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An economic evaluation of the randomized controlled trial of topical corticosteroid and home-based narrowband ultraviolet B for active and limited vitiligo (the HI-Light Vitiligo Trial)

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Summary

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Background Economic evidence for vitiligo treatments is absent.

Objectives To determine the cost-effectiveness of (i) handheld narrowband ultraviolet B (NB-UVB) and (ii) a combination of topical corticosteroid (TCS) and NB-UVB compared with TCS alone for localized vitiligo.

Methods Cost-effectiveness analysis alongside a pragmatic, three-arm, placebo-controlled randomized controlled trial with 9 months' treatment. In total 517 adults and children (aged ≥ 5 years) with active vitiligo affecting < 10% of skin were recruited from secondary care and the community and were randomized 1: 1: 1 to receive TCS, NB-UVB or both. Cost per successful treatment (measured on the Vitiligo Noticeability Scale) was estimated. Secondary cost–utility analyses measured quality-adjusted life-years using the EuroQol 5 Dimensions 5 Levels for those aged ≥ 11 years and the Child Health Utility 9D for those aged 5 to < 18 years. The trial was registered with number ISRCTN17160087 on 8 January 2015.

economic results. A full and detailed trial report will be published within the National Institute for Health Research journal and copyright retained by the Crown.

Results The mean $\pm$ SD cost per participant was £775 $\pm$ 83·7 for NB-UVB, £813 $\pm$ 111.4 for combination treatment and £600 $\pm$ 96·2 for TCS. In analyses adjusted for age and target patch location, the incremental difference in cost for combination treatment compared with TCS was £211 (95% confidence interval 188–235), corresponding to a risk difference of 10·9% (number needed to treat = 9). The incremental cost was £1932 per successful treatment. The incremental difference in cost for NB-UVB compared with TCS was £173 (95% confidence interval 151–196), with a risk difference of 5·2% (number needed to treat = 19). The incremental cost was £3336 per successful treatment.

Conclusions Combination treatment, compared with TCS alone, has a lower incremental cost per additional successful treatment than NB-UVB only. Combination treatment would be considered cost-effective if decision makers are willing to pay £1932 per additional treatment success.

What is already known about this topic?

- Vitiligo is a common skin condition with significant psychological impact.
- Topical corticosteroids (TCS) are standard care for vitiligo. Narrowband ultraviolet B (NB-UVB) is only available in secondary care as full-body treatment.
- Economic evidence for handheld NB-UVB in combination with TCS is absent.

What does this study add?

- Combination treatment, compared with TCS alone, has the lowest incremental cost per successful treatment. Whether this is considered cost-effective depends on decision makers' judgement on how much they are willing to pay to achieve a successful treatment.
- Generic utility instruments, such as the EuroQol 5 Dimensions 5 Levels, may not be appropriate for vitiligo studies due to high ceiling effects. Measurement of quality of life for this condition warrants further research.
- This study provides results that can be compared with those of new emerging vitiligo treatments.

A 2018 systematic review showed that the economic evidence for vitiligo treatment is virtually nonexistent.[1] One of two studies identified in this review estimated the annual direct cost of treating vitiligo in the USA to be $15 million for the price year 2004.[2] The other study demonstrated that 32·5% of people with vitiligo would be willing to make a one-off payment of €5000 for a cure (2006 price year),[3] allowing an estimate of the maximum potential for benefit should a 'cure' be found. Although these papers indicate the cost to an affected person and healthcare system, they do not provide evidence to inform resource allocation decisions. No papers were identified that undertook full economic evaluations (those that compare costs and benefits of two or more interventions)[4] of vitiligo treatments alongside clinical trials or as economic modelling. This paper reports the first full economic evaluation of treatment for localized, nonsegmental vitiligo, including the current standard treatment topical corticosteroids (TCS) and new treatment [home-based narrowband ultraviolet B (NB-UVB)], alone and in combination with TCS, with the aim of estimating the cost-effectiveness of these treatments for

the UK National Health Service (NHS). Additional explanations of the terms used in this paper are provided in Appendix S1 (see Supporting Information).

Materials and methods

This health economic evaluation estimated the within-trial cost-effectiveness of (i) active handheld NB-UVB compared with TCS (standard care) and (ii) the combination of active handheld NB-UVB plus TCS compared with TCS (standard care). Estimates were made in terms of cost per additional treatment success (henceforth referred to as treatment success) at the end of the treatment period (9 months) for the treatment of limited, nonsegmental vitiligo, using individual-level data collected within the trial. A treatment period of 9 months was chosen to reflect clinical practice, where clinical experience and clinical guidelines suggest that treatment should be initiated for a minimum of 3–4 months, but that treatment would normally be required for a longer period in order to achieve a clinically meaningful treatment response.

A secondary objective was to undertake cost–utility analyses for those aged ≥ 11 years using the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) and separately for participants aged < 18 years using the Child Health Utility 9D (CHU-9D). Typically, a cost–utility analysis would form the primary analysis as it enables decision makers to compare the cost-effectiveness of a range of interventions for different conditions on a common scale. As utility is measured differently in adults and children, a common cost–utility analysis was not possible, so a clinical outcome was used. Also, cost–utility instruments are considered less effective at capturing the psychological impact on quality of life, which is considered to be more important than physical impacts in vitiligo. A priori we were also sceptical that available generic utility instruments would capture the health-related quality-of-life aspects that people living with vitiligo experience.

The evaluation was undertaken in line with published guidelines for the economic evaluation of healthcare interventions.[4–8] A health economics analysis plan was written and approved before the trial database was locked. A full trial report will be available through the NIHR journal series,[9] and the clinical results paper is available in this journal.[10]

The trial was conducted in the UK NHS, which provides publicly funded healthcare that is largely free of charge at the point of use. Therefore, the analysis was primarily from an NHS perspective, in keeping with the National Institute for Health and Care Excellence reference case.[8] In a sensitivity analysis, out-of-pocket costs incurred by participants (or parents or guardians) are presented reflecting a personal perspective.

Resources use and costs

The primary analysis captured the intervention costs (including any side-effect costs) to the NHS and the participant's wider use of the NHS (including primary care visits; secondary care outpatient, inpatient and accident and emergency visits; and prescriptions) as a result of vitiligo. Participants' personal out-of-pocket expenses (for example, camouflage or makeup, suncream and sun care) incurred from vitiligo were also captured in a separate sensitivity analysis taking a broader perspective. Participant time burden for home treatment was not costed, but is reported elsewhere.[9,10]

Resource use data for the intervention phase were collected at 3, 6 and 9 months using information recorded by participants in daily diaries and collated by the researcher at follow-up visits. Resource use related to the intervention and side-effects was recorded in clinical reports forms. Further questionnaires collected resource use data at 12, 15, 18 and 21 months for the follow-up phase.

Intervention cost was estimated at the individual level. Participants randomized to NB-UVB alone were also given a placebo ointment while those in the TCS alone group received a dummy NB-UVB device. The dummy devices and placebo ointment were not costed.

Narrowband ultraviolet B device

The cost of the handheld device was estimated using the manufacturer's purchase price divided by an annuity factor (interest rate 3·5%, 5 years) to give an equivalent annual cost. The equivalent annual cost was divided by 12 months and multiplied by 9 to reflect the 9-month timeframe. The purchase prices of personal protective equipment (goggles and glasses) were included at full cost as these are unlikely to be as durable as the devices. Costs of the quality-assurance process for the devices were included. Device repair and replacement costs were not included in the analysis. Faulty devices were replaced in the study, although in practice some might be repaired. Time spent by investigators training participants on using the device was recorded and costed.

Topical corticosteroid

Participants in the TCS intervention group were supplied with two 90-g tubes of mometasone furoate 0·1% ointment (Elocon® 0·1% Ointment; Merck Sharp & Dohme, Hertford, UK). TCS costs were sourced from the Prescription Cost Analysis for 2017[11] and had the National Average Discount Percentage of 7·37% deducted.[12] The professional pharmacist fee of £1·29 was added, assuming that a single tube would be prescribed at any one time. Additional ointment requested by participants was recorded and costed.

Trial participants in all treatment groups were offered appointments with a dermatologist at 0, 3, 6 and 9 months, as we assumed in the analysis that this would happen in routine care. These were costed even though they cancel each other out between treatment groups. Side-effects requiring medical attention from either treatment were recorded as one type of unscheduled contact. Unit costs were identified from published sources (Table 1) and were valued in UK pound sterling 2017.[13,14] Patient-reported estimates of out-of-pocket costs resulting from vitiligo were captured.

Clinical outcome: treatment success

The primary clinical outcome measure in the HI-Light trial was participant-reported treatment success, measured at 9 months, using the Vitiligo Noticeability Scale.[15] Treatment success, a binary outcome, was defined by whether the participant responded that their target vitiligo patch was 'a lot less noticeable' or 'no longer noticeable' in response to the question: 'Compared with the start of the study, how noticeable is the vitiligo now?'. Because no previous studies have compared the treatments or outcome used in this study, we used a single study-based estimate of effectiveness in the cost-effectiveness analysis.

Quality of life

Quality-adjusted life-years (QALYs) were estimated in secondary analyses using utility scores obtained from the CHU-

Table 1 Unit costs (UK £ sterling, 2017)

Resource item	Unit cost	Source (notes)
Intervention resources		
Annuity factor	4·515 based on r = 3·5% and n = 5	Drummond *et al.*[4]
Purchase price	149·00	Dermfix Ltd website
Annuitized 9-month purchase price[a]	24·75	Purchase price divided by annuity factor to give equivalent annual cost (EAC). EAC divided by 12 months and multiplied by 9
Annuitized 9-month quality assurance (£17·83 multiplied by annuity factor)	2·96	Quality assurance: Medical Physics, Nottingham University Hospitals
Glasses (per set)	15·00	Dermfix Ltd website
Goggles (per set)	7·00	Dermfix Ltd website
TCS (per 90-g tube of mometasone furoate 0·1%)	12·13	Health and Social Care Information Centre prescription cost analysis[11]
Investigator face-to-face and telephone support (per minute; assumed band 7, £54 per hour)	0·90	PSSRU 2017[13]
Dermatologist face-to-face first appointment consultant led	159·00	NHS Schedule of Reference Costs[14]
Dermatologist face-to-face follow-up appointment consultant led	129·00	NHS Schedule of Reference Costs[14]
Dermatologist telephone appointment consultant led	100·00	NHS Schedule of Reference Costs[14]
Training time (per minute; assumed band 7, £54 per hour)	0·90	PSSRU 2017[13]
Primary care resources (per visit)		
General practitioner	37·00	PSSRU 2017[13]
Practice nurse	10·85	PSSRU 2017[13]
Pharmacist (assumed to be a community pharmacist)	11·11	PSSRU 2017[13]
Hospital doctor	53·33	PSSRU 2017[13]
Hospital nurse	15·00	PSSRU 2017[13]
Therapist	27·00	PSSRU 2017[13]
Other (reported by participants)	Range from 15·00 to 86·00	PSSRU 2017[13] and NHS Schedule of Reference Costs[14]
Other resources		
Medication (various, NIC per item less NADP plus professional fee)	Range from 3·37 to 36·92	PCA 2017[11]
Participant and family out-of-pocket costs	Various	Estimates reported by participants

NADP, National Average Discount Percentage; NIC, net ingredient cost; PSSRU, Personal Social Services Research Unit; TCS, topical corticosteroids.

9D in the analysis focused on children aged < 18 years,[16–18] and the EQ-5D-5L instrument for participants aged ≥ 11 years,[19] For participants aged 5–6 years, the CHU-9D was completed by parental proxy. For all other ages these instruments were self-completed. We chose to use just one version of the EQ-5D-5L in the study for consistency. We chose the CHU-9D for the youngest participants because the EQ-5D-Y (youth) does not currently have a UK valuation set.

Utility measurements were collected in clinic at baseline and 9 and 21 months to reflect the likely timeframe for observing a clinically meaningful treatment response and in order to observe whether any response found was sustained in the longer term. In the cost–utility analysis, quality-of-life instrument responses were converted to utility scores using the EQ-5D-5L crosswalk[20] UK preference weights in line with current recommendations.[21,22] The CHU-9D was valued using the UK value set.[16] Following this, the utility values were used to calculate QALYs generated over the trial treatment period of 9 months, using both linear interpolation and area-under-the-curve analysis with baseline adjustment.[23]

Economic analysis

The economic primary analysis was performed on the full analysis set. In line with the primary statistical analysis,[10] multiple imputation was used to account for missing primary outcome data at 9 months. Cost analyses employed multiple imputation with chained equations using MI impute in Stata (StataCorp, College Station, TX, USA), generating 60 (m = 60) datasets using predictive mean matching and separately by treatment allocation as reported by Faria *et al.*[24] Given the 9-month time horizon, costs and benefits were not discounted.

Mean ± SD resource use and cost per participant were estimated for each randomized group. The mean difference with 95% confidence interval (CI) in resource use and cost between arms (NB-UVB vs. TCS and combination treatment vs. with TCS) is presented. Costs and QALYs were adjusted for age and location of target patch, as well as baseline utility, using seemingly unrelated regression.[25]

Nonparametric bootstrapping was used to determine sampling uncertainty surrounding the mean incremental cost-effectiveness ratios by generating

10 000 estimates of incremental costs and benefits. These estimates were used to produce cost-effectiveness acceptability curves to show the probability that each intervention arm is cost-effective at different values of willingness to pay.

Other than preplanned secondary analysis based on the different utility instruments used (EQ-5D-5L and CHU-9D), no subgroup analyses were undertaken. The secondary outcome for the economic evaluation was QALYs per participant over 9 months. The mean ± SD utility and mean ± SD QALYs per participant per randomized group were estimated, as was the mean difference (95% CI) in QALYs between arms (NB-UVB vs. TCS, and combination treatment vs. TCS) adjusted for age and location of target patch. In secondary analyses, the reported economic analysis used a cost-effectiveness threshold of £20 000 per QALY.[8] All analyses were conducted in Stata MP4 version 15.

Sensitivity analyses were undertaken to explore key uncertainties including (i) comparing multiple-imputation analysis to a complete-case analysis, (ii) varying NB-UVB device costs (zero and double the price in the primary analysis), (iii) a wider cost perspective including vitiligo out-of-pocket costs, (iv) limiting analysis to participants with good adherence (defined as > 75% adherence), and (v) extending the time horizon to 21 months to include the 12-month follow-up period.

It was expected that the majority of costs and benefits would be captured in the treatment period such that a priori it was not considered necessary to develop a decision-analytical model for a longer timeframe. This proved appropriate, as quality-of-life scores were similar between treatment arms at 21 months.[10]

Data sharing

Anonymized patient-level data are available from Dr Jonathan Batchelor (jonathan.batchelor@nottingham.ac.uk) upon reasonable request.

Results

The baseline characteristics of the participants included in the cost-effectiveness analysis are described in Thomas *et al.*[10] With imputation, 517 participants were included (398 adults, 119 children; 173 TCS, 169 NB-UVB and 175 combined treatment).

Intervention costs

The mean drug and training costs and numbers of devices, goggles, glasses, dermatology appointments and unscheduled visits or telephone appointments by group are reported in Table 2 and the mean costs in Table 3. The mean cost of the intervention per participant was £583 ± 29·6 for TCS (standard care), £753 ± 59·2 for NB-UVB and £792 ± 94·6 for combination treatment. Details of the time and cost of quality-assurance processes are shown in Table S1 (see Supporting Information).

The training time was a mean of 73·1 min for NB-UVB and 69·2 min for combination treatment, noting that all participants received both a device and ointment (dummy devices and placebo ointment were not costed).

Wider resource use and costs

Wider healthcare resource use (primary care, secondary care and medicines) for vitiligo beyond those required for the intervention were not significantly different between groups (Table 2). Patients with vitiligo reported low NHS healthcare usage. Table 3 displays the mean costs per participant by treatment group using available case data. The overall mean cost per participant for NB-UVB was £775 ± 83·7, compared with £600 ± 96·2 TCS – an unadjusted mean difference in cost of £175 (95% CI 153–197). Combination treatment had overall mean costs per participant of £813 ± 111; compared with TCS this gave an unadjusted mean difference of £213 (95% CI 188–238) per participant. These figures suggest that the costs of the interventions were not offset by reductions in wider healthcare resource use related to vitiligo.

Primary economic analysis

Cost-effectiveness analysis of narrowband ultraviolet B compared with topical corticosteroid (standard care)

The adjusted incremental difference in cost was £173 (95% CI 151–196). The adjusted risk difference for NB-UVB compared with TCS was 5·2%. This equates to a number needed to treat of 19; in other words, 19 participants would need to be treated for one of them to gain treatment success. The adjusted incremental cost was £3336 per additional successful treatment, which was estimated by dividing the adjusted incremental difference in cost, £173, by the adjusted risk difference, 0·052.

Figure 1(a) shows the probability that NB-UVB is cost-effective at different possible levels of willingness to pay for an additional treatment success; probability increases as willingness to pay increases. Figure 1(a) shows considerable uncertainty surrounding the decision as to whether NB-UVB, compared with TCS, represents value for money, as there is always at least 40% probability of making the wrong decision if choosing to fund NB-UVB alone below a threshold value of willingness to pay of £10 000 per additional treatment success.

Cost-effectiveness analysis of combination treatment compared with topical corticosteroid (standard care)

The adjusted incremental difference in cost was £211 (95% CI 188–235). The adjusted risk difference for combination treatment compared with TCS was 10·9%. This equates to a number needed to treat of 9. The adjusted incremental cost was £1932 per additional successful treatment.

Figure 1(b) shows the probability that combination treatment is cost-effective at different possible levels of willingness

Table 2 Mean resource use according to intervention arm over the 9-month treatment phase for all participants (based on available data)

	TCS (standard care) (n = 173), mean ± SD (n)	NB-UVB (n = 169), mean ± SD (n)	Difference (NB-UVB minus TCS), mean (95% CI)	Combination treatment (n = 175), mean ± SD (n)	Difference (combination minus TCS), mean (95% CI)
Intervention					
NB-UVB intervention[a]	0·00 ± 0·00 (173)	1·08 ± 0·30 (169)	1·08 (1·04 to 1·13)	1·07 ± 0·30 (175)	1·07 (1·03 to 1·12)
Glasses[b]	0·00 ± 0·00 (173)	1·41 ± 0·58 (169)	1·41 (1·33 to 1·50)	1·50 ± 0·56 (175)	1·50 (1·41 to 1·58)
Goggles[b]	0·00 ± 0·00 (173)	0·46 ± 0·60 (169)	0·46 (0·37 to 0·54)	0·40 ± 0·56 (175)	0·40 (0·32 to 0·48)
TCS	2·15 ± 0·55 (173)	0·00 ± 0·00 (169)	−2·15 (−2·23 to −2·07)	2·12 ± 0·49 (175)	−0·03 (−0·14 to 0·08)
Training time (min)	0·00 ± 0·00 (173)	73·1 ± 40·5 (169)	73·1 (67·0 to 79·1)	69·2 ± 34·5 (175)	69·2 (64·0 to 74·3)
Dermatologist time (clinic + telephone)	4·00 ± 0·00 (173)	4·00 ± 0·00 (169)	0·00 (0·00 to 0·00)	4·00 ± 0·00 (175)	4·00 (4·00 to 4·00)
Nurse time (clinic + telephone)	0·00 ± 0·00 (173)	2·00 ± 0·00 (169)	2·00 (2·00 to 2·00)	2·00 ± 0·00 (175)	2·00 (2·00 to 2·00)
Unscheduled clinic with nurse	0·01 ± 0·11 (173)	0·03 ± 0·20 (169)	0·02 (−0·02 to 0·05)	0·13 ± 0·51 (175)	0·12 (0·04 to 0·20)
Unscheduled telephone with nurse	0·39 ± 0·87 (173)	0·46 ± 0·95 (169)	0·07 (−0·13 to 0·26)	0·66 ± 1·29 (175)	0·28 (0·04 to 0·51)
Unscheduled clinic with dermatologist	0·02 ± 0·13 (173)	0·04 ± 0·20 (169)	0·02 (−0·01 to 0·06)	0·10 ± 0·43 (175)	0·09 (0·02 to 0·15)
Unscheduled telephone with dermatologist	0·02 ± 0·17 (173)	0·03 ± 0·20 (169)	0·01 (−0·03 to 0·05)	0·05 ± 0·27 (175)	0·03 (−0·01 to 0·08)
Primary care and community					
Number	0·12 ± 0·44 (136)	0·17 ± 0·64 (132)	0·06 (−0·07 to 0·19)	0·12 ± 0·55 (142)	0·002 (−0·12 to 0·12)
Secondary care					
Number	0·48 ± 4·47 (136)	0·20 ± 0·61 (132)	−0·28 (−1·05 to 0·49)	0·20 ± 0·63 (142)	−0·28 (−1·03 to 0·46)
Other					
Medication	0·12 ± 0·50 (138)	0·08 ± 0·35 (133)	−0·04 (−0·14 to 0·06)	0·09 ± 0·34 (141)	−0·03 (−0·13 to 0·07)
Out-of-pocket purchases	0·40 ± 1·44 (141)	0·28 ± 0·88 (137)	−0·12 (−0·40 to 0·16)	0·31 ± 1·27 (144)	−0·09 (−0·41 to 0·23)

CI, confidence interval; NB-UVB, narrowband ultraviolet B; TCS, topical corticosteroid. [a]Includes the number of NB-UVB devices only. [b]Participants could choose to have more than one set, for instance if they needed a parent or partner to help them deliver the treatment.

to pay for an additional treatment success. It shows that combination treatment is likely to be cost-effective if decision makers are willing to pay more than £3000 per additional treatment success, as the probability of making the wrong decision is < 50%.

Sensitivity analyses exploring key uncertainties in the economic evaluation are summarized in Table S2 (see Supporting Information). Limiting analysis to only adherent participants made the most difference to the incremental cost-effectiveness ratio (£1151 for combination treatment compared with TCS, and £1394 for NB-UVB compared with TCS). Those who were adherent to treatment were more likely to be cost-effective to treat.

Secondary economic analysis

In total 248 (55%) trial participants reported having no problems on any of the five domains of the EQ-5D-5L at baseline,

suggesting that over half of the sample started the study in perfect health as defined by EQ-5D-5L. To put this value into perspective, in a general population sample from England the number of participants reporting no limitations on any dimension of the EQ-5D-5L was 43·9%.[26] Thus, the ceiling effect in this study can be considered large and of an order such as to limit the discriminatory power of the instrument for this patient population. Similar levels of ceiling effect were observed at subsequent follow-up. Similarly, for the CHU-9D, 30% of participants aged < 18 years had no problems according to any of the nine dimensions on the CHU-9D at baseline. Anxiety and depression on the EQ-5D-5L, and worry, tiredness and sleeping on the CHU-9D were the domains for which problems were reported most commonly. No floor effect was observed at any timepoint on either instrument.

As these high ceiling ratios suggest that these instruments are unlikely to be able to detect change, we report the

Table 3 Mean costs and outcomes according to intervention arm over the 9-month treatment phase (UK £ Sterling, 2017) for all participants (based on available data)

	TCS (standard care) (n = 173), mean ± SD (n)	NB-UVB (n = 169), mean ± SD (n)	Mean difference (NB-UVB minus TCS) (95% CI)	Combination treatment (n = 175), mean ± SD (n)	Mean difference (combination minus TCS) (95% CI)
Intervention					
NB-UVB device	0·00 ± 0·00 (173)	24·8 ± 0·00 (169)	24·8 (24·8 to 24·8)	24·8 ± 0·00 (175)	24·8 (24·8 to 24·8)
Quality assurance for device	0·00 ± 0·00 (173)	2·96 ± 0·00 (169)	2·96 (2·96 to 2·96)	2·96 ± 0·00 (175)	2·96 (2·96 to 2·96)
Glasses	0·00 ± 0·00 (173)	21·2 ± 8·74 (169)	21·2 (19·9 to 22·5)	22·5 ± 8·34 (175)	22·5 (21·2 to 23·7)
Goggles	0·00 ± 0·00 (173)	3·19 ± 4·18 (169)	3·19 (2·56 to 3·81)	2·80 ± 3·90 (175)	2·80 (2·22 to 3·38)
TCS	26·1 ± 6·67 (173)	0·00 ± 0·00 (169)	−26·1 (−27·1 to − 25·1)	25·7 ± 5·99 (175)	−0·37 (−1·70 to 0·97)
Training time	0·00 ± 0·00 (173)	65·8 ± 36·4 (169)	65·8 (60·3 to 71·2)	62·3 ± 31 (175)	62·3 (57·6 to 66·9)
Dermatologist (clinic + telephone)	546 ± 0·00 (173)	546 ± 0·00 (169)	0·00 (0·00 to 0·00)	546 ± 0·00 (175)	546 (546 to 546)
Nurse (clinic + telephone)	0·00 ± 0·00 (173)	72·0 ± 0·00 (169)	72·0 (72·0 to 72·0)	72·0 ± 0·00 (175)	72·0 (72·0 to 72·0)
Unscheduled clinic with nurse	0·21 ± 1·93 (173)	0·53 ± 3·64 (169)	0·32 (−0·29 to 0·94)	2·41 ± 9·53 (175)	2·20 (0·75 to 3·66)
Unscheduled telephone with nurse	7·16 ± 16·30 (173)	8·34 ± 17·5 (169)	1·19 (−2·41 to 4·79)	12·3 ± 23·9 (175)	5·14 (0·82 to 9·46)
Unscheduled clinic with dermatologist	2·24 ± 16·89 (173)	5·34 ± 25·8 (169)	3·11 (−1·52 to 7·73)	13·3 ± 55·5 (175)	11·0 (2·37 to 19·7)
Unscheduled telephone with dermatologist	1·73 ± 16·96 (173)	2·96 ± 20·2 (169)	1·22 (−2·74 to 5·19)	5·14 ± 26·8 (175)	3·41 (−1·33 to 8·15)
Total cost of intervention	583 ± 29·6 (173)	753 ± 59·2 (169)	170 (159·7 to 180)	792 ± 94·6 (175)	209 (194 to 223)
Primary care and community					
Cost	3·90 ± 15·2 (136)	5·90 ± 22·2 (132)	2·00 (−2·56 to 6·57)	2·84 ± 14·1 (142)	−1·06 (−4·52 to 2·40)
Secondary care					
Cost	11·1 ± 77·1 (136)	9·30 ± 30·1 (132)	−1·74 (−15·9 to 12·4)	8·52 ± 26·9 (142)	−2·53 (−16·1 to 11·0)
Other					
Medication	2·48 ± 10·5 (138)	1·49 ± 7·06 (133)	−0·99 (−3·14 to 1·16)	1·20 ± 6·09 (140)	−1·28 (−3·30 to 0·75)
Total mean cost per participant	600 ± 96·2 (132)	775 ± 83·7 (131)	175 (153 to 197)	813 ± 111 (136)	213 (188 to 238)
Out-of-pocket costs	14·4 ± 96·8 (141)	4·94 ± 20·1 (137)	−9·49 (−26·1 to 7·12)	6·62 ± 28·5 (144)	−7·81 (−24·4 to 8·75)
Primary outcome					
VNS, n/N (%)[a]	20/119 (16·8)	27/123 (22·0)	7 (5·1)[b]	34/128 (26·6)	14 (9·8)[b]

[a]The number of participants who reported treatment success (on the Vitiligo Noticeability Scale: a lot less noticeable or no longer noticeable) at 9 months divided by the number of participants with primary outcome recorded at 9 months. [b]Between-group difference is the number of participants experiencing a treatment success (between-group risk difference percentage).

mean utility estimates in Tables S3 and S4 and the cost–utility analyses in Table S5 (see Supporting Information). With this limitation in mind, both NB-UVB and combination treatment compared with TCS (standard care) had cost–utility ratios within accepted thresholds (< £20 000 per QALY) for the sample aged ≥ 11 years (NB-UVB was more superior to TCS than combination treatment was vs. TCS, in contrast to the cost-effectiveness analysis). Neither treatment was cost-effective in the analyses of those participants aged < 18 years, but this may reflect the small sample size (n = 119).

Discussion

We present the first full economic evaluation of treatments for vitiligo using the standard care TCS as the comparator. The additional cost of the combination treatment was not offset by NHS cost savings but did result in significant treatment success over the 9-month treatment period. This benefit could be gained if decision makers were willing to pay more than the adjusted incremental cost of £1932 per additional successful treatment. NB-UVB was less costly than combination treatment but also less effective, such that the incremental cost per
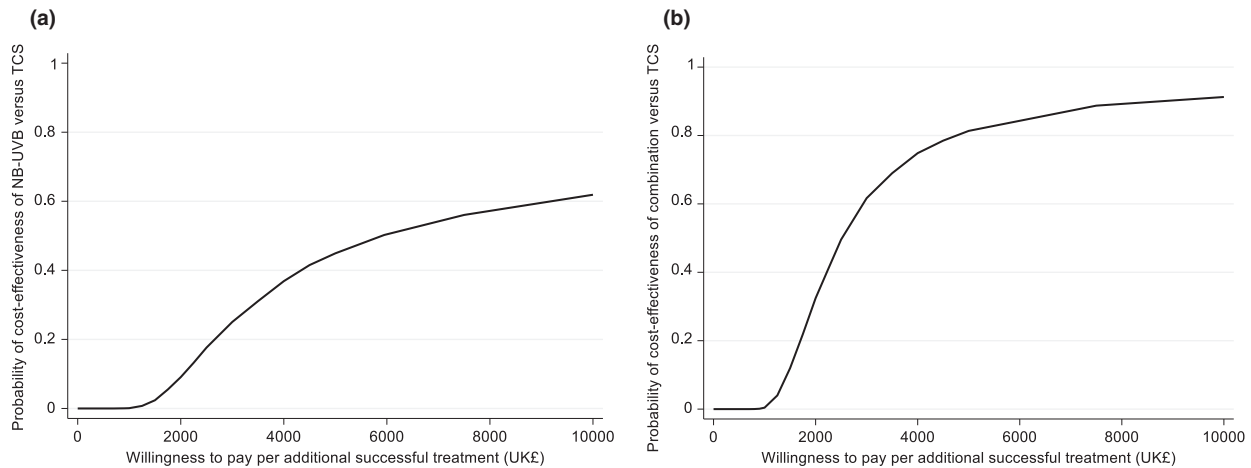
Figure 1 Cost-effectiveness acceptability curves. (a) Narrowband ultraviolet B (NB-UVB) vs. topical corticosteroid (TCS); (b) combination NB-UVB + TCS vs. TCS.

successful treatment was higher than for combination treatment, suggesting that the NHS would get better value for money from combination treatment than NB-UVB therapy alone. There is currently no evidence to indicate how much a decision maker would be willing to pay for an additional treatment success as defined in this study. Should the decision makers' willingness to pay per additional treatment success be low, then uncertainty surrounding the decision to fund combination treatment is high. Treatment options are limited for vitiligo and existing treatments are used little in the NHS, which may be due to treatments not being offered rather than absence of need.[27]

Cost-effectiveness analysis was undertaken as the primary analysis because it enabled us to analyse all participants together, irrespective of age. We had a prior belief that generic utility instruments may not fully capture the health-related quality-of-life impairment of people living with vitiligo. This was supported by high ceiling effects on the EQ-5D-5L and CHU-9D at baseline, such that there was no capacity to measure any gain using these instruments for many participants. The cost–utility analysis gave different results from the clinical and cost-effectiveness results, in that NB-UVB appeared more cost-effective than combination treatment, compared with TCS, for those aged ≥ 11 years.

There was also a difference in results between the cost–utility analyses undertaken by age; the new interventions were estimated as cost-effective in those aged ≥ 11 years but not in those aged < 18 years. This could reflect the different utility instrument used, but more likely reflects the small sample size of the group aged < 18 years and the fact that there was a lot of uncertainty around the QALYs gained, as the gain between groups was very close to zero in all comparisons. Therefore, more weight should be attached to the clinical effectiveness results and further work to explore the validity of the EQ-5D-5L and CHU-9D in this patient group is warranted, given the high ceiling effect observed in this study. It may be that a disease-specific utility instrument needs to be developed for vitiligo.

Sensitivity analyses suggested that a wider perspective, the cost of the NB-UVB device, and a method of dealing with missing data did not change the conclusions reached. Incremental cost per treatment success was lowest for those with greatest adherence.

New treatments such as Janus kinase inhibitors are being developed for vitiligo and are likely to be costly. The relatively low cost of the interventions assessed in this trial may make them affordable when resources are limited. The trial has yielded useful cost-effectiveness data, which can be used for future comparisons with novel treatments.

A strength of the study was that the HI-Light trial was a large, pragmatic trial of home interventions for people with active, limited vitiligo that controlled for common causes of bias. Retention throughout the trial was challenging, and the treatments placed considerable time burden on participants. Because < 50% responded to secondary outcomes at 21 months, a longer-term economic evaluation to 21 months was not undertaken, which is a limitation of the present study. However, given that treatment effects beyond the 9-month period were not sustained one can assume that the cost-effectiveness of the interventions would likely decline over time if treatments were not continued.

In conclusion, combination treatment compared with TCS alone has a lower incremental cost per successful treatment than NB-UVB vs. TCS, but whether this is considered cost-effective will depend on how much healthcare decision makers are willing to pay to achieve a successful treatment. The fact that vitiligo has few treatment options available, and the likely high cost of newer treatments being developed, may influence these decisions.

Acknowledgments

References

1 McManus E, Sach T, Levell NJ. Are vitiligo treatments cost-effective? A systematic review. *Br J Dermatol* 2018; **178**:e57–8.

2 Bickers DR, Lim HW, Margolis D *et al.* The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol* 2006; **55**:490–500.

3 Radtke MA, Schafer I, Gajur A *et al.* Willingness-to-pay and quality of life in patients with vitiligo. *Br J Dermatol* 2009; **161**:134–9.

4 Drummond MF, Sculpher MJ, Claxton K *et al. Methods for the Economic Evaluation of Health Care Programmes*, 4th edn. Oxford: Oxford University Press, 2015.

5 Husereau D, Drummond M, Petrou S *et al.* Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Cost Eff Resour Alloc* 2013; **11**:6.

6 Ramsey SD, Willke RJ, Glick H *et al.* Cost-effectiveness analysis alongside clinical trials II – an ISPOR Good Research Practices Task Force report. *Value Health* 2015; **18**:161–72.

7 Glick HADJ, Sonnad SS, Polsky D. *Economic Evaluation in Clinical Trials (Handbooks in Health Economic Evaluation)*, 2nd edn. Oxford: Oxford University Press, 2014.

8 National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Available at: https://www.nice.org.uk/process/pmg9/chapter/foreword (last accessed 6 October 2020).

9 National Institute for Health Research. Home Interventions and Light therapy for the treatment of vitiligo (HI-Light Vitiligo Trial). Available at: https://www.journalslibrary.nihr.ac.uk/programmes/hta/122402/# (last accessed 7 October 2020).

10 Thomas K, Batchelor J, Akram P *et al.* Randomized controlled trial of topical corticosteroid and home-based narrowband ultraviolet B for active and limited vitiligo: results of the HI-Light Vitiligo Trial. *Br J Dermatol* 2020. https://doi.org/10.1111/bjd.19592.

11 Health and Social Care Information Centre. Prescription Cost Analysis, England. Available at: https://data.gov.uk/dataset/prescription-cost-analysis-england (last accessed 6 October 2020).

12 National Health Service. Financial forecasting. Available at: https://www.nhsbsa.nhs.uk/prescription-data/understanding-our-data/financial-forecasting (last accessed 6 October 2020).

13 Curtis L, Burns A. Unit costs of health and social care 2017. Available at: http://www.pssru.ac.uk/project-pages/unit-costs (last accessed 6 October 2020).

14 NHS Improvement. NHS Schedule of Reference Costs 2017–2018. Available at: https://improvement.nhs.uk/resources/reference-costs (last accessed 6 October 2020).

15 Batchelor JM, Tan W, Tour S *et al.* Validation of the Vitiligo Noticeability Scale: a patient-reported outcome measure of vitiligo treatment success. *Br J Dermatol* 2016; **174**:386–94.

16 Stevens K. Valuation of the Child Health Utility 9D Index. *Pharmacoeconomics* 2012; **30**:729–47.

17 Stevens KJ. Assessing the performance of a new generic measure of health related quality of life for children and refining it for use in health state valuation. *Appl Health Econ Health Policy* 2010; **8**:157–69.

18 Herdman M, Gudex C, Lloyd A *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20**:1727–36.

19 EuroQol. EQ-5D-Y User Guide. Available at: https://euroqol.org/wp-content/uploads/2020/09/EQ-5D-Y-User-Guide_version-2.0.pdf (last accessed 6 October 2020).

20 van Hout B, Janssen MF, Feng YS *et al.* Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012; **15**:708–15.

21 Devlin N, Shah KK, Feng Y *et al.* Valuing health-related quality of life: an EQ-5D-5L value set for England. *Health Econ* 2018; **27**:7–22.

22 National Institute for Health and Care Excellence. Position statement on the use of the EQ-5D-5L value set for England. Available at: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l (accessed 7 October 2020).

23 Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005; **14**:487–96.

24 Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *Pharmacoeconomics* 2014; **32**:1157–70.

25 Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Econ* 2004; **13**:461–75.

26 Thompson AJ, Turner AJ. A comparison of the EQ-5D-3L and EQ-5D-5L. *Pharmacoeconomics* 2020; **38**:575–91.

27 Teasdale E, Muller I, Sani AA *et al.* Views and experiences of seeking information and help for vitiligo: a qualitative study of written accounts. *BMJ Open* 2018; **8**:e018652.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Supplementary index of definitions.
Table S1 Quality-assurance process (time and costs) for narrowband ultraviolet B devices.
Table S2 Summary of sensitivity analyses (adjusted results).
Table S3 Mean utility estimates for the EuroQol 5 Dimensions 5 Levels (participants aged ≥ 11 years).
Table S4 Mean utility estimates for the Child Health Utility 9D (participants aged < 18 years).
Table S5 Cost–utility analyses.
Appendix S2 Contributors to the study.