An economic evaluation of the randomised controlled trial of topical corticosteroid and home-based narrowband UVB for active and limited vitiligo (The HI-Light Trial)

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This paper represents a summary of the economic results. A full and detailed trial report will be published within the NIHR Journal and copyright retained by the Crown.

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What's already known about this topic?

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

What does this study add?

- Combination treatment, compared to 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 EQ-5D-5L, 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 new emerging vitiligo treatments.

Summary (240 words)

Background: Economic evidence for vitiligo treatments is absent.

Objective: To determine the cost-effectiveness of (a) hand-held narrowband-UVB (NB-UVB) and (b) combination of topical corticosteroid (TCS) and NB-UVB compared to TCS for localised vitiligo.

Methods: Cost-effectiveness analysis alongside a pragmatic, 3-arm, placebo-controlled RCT with 9 months' treatment. 517 Adults and children (aged ≥5 years) with active vitiligo affecting <10% of skin recruited from secondary care and community were randomised 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 QALYs using the EQ-5D-5L for those aged 11+ and CHU-9D for those aged 5 to <18.

Results: Mean (SD) cost per participant was £774.4 (83.71) for NB-UVB, £813.38 (111.39) for combination treatment and £599.98 (96.18) for TCS. In analyses adjusted for age and target patch location, incremental difference in cost for combination treatment compared to TCS was £211.46 (95% CI 188.10 to 234.81), corresponding to a risk difference of 10.94% (Number-Needed-To-Treat (NNT= 9). Incremental cost was £1,932.35 per successful treatment. The incremental difference in cost for NB-UVB compared to TCS was £173.44 (95% CI 150.55 to 196.32) with a risk difference of 5.20% (NNT=19). Incremental cost was £3,335.74 per successful treatment.

Conclusion: Combination treatment, compared to 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 £1,932 per additional treatment success.

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Introduction

A 2018 systematic review showed that the economic evidence for vitiligo treatment is virtually non-existent[1]. One of two studies identified in this review estimated the annual direct cost of treating vitiligo in the USA to be $15,000,000 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 health care system, they do not provide evidence to inform resource allocation decisions. No papers were identified that undertook full economic evaluations (those which 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 localised, non-segmental vitiligo, including current standard treatment Topical Corticosteroids (TCS) and new treatment (home-based NB-UVB light therapy), alone and in combination with TCS, with the aim of estimating the cost effectiveness of these treatments for the UK NHS.

Methods

This health economic evaluation estimated the within-trial cost-effectiveness of

i) active hand-held NB-UVB light compared to TCS (standard care) and
ii) combination of active hand-held NB-UVB plus TCS compared to TCS (standard care)

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, non-segmental 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 and over using the EQ-5D-5L and separately for participants aged under 18 years using the 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 health care 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 National Health Service (the NHS) - a 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 NICE reference case[8]. In a sensitivity analysis, out of pocket costs incurred by participants (or parents/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 A&E visits; and prescriptions) as a result of vitiligo. Participants' personal out of pocket expenses (for example, camouflage/ makeup, sun cream 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 for the intervention phase was collected at 3, 6, and 9 months using information recorded by participants in daily diaries and collated by the researcher at

follow-up visits. Intervention and side effect related resource use 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 randomised to NB-UVB alone were also given a placebo ointment whilst those in the TCS alone group received a dummy NB-UVB device. The dummy devices and placebo ointment were not costed.

NB-UVB Device:

The hand-held device cost was estimated using manufacturer's purchase price divided by an annuity factor (interest rate 3.5%, 5 years) to give an equivalent annual cost (EAC). EAC was divided by 12 months and multiplied by 9 to reflect the 9-month timeframe. The purchase price of personal protective equipment (goggles and glasses) were included at full cost since these are unlikely to be as durable as the devices. Costs of 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: though 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 90g tubes of mometasone furoate 0.1% ointment (Elocon® 0.1% Ointment, Merck Sharp & Dohme, Hertford). TCS costs were was sourced from the Prescription Cost Analysis for 2017[11] and had the National Average Discount Percentage of 7.37% (https://www.nhsbsa.nhs.uk/prescription-data/understanding-our-data/financial-forecasting) deducted. 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, 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, see Table 1, and valued in UK£Sterling 2017. 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 (VNS)[14]. 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 to 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 EQ-5D-5L instrument for participants aged 11+ years[18], and the CHU-9D in the analysis focussed on children <18 years.[15-17] For participants aged 5-6 years old, 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 does not currently have a UK valuation set. .

Utility measurements were collected in clinic at baseline, 9, and 21 months to reflect the likely timeframe for observing a clinically meaningful treatment response and in order to observe if any response found was sustained longer term.

In the cost utility analysis, quality of life instrument responses were converted to utility scores using the EQ-5D-5L Crosswalk[19] UK preference weights in line with current recommendations[20, 21]. The CHU-9D was valued using the UK value set[15]. Following this, the utility values were used to calculate quality adjusted life years

(QALYs) generated over the trial treatment period of 9 months, using both linear interpolation and area under the curve analysis with baseline adjustment[24].

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 generating 60 (m=60) datasets using predictive mean matching and separately by treatment allocation as reported by Faria *et al*[23]. Given the 9-month time horizon, costs and benefits were not discounted.

Mean (SD) resource use and cost per participant was estimated for each randomised group. Mean difference (95% CI) in resource use and cost between arms (NB-UVB compared to TCS; and combination treatment compared 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 (SUR)[24].

Non-parametric bootstrapping was used to determine sampling uncertainty surrounding the mean Incremental Cost Effectiveness Ratios (ICERs) by generating 10,000 estimates of incremental costs and benefits. These estimates were used to produce Cost-Effectiveness Acceptability Curves to show the probability each intervention arm is cost effective at different values of willingness to pay.

Other than pre-planned 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 is quality-adjusted life years (QALYs) of participants over 9 months. Mean (SD) utility and mean (SD) QALYs per participant per randomised group is estimated, as is mean difference (95% CI) in QALYs between arms (NB-UVB to TCS; and combination treatment compared with 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) wider cost perspective including vitiligo out-of-pocket costs, (iv) limiting analysis to participants with good adherence (defined as greater than 75% adherence), and (v) extending the time horizon to 21 months to include the 12 months 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-analytic model for a longer timeframe. This proved appropriate, as quality of life scores were similar between treatment arms at 21 months (see supplementary Table 6 in the clinical paper[10]).

Results

Baseline characteristics of the participants included in the cost effectiveness analysis are described in Table 1 of Thomas *et al* (submitted)[10]. With imputation 517 participants (398 adults, 119 children; 173 TCS, 169 NB-UVB, and 175 Combined treatment) were included.

Intervention costs

Mean number of devices, googles, glasses, drug costs, dermatology appointments, training and unscheduled visit/telephone by group (Table 2) and mean costs (Table 3) are reported. The mean cost of the intervention per participant for TCS (standard care) was £583.42 (SD 29.59), £753.06 (SD 59.16) for NB-UVB, and £792.06 (SD 94.61) for combination treatment. Details of the time and cost of quality assurance processes are shown in Supplementary Table 1.

Training time was a mean of 73.08 minutes for NB-UVB and 69.17 minutes 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 health care resource use (primary care, secondary care and medicines) for vitiligo beyond those required for the intervention were not significantly different between groups (Table 2). Vitiligo patients reported low NHS healthcare usage. Table 3 displays mean costs per participant by treatment group using available case data. The overall mean cost per participant for NB-UVB was £774.64 (SD 83.71) compared to £599.98 (SD 96.18) for TCS - an unadjusted mean difference in cost of £174.66 (95% CI 152.75 to 196.66). Combination treatment had overall mean costs per participant of £813.38 (SD 111.39); compared to TCS this gave an unadjusted mean difference of £213.40 (95% CI 188.33 to 238.46) 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 NB-UVB compared to TCS (standard care)

The adjusted incremental difference in cost was £173.44 (95% CI 150.55 to 196.32). The adjusted risk difference for NB-UVB compared to TCS was 5.20%, this equates to a number needed to treat (NNT) 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 £3,335.74 per additional successful treatment (estimated by dividing the adjusted incremental difference in cost, £173.44, by the adjusted risk difference, 0.052).

Figure 1a 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 1a shows considerable uncertainty surrounding the decision as to whether NB-UVB, compared to TCS, represents value for money as there is always at least 40% probability of making the wrong decision if choosing to fund NV-UVB alone below a threshold value of willingness to pay of £10,000 per additional treatment success.

Cost effectiveness analysis of combination treatment compared to TCS (standard care)

The adjusted incremental difference in cost was £211.46 (95% CI 188.10 to 234.81). The adjusted risk difference for combination treatment compared to TCS was 10.94%. This equates to a NNT of 9. The adjusted incremental cost was £1,932.35 per additional successful treatment.

Figure 1b shows the probability that combination treatment is cost-effective at different possible levels of willingness to pay for an additional treatment success and shows that combination treatment is likely to be cost effective if decision makers are willing to pay more than £3,000 per additional treatment success as the probability of making the wrong decision is less than 50%.

Sensitivity analyses exploring key uncertainties in the economic evaluation are summarised in Supplementary Table 2. Limiting analysis to only adherent participants made the most difference to the incremental cost effectiveness ratio (£1,836.31 for combination treatment compared to TCS and £3,152.30 for NB-UVB compared to TCS), with those adherent to treatment being more likely to be cost effective to treat.

Secondary Economic Analysis

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 43.87%[25]. 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 under 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 time

point on either instrument. As these high ceiling ratios suggests these instruments are unlikely to be able to detect change, we report the mean utility estimates in supplementary Tables 3 and 4 and the cost utility analyses in supplementary Table 5. With this limitation in mind, both NB-UVB and combination treatment compared to TCS (standard care) had cost utility ratios within accepted thresholds (<£20,000 per QALY) for the sample aged 11 + years (NB-UVB was superior compared to TCS than combination treatment 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 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 which could be gained if decision makers were willing to pay more than the adjusted incremental cost of £1,932.35 per additional successful treatment. NB-UVB was less costly than combination treatment but also less effective, such that the incremental cost per successful treatment was higher than for combination treatment, suggesting that the NHS would get better value for money from combination treatment than light 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.[26]

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 a high ceiling

effect 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 to the clinical and cost effectiveness results, in that NB-UVB appeared more cost effective than combination treatment, compared to TCS for those aged 11 and over. 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 and over 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 <18 years analysis 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, cost of the NB-UVB light device, and 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 (JAK) 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 less than 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 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.

Conclusion

Combination treatment, compared to TCS alone, has a lower incremental cost per successful treatment than NB-UVB 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.

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Data sharing

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

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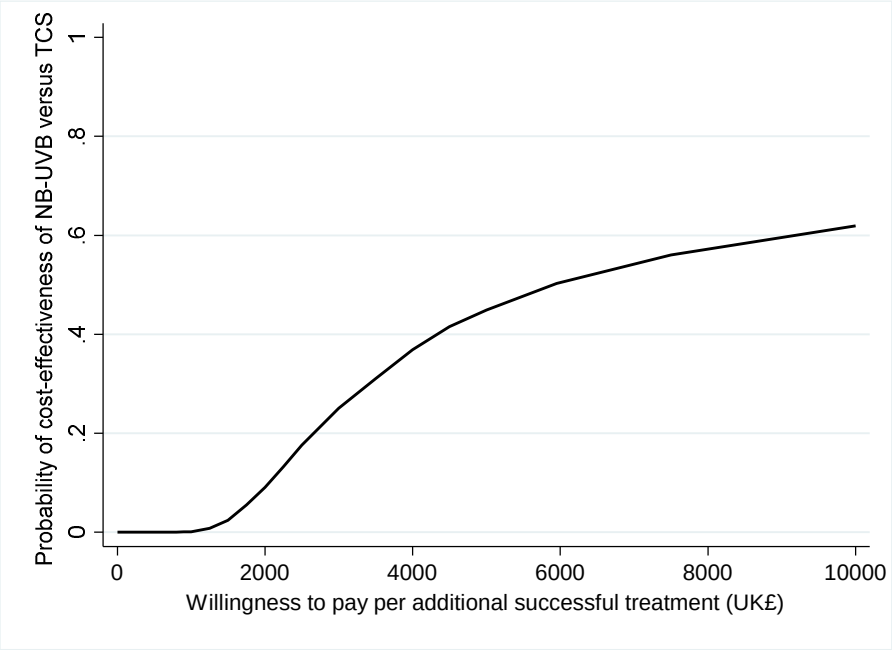

Figure 1a: Cost effectiveness Acceptability curve for NB-UVB versus TCS

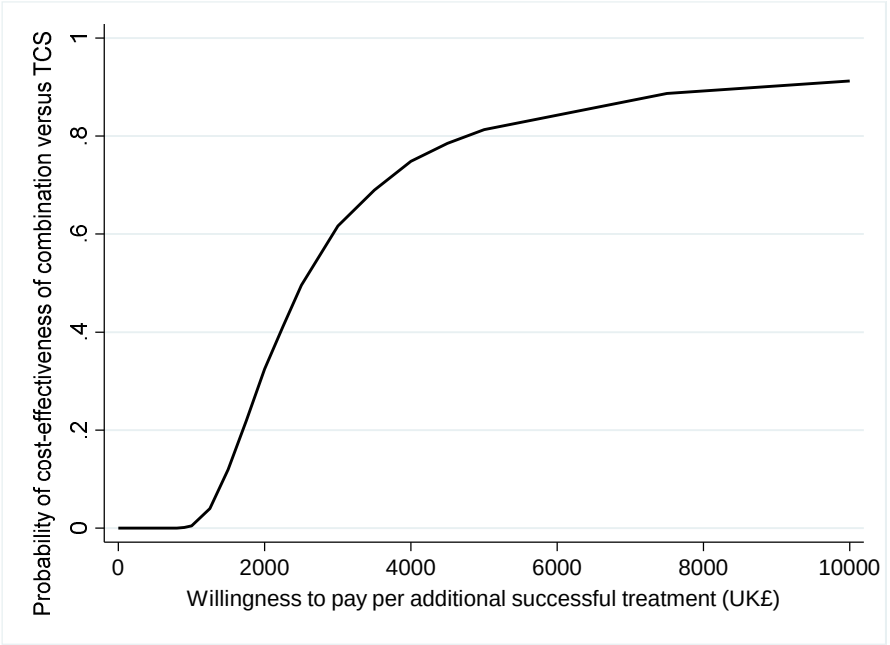

Figure 1b: Cost effectiveness Acceptability curve for NB-UVB versus TCS

Table 1 Unit Costs Table (UK£ sterling, 2017)

Resource Item	Unit Cost (£2017)	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
Annuitised 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.)
Annuitised 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 90g 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[12]

Dermatologist Face to face first appointment consultant-led	159.00	NHS Schedule of Reference Costs[13]
Dermatologist Face to face follow-up appointment consultant-led	129.00	NHS Schedule of Reference Costs[13]
Dermatologist telephone appointment consultant-led	100.00	NHS Schedule of Reference Costs[13]
Training time (per minute, assumed band 7 £54 per hour)	0.90	PSSRU 2017[12]
Primary Care resources (per visit)		
GP	37.00	PSSRU 2017[12]
Practice Nurse	10.85	PSSRU 2017[12]
Pharmacist (assumed to be a community pharmacist)	11.11	PSSRU 2017[12]
Hospital Doctor	53.33	PSSRU 2017[12]
Hospital Nurse	15.00	PSSRU 2017[12]
Therapist	27.00	PSSRU 2017[12]
Other (reported by participants)	Range from 15.00 to 86.00	PSSRU 2017[12] and NHS Schedule of Reference Costs[13]
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

Acronyms: NADP = National Average Discount Percentage; NIC = Net Ingredient Costs; TCS = Topical Corticosteroids.

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

	TCS (Standard Care) (n=173)		NB-UVB (n=169)		Mean difference (NB-UVB minus TCS)	Combination treatment (n=175)		Mean difference (Combination minus TCS)
	Mean	Std dev (n)	Mean	Std dev (n)	(95% CI)	Mean	Std dev (n)	(95% CI)
Intervention								
NB-UVB intervention*	0.00	0.00 (173)	1.08	0.30 (169)	1.083 (1.04 to 1.13)	1.07	0.30 (175)	1.07 (1.03 to 1.12)
Glasses^	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^	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 (mins)	0.00	0.00 (173)	73.08	40.47 (169)	73.08 (67.03 to 79.13)	69.17	34.51 (175)	69.17 (64.01 to 74.33)
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)	.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)

* Includes number of NB-UVB devices only.^ participants could choose to have more than one set, for instance if they needed a parent or partner to help them deliver the treatment.

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

	TCS (Standard Care) (n=173)		NB-UVB (n=169)		Mean difference (NB-UVB minus TCS)	Combination treatment (n=175)		Mean difference (Combination minus TCS)
	Mean	Std dev (n)	Mean	Std dev (n)	(95% CI)	Mean	Std dev (n)	(95% CI)
Intervention								
NB-UVB Device	0.00	0.00 (173)	24.75	0.00 (169)	24.75 (24.75 to 24.75)	24.75	0.00 (175)	24.75 (24.75 to 24.75)
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)	21.21	8.74 (169)	21.21 (19.91 to 22.52)	22.46	8.34 (175)	22.46 (21.21 to 23.70)
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	26.08	6.67 (173)	0.00	0.00 (169)	-26.08 (-27.09 to -25.07)	25.71	5.99 (175)	-0.37 (-1.70 to 0.97)
Training time	0.00	0.00 (173)	65.77	36.42 (169)	65.77 (60.32 to 71.22)	62.25	31.06 (175)	62.25 (57.61 to 66.90)
Dermatologist (clinic + telephone)	546.00	0.00 (173)	546.00	0.00 (169)	0.00 (0.00 to 0.00)	546.00	0.00 (175)	546 (546.00 to 546.00)
Nurse (clinic + telephone)	0.00	0.00 (173)	72.00	0.00 (169)	72.00 (72.00 to 72.00)	72.00	0.00 (175)	72.00 (72.00 to 72.00)
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	17.53 (169)	1.19 (-2.41 to4.79)	12.30	23.92 (175)	5.14 (0.82 to 9.46)
Unscheduled clinic with dermatologist	2.24	16.89 (173)	5.34	25.78 (169)	3.11 (-1.52 to 7.73)	13.27	55.45 (175)	11.03 (2.37 to 19.70)
Unscheduled telephone with dermatologist	1.73	16.96 (173)	2.96	20.20 (169)	1.22 (-2.74 to 5.19)	5.14	26.84 (175)	3.41 (-1.33 to 8.15)
Total cost of intervention	**583.42**	**29.59 (173)**	**753.06**	**59.16 (169)**	**169.64 (159.73 to 179.56)**	**792.06**	**94.61 (175)**	**208.64 (193.82 to 223.46)**
Primary Care and Community								
Cost	3.90	15.21 (136)	5.90	22.20 (132)	2.00 (-2.56 to 6.57)	2.84	14.09 (142)	-1.06 (-4.52 to 2.40)
Secondary Care								
Cost	11.05	77.14 (136)	9.30	30.05 (132)	-1.74 (-15.90 to 12.42)	8.52	26.87 (142)	-2.53 (-16.05 to 11.00)
Other								
Medication	2.48	10.52 (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	**599.98**	**96.18 (132)**	**774.64**	**83.71 (131)**	**174.66 (152.75 to 196.56)**	**813.38**	**111.39 (136)**	**213.40 (188.33 to 238.46)**
Out of pocket costs	14.44	96.78 (141)	4.94	20.09 (137)	-9.49 (-26.11 to 7.12)	6.62	28.45 (144)	-7.81 (-24.37 to 8.75)
Primary outcome								
VNS*	20/119 (16.81%)		27/123 (21.95%)		7 (5.14%)^	34/128 (26.56%)		14 (9.75%)

*The number (the percentage) of participants who reported a treatment success (VNS) (a lot less noticeable or no longer noticeable) at 9 months divided by the number of participants with primary outcome recorded at 9 months. ^ Between group difference is number of participants experiencing a treatment success (between group risk difference %).

Supplementary Table 1: Quality assurance process (time and costs) for NB-UVB devices

Device out	Set-up time per batch (mins)	Cost of set-up per device (£)	Time per device (mins)	Cost per device (£)	Total cost
Electrical safety testing	10	0.52	5	2.58	3.10
Output testing	20	1.03	8	4.13	5.17
Spectral characterisation	30	1.55	10	5.17	6.72
Data administration	5	0.26	5	2.58	2.84
Device in	Set-up time (mins)	Cost of set-up (£)	Time per device (mins)	Cost per device (£)	Total cost
Output testing	20	1.03	8	4.13	5.17
Data administration			5	2.58	2.58

The quality assurance process involved device in and device out processes. Before devices were issued to participants they were tested for electrical safety and output, spectral characterisation was undertaken, and some data administration was involved. When devices were returned, they again had their output tested and some data administration was involved. Supplementary table 1 shows the time and cost for each aspect, estimated using the expert opinion of staff based in Medical Physics at the Queen's Medical Centre. Staff time was assumed to be a mid-point band 5 on Agenda for Change and the batch size was assumed to be 10 devices at once. Quality assurance costs were also multiplied by the annuity factor to gain the cost over the study period. In reality, quality assurance might be undertaken more frequently than every 5 years or may be provided using a different service model (e.g. specialist versus local sites undertaking the activity) which may affect cost but the impact of this assumption is tested in the sensitivity analysis section, where price is varied to see the impact on cost per treatment success.

Supplementary Table 2: Summary of sensitivity analyses (adjusted results)

	NB-UVB versus TCS			Combination treatment versus TCS		
Analysis	Incremental costs	Incremental effect (Risk difference)	Incremental cost per treatment success	Incremental costs	Incremental effect (Risk difference)	Incremental cost per treatment success
Primary imputed	£173.44	5.20%	£3,335.74	£211.46	10.94%	£1,932.35
Complete case	£172.61	4.88%	£3,535.40	£212.59	9.96%	£2,134.11
Cost of device zero	£121.79	5.20%	£2,342.35	£158.54	10.94%	£1,448.82
Cost of device doubled	£225.02	5.20%	£4,327.78	£264.33	10.94%	£2,415.55
Wider cost perspective	£163.90	5.20%	£3,152.30	£200.95	10.94%	£1,836.31
Adherent patients only	£193.34	13.87%	£1,393.98	£230.83	20.06%	£1,150.65

Complete case analysis

The primary analysis assumed data to be missing at random and undertook imputation to allow for this[23]. Supplementary Table presents the results for a

complete case analysis, which only includes participants with complete resource use and outcome data in order to see if this changes the conclusions reached in the primary analysis. Three hundred and forty eight participants had complete data on both cost and outcome (success of treatment) – 113 in TCS only, 115 in NB-UVB only and 120 in combination treatment.

The cost of the NB-UVB device

There is uncertainty about how the device would be prescribed and used within the NHS. If adopted as an effective treatment, patients may have to pay for the device themselves (with training, support and quality assurance paid for by the NHS), or the device might be adopted and provided free at point of use by the NHS for NHS patients. The primary analysis annuitised the device cost, assuming that the device would be used for a period of 5 years, but there is uncertainty surrounding this period of use and in practice it may be that the devices are not returned by patients at the end of treatment. We re-estimated the incremental cost per successful treatment assuming that patients paid for the device, quality assurance, glasses and goggles as one extreme and at the other we doubled the price of the device, quality assurance, goggles and glasses to provide an upper estimate.

Wider cost perspective

As part of the trial, participants were asked about the out of pocket costs (if any) incurred by themselves or their families as a result of their vitiligo. These costs were added to the primary analysis results (NHS perspective only) to see how they would impact on the incremental cost per treatment success. Forty-seven (11.1%) of participants reported incurring out of pocket costs during the 9-month treatment period: 17 in TCS only, 17 in NB-UVB only and 13 in the combination group. The mean number of items and mean cost per participant by group can be seen in Table 2 and Table 3 in the main paper. The type of items included (from most to least purchased), camouflage / makeup, sun cream and sun care, clothes/scarves, face creams / moisturisers / emollients, fake tan / tanning products, travel for appointments, private appointment including multivitamins, and herbal remedies.

Taking into account the participant out of pocket costs in relation to vitiligo reduced the incremental cost per treatment success, as these costs were higher in the standard care arm (TCS only) (Supplementary table 2 for estimates).

Impact of Adherence

Since significant clinical effectiveness was found and a little under half of the participants used the treatment for over 75% of the expected duration, the primary economic analysis was repeated including only the adherent sample, where adherence was estimated as total sessions used divided by total expected sessions. 227 participants adhered to treatments >75% of the time; this sample was used as the adherent sample, minus 3 participants (1 of whom had the primary outcome missing and 2 whom had cost data missing). The intervention was more cost-effective for patients who adhered to treatment, as they were the ones most likely to achieve a successful outcome (See Supplementary table 2 for estimates).

Longer term analysis (21 months)

In the health economics analysis plan we intended to repeat the analysis over a 21 month timeframe to see if value for money was sustained. However, in the trial, only 30.4% of participants had complete data on NHS resource use in months 10-21, 44.5% of participants aged 11+ completed the EQ-5D -5L at 21 months, and 43.3% of participants aged <18 had completed the CHU-9D at 21 months. Given the sparsity of data an economic evaluation over the longer-term follow up was not conducted. Mean estimates of the participant's (all ages, n=517) wider NHS use over months 10 to 21 (the follow-up period) and utility at 21 months were estimated. Only 157 participants had complete resource use data for the whole 12 month follow-up period (which may have been for zero use), 64 had nine months of data available, 56 had six months of data available, 59 had three months worth of data available and 181 had no resource use data recorded for the follow-up period. The mean quarterly NHS cost per participant over the 12 month follow-up period was £21.26 (sd 46.32) for combination treatment (n=114), £25.89 (sd 52.82) for NB-UVB alone (n=117), and £21.74 (sd 42.33) for TCS alone (n=105). The mean prescription cost per participant over the 12 month follow-up period was £14.82 (sd 45.22) for combination treatment (n=114), £13.78 (sd 45.63) for NB-UVB alone (n=117), and £13.20 (sd 51.44) for TCS alone (n=107). The mean out of pocket cost per participant over the 12 month follow-up period was £42.85 (sd 398.74) for combination treatment (n=114), £3.62 (sd 16.93) for NB-UVB (n=117), and £8.48 (sd 39.41) for TCS (n=107).

Mean utility (EQ-5D-5L) per participant aged 11+ at 21 months was 0.856 (sd 0.230) for combination treatment (n=73), 0.865 (sd 0.231) for NB-UVB (n=61), and 0.833 (sd 0.274) for TCS (n=69). Mean utility (CHU-9D) per participant (aged <18 years) at 21 months was 0.938 (sd 0.054) for combination treatment (n=20), 0.941 (sd 0.056) for NB-UVB (n=16), and 0.937 (sd 0.118) for TCS (n=16)).

Supplementary Table 3: Mean utility estimates for the EQ-5D-5L (participants aged 11+ years) (based on available data)

	NB-UVB only (n=148)		**TCS only (n=155)**		**Mean difference (95% CI)**
	Mean	**Std dev**	**Mean**	**Std dev**	
Van Hout et al 2012 utility value set known as the 'crosswalk'					
Secondary outcomes					
EQ-5D-5L Baseline	0.8920	0.1866 (140)	0.9172	0.1145 (151)	-0.0252 (-0.0607 to 0.0102)
EQ-5D-5L 9 months	0.9287	0.1422 (89)	0.8843	0.1666 (97)	0.0444 (-0.0006 to 0.0894)
QALYs at 9 months	0.6871	0.0913 (89)	0.6721	0.0983 (97)	0.0150 (-0.0125 to 0.0425)
	Combination treatment (n=153)		**TCS only (n=155)**		**Mean difference (95% CI)**
	Mean	**Std dev**	**Mean**	**Std dev**	
Secondary outcomes					
EQ-5D-5L Baseline	0.8906	0.1719 (147)	0.9172	0.1145 (151)	-0.0266 (-0.0599 to 0.0066)
EQ-5D-5L 9 months	0.9182	0.1325 (98)	0.8843	0.1666 (97)	0.0339 (-0.0086 to 0.0764)
QALYs at 9 months	0.6843	0.0993 (96)	0.6721	0.0983 (97)	0.0122 (-0.0159 to 0.0402)

Note: Utility estimates between adults and those participants aged under 18 years were not significantly different.

Supplementary Table 4: Mean utility estimates for the CHU-9D (participants aged <18 years) (based on available data)

	NB-UVB only (n=39)		**TCS only (n=40)**		**Mean difference (95% CI)**
	Mean	**Std dev**	**Mean**	**Std dev**	
Secondary outcomes					
CHU-9D Baseline	0.9450	0.0635 (35)	0.9506	0.0528 (40)	-0.0056 (-0.0324 to 0.0212)
CHU-9D 9 months	0.9538	0.0416 (28)	0.9513	0.0523 (31)	0.0025 (-0.0223 to 0.0273)
QALYs at 9 months	0.7154	0.0312 (28)	0.7135	0.0392 (31)	0.0019 (-0.0167 to 0.0205)
	Combination treatment (n=40)		**TCS only (n=40)**		**Mean difference (95% CI)**
	Mean	**Std dev**	**Mean**	**Std dev**	
Secondary outcomes					
CHU-9D Baseline	0.9326	0.0605 (39)	0.9506	0.0528 (40)	-0.0180 (-0.043 to 0.0074)
CHU-9D 9 months	0.9318	0.0590 (28)	0.9513	0.0523 (31)	-0.0195 (-0.0471 to 0.0080)
QALYs at 9 months	0.6988	0.0443 (35)	0.7135	0.0392 (31)	-0.0147 (-0.0353 to 0.0060)

Supplementary Table 5: Cost utility analyses

Adjusted	**Incremental costs (95% CI)**	**Incremental QALYs (95% CI)**	**Incremental Cost per QALYs**
Adults and children aged 11+ years (Imputed and adjusted analysis)			
NB-UVB compared to TCS	£169.58 (165.50 to 173.65)	0.0204 (0.0180 to 0.0229)	£8,293.88
Combination treatment compared to TCS	£203.93 (199.39 to 208.47)	0.0145 (0.0123 to 0.0167)	£14,081
	Incremental costs (95% CI)	**Incremental QALYs (95% CI)**	**Incremental Cost per QALYs**
Children aged 17 years or less (Complete case, unadjusted analysis)*			
NB-UVB compared to TCS	171.50 (137.35 to 205.65)	0.0019 (-0.0167 to 0.0205)	£92,381.98
Combination treatment compared to TCS	220.96 (184.23 to 257.69)	-0.0147 (-0.0353 to 0.0060)	Standard care (TCS) dominates

*due to the small sample sizes for those aged <18 years of age (31 had complete cost and QALY data for TCS, 28 NB-UVB and 35 combination treatment) adjusted analyses would not run.

Supplementary index of definitions:

Terminology	Definition
Adjusted analysis	An adjusted analysis takes into account differences in baseline characteristics between treatment groups that may influence the outcome. In this study age and location of target patch were adjusted for.
Bootstrapping	Bootstrapping is a non-parametric statistical technique which draws repeated random samples, the same size as the original sample, with replacement from the data. It can be used to help explore sampling uncertainty surrounding the mean Incremental Cost Effectiveness Ratios (ICERs).
Cost effectiveness analysis	A cost effectiveness analysis compares two or more treatments in terms or their cost and outcomes, where outcomes are measured in a natural unit, in this study treatment success.
Cost Effectiveness Acceptability Curve (CEAC)	The CEAC shows the probability of each treatment being cost-effective for different levels of the cost-effectiveness threshold.
Cost utility analysis	A cost utility analysis is a special case of cost effectiveness analysis where the outcomes are measured in terms of Quality-Adjusted Life Years.
CHU-9D	The CHU-9D stands for Child Health Utility – Nine Dimensions and is an instrument used to elicit participants health-related quality of life in terms of utility which is measured on a scale of 0 (death) to 1 (perfect health). The instrument consists of 9 domains (worry, sadness, pain, tiredness, annoyance, school, sleep, daily routine and activities), each with 5 response categories that assess the child's functioning "today". A proxy version is available for children under the age of 7 years and a self-complete version for those aged 7 to 17 years.
Discounted	In economic evaluations longer than one year it is important to take account of when costs and outcomes occur this is done by discounting costs and benefits that occur in the future. This is done to reflect the fact that people generally value future costs and outcomes less than current costs and outcomes.
Economic evaluation	An economic evaluation is a form of analysis that compares two or more interventions in terms of both their costs and outcomes. In this study we undertake a cost effectiveness analysis in the primary analysis and cost utility analyses as secondary analysis.

EQ-5D-5L	The EQ-5D-5L stands for EuroQol five dimensions with five levels and is an instrument used to elicit participants health-related quality of life in terms of utility which is measured on a scale of 0 (death) to 1 (perfect health). The EQ-5D-5L describes 3,125 possible health states.
Incremental cost or Incremental difference in costs	These terms refer to the difference in cost between two interventions in terms of their mean cost per participant.
Incremental cost per treatment success	In this study this is the incremental cost effectiveness ratio (ICER) which is derived by dividing the incremental cost by the incremental benefit, where incremental benefit in this study is the risk difference.
Multiple Imputation	Multiple imputation is a statistical method for dealing with missing data.
Primary analysis	In this study we use the term primary analysis to refer to the main or base-case analysis which is the cost effectiveness analyses.
Quality-Adjusted Life Year	A quality-adjusted life year combines morbidity and mortality into a single number where 1 is a year of perfect health. This is equivalent to 1 QALY distributed as 0.5 QALY in each of two years (i.e. 50% of perfect health for two years).
Risk difference (incremental benefit or incremental outcome)	The risk difference in this study is the difference between the observed risks (proportions of individuals experiencing a treatment success) in the two treatment groups being compared.
Secondary analysis	In this study we use the term secondary analysis to refer to cost utility analyses. Less weight is placed on the secondary analysis because of the ceiling effect found on the EQ-5D-5L.
Sensitivity analysis	A number of factors (e.g. how missing data is dealt with, the unit costs attached to intervention resources, perspective taken etc) can impact on estimates of cost-effectiveness. To explore the impact of these factors on estimates of the incremental cost effectiveness ratio sensitivity analysis is undertaken. If changing any of the factors shifts the conclusions reached it highlights that the factor is a key determinant and decision makers ought to consider the role played by that factor in the analysis and in reaching a decision. If changing a factor doesn't change the conclusion reached that is reassuring and suggests there is less uncertainty around the results.
Willingness-to-pay	An incremental cost effectiveness ratio (in this study the incremental cost per treatment success) indicates how much it costs to gain one additional treatment success for one patient. Decision makers

	responsible for making decisions about what to fund in the NHS will have to decide how much they are willing to pay for one additional treatment success – if their willingness-to-pay is higher than the incremental cost effectiveness ratio then the intervention can be considered cost effective if it is lower then the intervention would not be considered cost effective.