondary analyses will be conducted using continuous data from the SASSAD scale, the DFI scale and the generic measure of health utility as measured on the child version of the EQ-5D (for children aged 3–6 years, the proxy version will be used) to estimate the incremental

cost per quality-adjusted life year (QALY) over the trial period.

If nondominance occurs (that is if the intervention is found to be more costly and more effective or less costly and less effective) an incremental cost-effectiveness ratio will be produced for the trial period. Probabilistic sensitivity analysis will be undertaken to test the robustness of results in the face of any uncertainties or assumptions made in the analysis. Decision uncertainty will be presented graphically using cost-effectiveness acceptability curves (CEACs). However, as CEACs cannot be used to identify the optimal decision¹⁷ a cost-effectiveness acceptability frontier will be drawn to show the probability of the optimal intervention being cost-effective at different levels of willingness to pay (WTP) per QALY. An expected value of perfect information analysis will be undertaken to assess the value of undertaking further research in order to reduce the level of uncertainty surrounding the decision about whether water softener devices are optimal compared with standard care.

In addition to the cost-effectiveness analysis, contingent valuation (CV) methodology will be employed to measure parental WTP for the water softener device as a measure of benefit. CV methodology is now more widely used as a measure of benefit in the healthcare field.¹⁸ It is an important issue in the context of this study, as it is not clear at this stage who will, or should, pay for the device: the parent or the NHS. WTP will be ascertained pre-intervention at the recruitment visit to get an *ex-ante* hypothetical WTP, and again at week 12. The use of the water softener device will be free to participants (group A in weeks 0–12 and group B in weeks 12–16) during the study period. At the end of the study, all participants will get the opportunity to purchase the device that they used in the study at a fixed reduced price, thus giving us a partial measure of parental actual WTP. This will enable us to assess convergent validity by comparing the hypothetical values with the dichotomous variable of whether they actually paid for the device or not at the fixed price: few such opportunities exist in the healthcare context.

Study organization and funding

SWET is co-ordinated from the Centre of Evidence Based Dermatology at the University of Nottingham. It is an independent trial funded by the National Institute for Health Research Health Technology Assessment programme. The study has a Trial Steering Committee (including independent members as well as key investigators from the Trial Management Group). Service user involvement is co-ordinated through Mr David Potter, who is responsible for liaising with a panel of service users.

Support has also been given from a consortium of water softening companies who are providing the water softening units, the salt and water testing for the trial. These contributions are being co-ordinated through their trade association, U.K. Water Treatment Association. In addition, Dr Ian Pallett (from British Water) is a member of the Trial Steering

Committee and has played a key role during the development of the study protocol.

Summary

SWET addresses two key questions for the management of children with moderate or severe eczema. Namely, does the installation of an ion-exchange water softener improve the symptoms and associated morbidity of eczema? And if so, how cost-effective is the intervention? This is the first clinical trial in this important area and analysis is therefore planned on both an intention-to-treat basis (in order to explore treatment effectiveness) and on a per protocol basis (in order to explore the proof of concept).

This summary is based on version 4 of the study protocol, dated 2 January 2008 (ISRCT: 71423189). A full copy of the protocol is available on request.

Authors' contributions

This paper has been written by Kim Thomas and Tracey Sach. Hywel Williams (Chief Investigator), Ian Pollock, Tara Dean, Nigel Burrows, Ian Pallett, Andrew Nunn, Sarah Meredith and David Potter were co-applicants on the funding application to the National Institute for Health Research Health Technology Assessment programme. They have contributed to the design of the study and commented on the draft of the paper. All other investigators are assisting with the delivery of the trial and have commented on the draft of the paper.

Acknowledgments

This project is funded by the National Institute for Health Research Health Technology Assessment programme (project number HTA 05/16/01). We are grateful for the support of the water softening industry and for the assistance of the trade associations (U.K. Water Treatment Association and British Water) in co-ordinating this involvement in a way that prevents conflicts of interest for the research team. We are also grateful to our panel of service users who have advised on the design and conduct of the study to date.

Thanks also go to Dr Alan Irvine and Prof. Irwin McLean for their assistance in testing the saliva samples for mutations on the filaggrin gene.

Appendix

The SWET Trial Investigators are as follows: Trial Steering Committee: Dr David Paige (Independent Chair), Consultant Dermatologist, The Royal London Hospital, London; Prof. Hywel Williams (Chief Investigator), Consultant Dermatologist, Centre of Evidence Based Dermatology, University of Nottingham; Dr Ian Pollock (Principal Investigator), Consultant Paediatrician, Barnet & Chase Farm Hospital, London; Mr David Potter (Consumer Representative), Research Biochemist

(retired); Prof. Andrew Nunn (Lead Statistician), MRC Clinical Trials Unit, London; Dr Nerys Roberts (Independent Deputy Chair), Consultant Dermatologist, Chelsea & Westminster Hospital, London; Dr Ian Pallett (Water Industry Representative), British Water, London; Dr Karin Koller (Trial Manager), Centre of Evidence Based Dermatology, University of Nottingham; Trial Management Group: Prof. Hywel Williams (Chief Investigator), Centre of Evidence Based Dermatology, University of Nottingham; Dr Kim Thomas (Lead Applicant/Trial Advisor), Centre of Evidence Based Dermatology, University of Nottingham; Dr Sarah Meredith (Trial Advisor), MRC Clinical Trials Unit, London; Prof. Andrew Nunn (Lead Statistician), MRC Clinical Trials Unit, London; Dr Angela Crook (Trial Statistician), MRC Clinical Trials Unit, London; Dr Ian Pollock (Principal Investigator), Barnet & Chase Farm Hospital, London; Dr Nigel Burrows (Principal Investigator), Addenbrooke's Hospital, Cambridge; Prof. Tara Dean (Principal Investigator), St Mary's Hospital, Newport, Isle of Wight; Dr Robin Graham-Brown (Principal Investigator), University Hospitals of Leicester NHS Trust; Dr Tracey Sach (Health Economist), University of East Anglia; Mr Grant Audemard (Water Softener Industry Representative), Kinetico UK Ltd, Park Gate, Hampshire; Mr Tony Frost (Water Softener Industry Representative), Aqua Focus Ltd, Newport, Shropshire; Dr Karin Koller (Trial Manager), Centre of Evidence Based Dermatology, University of Nottingham; Mrs Jane Grundy (Research Nurse), St Mary's Hospital, Newport, Isle of Wight; Ms Rhiannon Medhurst (Research Nurse), Barnet & Chase Farm Hospital, London; Mrs Jane Devonshire (Research Nurse – March 2007 to October 2007), Addenbrooke's Hospital, Cambridge; Ms Rosalind Simmonds (Research Nurse – November 2007 to present), Addenbrooke's Hospital, Cambridge; Mrs Susan Davies-Jones (Research Nurse), QMC and University of Nottingham; Mr John Kyle (Engineers main contact, mainland), Kinetico UK Ltd, Park Gate, Hampshire; Mr John Bisset (Engineering Services Manager), Kinetico UK Ltd, Park Gate, Hampshire; Mr Robin Stevens (Engineers main contact, Isle of Wight), MG Heating, Newport, Isle of Wight.

References

- McNally NJ, Williams HC, Phillips DR et al. Atopic eczema and domestic water hardness. *Lancet* 1998; **352**:527–31.
- Miyake Y, Yokoyama T, Yura A et al. Ecological association of water hardness with prevalence of childhood atopic dermatitis in a Japanese urban area. *Environ Res* 2004; **94**:33–7.
- Hoare C, Li Wan Po A, Williams HC. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000; **4**:1–191.
- Williams HC, Burney PG, Hay RJ et al. The UK working party's diagnostic criteria for atopic dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol* 1994; **131**:383–96.
- Thomas KS, Armstrong S, Avery A et al. Randomised controlled trial of short bursts of a potent topical corticosteroid vs. prolonged use of a mild preparation for children with mild or moderate atopic eczema. *BMJ* 2002; **324**:768.
- Berth-Jones J. Six Area, Six Sign Atopic Dermatitis (SASSAD) severity score: a simple system for monitoring disease activity in atopic dermatitis. *Br J Dermatol* 1996; **135**:25–30.
- Charman CR, Venn AJ, Williams HC. The Patient-Oriented Eczema Measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol* 2004; **140**:1513–19.
- Langan SM, Thomas KS, Williams HC. What is meant by a 'flare' in atopic dermatitis? A systematic review and proposal. *Arch Dermatol* 2006; **142**:1190–6.
- Lawson V, Lewis-Jones MS, Finlay AY et al. The family impact of childhood atopic dermatitis: the Dermatitis Family Impact Questionnaire. *Br J Dermatol* 1998; **138**:107–13.
- Hennessy S, Kind P. Measuring health status in children: developing and testing a child-friendly version of EQ-5D. In: *EuroQol Scientific Meeting* (Kind P, Macran S, eds). York: Outcomes Research Group, Centre for Health Economics, University of York, 2002; 291–310.
- Palmer CNA, Irvine AD, Terron-Kwiatkowski A et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**:441–6.
- Sinclair C, O'Toole E, Leigh I et al. Filaggrin mutation is not a genetic risk factor for atopic dermatitis in the Bangladeshi population. *J Invest Dermatol* 2006; **126**:s40.
- Takwale A, Tan E, Agarwal S et al. Efficacy and tolerability of borage oil in adults and children with atopic eczema: randomised, double blind, placebo controlled, parallel group trial. *BMJ* 2003; **327**:1385.
- Curtis L, Netten A. *Unit Costs of Health and Social Care*. Canterbury: Personal Social Services Research Unit, 2007. Available at: <http://www.pssru.ac.uk/uc/uc2005contents.htm> (last accessed 4 June 2008).
- British National Formulary. *BNF 54*. London: BMJ Publishing Group and RPS Publishing, 2007.
- Department of Health. *NHS Reference Costs 2006–07*. London: Department of Health, 2007. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_062884 (last accessed 4 April 2008).
- Fenwick E, Claxton K, Sculpher MJ. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001; **10**:779–87.
- Olsen JA, Smith RD. Theory versus practice: a review of 'willingness-to-pay' in health and health care. *Health Econ* 2001; **10**:39–52.