THE SAFA TRIAL

Spironolactone for Adult Female Acne: A pragmatic multicentre double-blind randomised superiority trial to investigate the clinical and cost-effectiveness of spironolactone for moderate or severe persistent acne in women.

Health Economic Analysis Plan

Content:

Section 1: Administrative Information

1.1 Title: Spironolactone for Adult Female Acne: A pragmatic multicentre double-blind randomised superiority trial to investigate the clinical and cost-effectiveness of spironolactone for moderate or severe persistent acne in women. (The SAFA Trial): Health Economic Analysis Plan

1.2 Trial registration number: ISRCTN12892056

1.3 Source of funding:
This trial is independent research funded by the National Institute for Health Research (NIHR) under its Health Technology Assessment Programme (project number 16/13/02).

1.4 Purpose of HEAP:
This document will outline the methods to be used in the economic component of the SAFA trial. An economic evaluation will be conducted alongside the SAFA Trial if spironolactone is found clinically effective in the analysis of the primary endpoint. This HEAP details how data will be collected, analysed and reported. It will be finalised and reviewed prior to the trial database being locked. This HEAP has been written in line with the trial protocol and SAP in order to ensure there is consistency. The HEAP should therefore be read alongside these documents.

1.5 Trial protocol version*:*

This document has been written based on information contained in the trial protocol version 11, dated 14th May 2021.

1.6 Trial statistical analysis plan (SAP) version
SAP version 4, dated 15th September 2021

1.7 Trial HEAP version
HEAP version: 0.1, Date: 22nd February 2022

1.8 HEAP revisions

Protocol Version	Updated HEAP version No	Section number changed	Description of and reason for change	Individual making the change	Date changed
V11	0.2	5.14	A sensitivity analysis was added to compare Spironolactone to oral antibiotics. This change reflects a discussion between	Tracey Sach	11.7.22

			the trial management team about the importance of the comparator in the economic evaluation that took place between February and July 2022. In clinical practise it was noted that it would be unlikely for a woman with persistent acne to receive no active oral treatment. It was agreed a sensitivity analysis was the best way to explore this uncertainty.		
V11	0.2	5.14	A sensitivity analysis was added to cost the intervention according to the trial protocol (rather than as if accessed via primary care) in order to provide a range on cost effectiveness estimates.	Tracey Sach	11.7.22

1.9 Roles and responsibilities

This HEAP was written by the senior health economist (TS), who is a co-applicant on the grant. TS has inputted into the design of the wider trial as well as taken the lead on designing the economic evaluation component. The trial health economist (SP) will be analysing and writing up the economic evaluation under the guidance of TS. TS will check analyses and review the write-up for accuracy. SP has also reviewed and commented on the HEAP.

1.10 Abbreviations/glossary of terms/definitions

Abbreviation	Meaning
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CHU-9D	Child Health Utility - Nine Dimensions
CUA	Cost Utility Analysis
EQ-5D-5L	EuroQol Five Dimensions Five Levels
ICER	Incremental Cost Effectiveness Ratio
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PCOS	Poly-cystic ovary syndrome
QALY	Quality-Adjusted Life Year
QOL	Quality of Life
SAE	Serious Adverse Event

SECTION 2: TRIAL INTRODUCTION AND BACKGROUND

2.1 Trial background and rationale

Acne vulgaris (referred to as acne from here on) is a highly common condition that usually commences in adolescence. The majority of people aged 15 to 17 years' experience some degree of acne but 15–20% experience moderate or severe acne which often persists into adulthood. Acne can result in lower quality of life, with increased risk of depression and suicide.

For moderate acne, first-line treatment is typically fixed dose combination topical preparations. However, these frequently have side-effects that may lead to non-adherence. As a result, female patients may seek second-line treatments including oral antibiotics, co-cyprindiol or combined oral contraceptives. Those with severe acne may try isotretinoin.

Of particular concern is that around a third of people consulting a GP about acne are prescribed oral antibiotics for long periods. With rates of antibiotic resistance increasing there is a need for evidence to support different treatments, particularly for female patients for whom the combined oral contraceptive pill and co-cyprindiol may not suit them.

One such alternative treatment is Spironolactone, a potassium-sparing diuretic, that is commonly used in the UK for symptoms including hypertension. Spironolactone has long been used off-license for females with acne as it has antiandrogenic properties, but there is a lack of evidence about its benefit. The SAFA trial aims to see if spironolactone is (cost) effective, as long-term use of spironolactone instead of other second line treatments could reduce antibiotic use for acne in female patients.

2.2 Aim(s) of the trial:

The SAFA trial aims to determine the clinical effectiveness of spironolactone compared with placebo, in addition to standard care, in the treatment of moderate to severe persistent facial acne in adult women. A secondary objective is to evaluate the cost effectiveness of spironolactone plus standard care versus standard care alone for women aged 18 years and over, with moderate to severe persistent facial acne from the perspective of the NHS.

2.3 Objectives and/or research hypotheses of the trial

The primary objective is to determine the clinical effectiveness of spironolactone compared with placebo, in addition to standard care, in the treatment of moderate to severe persistent facial acne in adult women – initial treatment response (12 weeks).

The secondary objectives are:

1. To assess the clinical effectiveness of adding spironolactone to standard topical treatment, compared with placebo and standard topical treatment, for moderate to severe persistent facial acne in adult women.

2. To assess the cost-effectiveness of adding spironolactone to standard topical therapy for the management of moderate to severe acne in adult women over 24 weeks.

3. To assess the safety of adding spironolactone to standard topical treatment, compared with placebo and standard topical treatment, for moderate to severe persistent facial acne in adult women.

2.4 Trial population

The full inclusion and exclusion criteria can be seen on pages 21 and 22 of the protocol. In brief, women aged 18 years or over with facial acne vulgaris where symptoms present since at least 6 months with sufficient severity to warrant treatment with oral antibiotics, as judged by the study clinician are included. Women who have ever used spironolactone, whose acne was graded 0–1 using the Investigator's Global Assessment (i.e. clear or almost clear) or who are planning to become pregnant within 6 months, were excluded.

2.5 Intervention and comparator(s)

Women will be individually randomised (ratio 1:1) to either spironolactone or placebo, taking 1 x 50mg tablet daily for 6 weeks. After 6 weeks, participants will either stay at 1 tablet or increase to 2 x 50mg tablets. The total treatment duration will be 24 weeks.

2.6 Trial design

The trial is a pragmatic, multicentre, double-blind, randomised, superiority trial recruiting women with moderate to severe persistent acne to determine the clinical effectiveness of spironolactone compared with placebo, in addition to standard care.

The revised target sample size of this trial is 398 participants (199 per arm). Participants will be individually randomly allocated to the 2 study arms in a 1:1 ratio, and will undergo a 24-week treatment phase, followed by a 28-week follow-up phase.

The primary outcome measure is Acne-QoL symptom subscale score at 12 weeks.

Secondary outcome measures include:

- Acne-QoL symptom subscale score at 6 and 24 weeks
- Acne-QoL other subscales (self-perception, role-emotional and rolesocial) and total score at 6, 12 and 24 weeks
- Participant self-assessed improvement at 6, 12 and 24 weeks recorded on a 6-point Likert scale (with baseline photograph to assist recall)
- Investigator's Global Assessment at 6 and 12 weeks, adjusted for
- baseline variables
- Participant's Global Assessment at 6, 12 and 24 weeks, adjusted for

baseline variables
- Participant satisfaction with study treatment at 24 weeks (asked prior to unblinding)
- Health-related quality of life using EQ-5D-5L at 6, 12 and 24 weeks
- Cost at 6, 12 and 24 weeks and cost-effectiveness over 24 weeks

Other outcomes include:

- Acne-QoL symptom subscale score at up to 52 weeks
- Acne-QoL other subscales (self-perception, role-emotional and rolesocial) and total score at up to 52 weeks
- Participant self-assessed improvement at up to 52 weeks recorded on a 6-point Likert scale (with baseline photograph to assist recall)
- Participant's Global Assessment at up to 52 weeks, adjusted for baseline variables
- Adverse reactions (ARs) of special interest
- Use of other oral treatments for acne during follow-up
- Health-related quality of life using EQ-5D-5L at up to 52 weeks
- High-level resource use data will be described at up to 52 weeks

Full details of the trial can be found in the published protocol (Renz et al 2021).

2.7 Trial start and end dates

Trial recruitment started on 5th June 2019 and finished on 31st August 2021. The follow up period will run until the 15th February 2022.

SECTION 3: ECONOMIC APPROACH/OVERVIEW

3.1 Aim(s) of economic evaluation

The aim of the economic evaluation is to establish the cost-effectiveness of spironolactone treatment for moderate to severe persistent acne in women.

If clinically effective, then spironolactone is likely to be cost-effective for acne as it is cheaper than current alternatives, such as doxycycline (NHS Business Services Authority, 2021).To demonstrate this, if the intervention is found to be equally or more effective, a within-trial cost-effectiveness analysis will be undertaken to assess value for money of spironolactone plus standard care versus standard care for women aged 18 years and over with moderate to severe persistent facial acne from the perspective of the NHS (as personal social service resource use is unlikely to be incurred for the condition and participant population in the study PSS costs are essentially zero). If spironolactone is not found to be clinically effective a full economic evaluation will not be conducted. Instead, estimates of

mean costs and utility per participant will be presented at the various study time points as these may be informative for other researchers undertaking future economic studies or economic modelling in this clinical area.

3.2 Objectives(s)/hypotheses of economic evaluation

The primary objective of the health economic evaluation is to undertake a cost-utility analysis to estimate the cost-effectiveness of adding spironolactone to standard topical therapy for the management of moderate or severe acne in women, using individual level data collected within the SAFA Trial.

The secondary objectives are to undertake:

- A cost-effectiveness analysis using the disease-specific Acne-QoL to estimate incremental cost per unit of change on the Acne-QoL
- Measurement of Health-related quality of life using EQ-5D-5L at 6, 12, 24 and 52 weeks
- Comparison of Quality-Adjusted Life Years (QALYs) between arms, derived using the EQ-5D-5L and linear interpolation, adjusted for baseline variables
- Comparison of cost at 24 and 52 weeks, based on resource use data collected at the individual participant level at 6, 12, 24 and 52 weeks, including use of other oral treatments for acne during follow-up

3.3 Overview of economic analysis

If spironolactone is found clinically effective a within-trial economic analysis (24-week time frame) will be undertaken using individual participant level data from the SAFA trial. The base case analysis will undertake a cost-utility analysis from an NHS perspective for all participants. Secondary analyses will consider the cost-effectiveness of the comparators of interest using the disease-specific Acne-QoL to estimate incremental cost per unit of change on the Acne-QoL.

The evaluation will adhere to published guidelines for the economic evaluation of health care interventions as appropriate (Drummond et al 2015; Ramsey et al 2015; Glick et al 2014; Husereau, D., 2022; NICE 2013).

3.4 Jurisdiction

The trial is being conducted in the UK, which has a national health service (NHS), providing publicly funded healthcare, largely free of charge at the point of use.

3.5 Perspective(s)

The NICE reference case (NICE, 2013) requires an NHS and PSS perspective be taken. Given that Personal Social Service (PSS) resource use is unlikely to be incurred or affected as a

result of acne we have chosen not to explicitly measure these resource items and our analysis will therefore take an NHS perspective. Presented separately will be the out-of-pocket and productivity costs incurred by participants, reflecting a personal perspective.

3.6 Time horizon

The primary economic analysis will compare the costs and outcomes over the 24-week intervention period from randomisation.

SECTION 4: ECONOMIC DATA COLLECTION AND MANAGEMENT

4.1 Statistical software used for HE analysis

Stata MP version 17

4.2 Identification of resources

In keeping with the chosen perspective the base case will capture the intervention costs (including any side effect costs) to the NHS and the participant's wider use of the NHS (including primary care and secondary care visits and prescriptions). Participants personal out of pocket expenses and productivity costs incurred as a result of their acne will be captured in a separate analysis taking a broader perspective.

4.3 Measurement of resource use data

Resource use will be collected at baseline and for the intervention phase at 6, 12 and 24 weeks, using case report forms and participant questionnaires collected at follow-up visits. See appendix 2 for a table illustrating how mean resource use will be presented in the final report.

4.4 Valuation of resource use data

The cost of the intervention will be estimated at the individual level.

Spironolactone:

In costing the intervention, the cost of the spironolactone will be sourced from the Prescription Cost Analysis for the most recent year available at time of analysis (NHS Business Services Authority, 2021). Side effects requiring medical attention are thought to be uncommon but where they do occur, are likely to be captured in the self-reported data provided by participants, and thus to avoid double counting these resource items, data collected on adverse events in the CRF will not be used as the basis of estimating the side effect costs in the base case analysis.

Placebo:

The costs of placebo tablets will not be included in the analysis as they would not usually be issued as part of standard care.

Participants in both arms will be able to use their regular topical treatments and these will be included the wider NHS resource use and costs.

Unit Costs:

All resource use relevant to the NHS perspective will be valued using UK unit costs (in £Sterling) from the most current price year available at the time of the analysis. Unit costs will be identified from published sources, such as Unit Costs of Health and Social Care (Jones and Burns, 2021), Prescription Cost Analysis (NHS Business Services Authority, 2021) and National Cost Collection for the NHS (NHS England, 2020). A table of unit costs, together with their sources will be produced (see appendix 1 for example).

Personal costs incurred by participants as out of pocket costs due to their acne, will be valued using patient reported estimates.

Total Costs:

The cost of all reported resource use (relevant to an NHS perspective) will be calculated for each participant. These figures will then be summed for each participant, giving a total cost over the 24-week treatment period. For each study arm, a mean cost per participant will be calculated. See appendix 2 for a table illustrating how mean costs will be presented in the final report.

4.5 Identification of outcome(s)

Quality of Life:

Quality Adjusted Life Years (QALYs) estimated using utility scores obtained using the EQ-5D-5L instrument will be used in the base case primary economic analysis. The EQ-5D-5L has 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with 5 levels (no problems, slight problems, moderate problems, severe problems and extreme problems/unable) (Herdman et al, 2011). See appendix 3 for a table illustrating how mean resource use will be presented in the final report.

Acne-QOL:

Unit change on the Acne-QoL (a disease-specific instrument) will be used in the secondary cost-effectiveness analysis. In line with the primary end point in the clinical analysis we will use the symptom subscale score of the Acne-QoL questionnaire (i.e. summing items 15–19, see Appendix 4). There are 5 questions, each on a scale of 0–6 (“extensive, a whole lot, a lot,

a moderate amount, some, very few, none" for items 15-17 and "extremely, very much, quite a bit, a good bit, somewhat, a little bit, and not at all." for items 18 and 19) such that the domain score ranges from 0 to 30 (Acne-specific Quality of Life Questionnaire (Acne-QoL) Manual & Interpretation Guide, 2003).

4.6 Measurement of outcome(s)

Utility measurements will be collected at baseline, 6 and 12 weeks at clinic visits and at 24 weeks via a postal questionnaire.

4.7 Valuation of outcome(s)

In the cost utility analysis, the responses received on the quality-of-life instruments will be converted to utility scores using UK preference weights in line with current recommendations at the time of the analysis (NICE 2019; Van Hout et al 2012). Following this, the utility values will be used to calculate the number of QALYs generated over the trial treatment period of 24 weeks, using both linear interpolation and area under the curve analysis, with and without baseline adjustment (Manca, 2005).

SECTION 5: ECONOMIC DATA ANALYSIS

A full within trial economic evaluation will only be conducted if spironolactone is found effective. If Spironolactone is not found to be clinically effective a full economic evaluation will not be conducted. Instead, estimates of mean costs and utility per participant (sections 5.6, 5.7, and 5.8 of this HEAP) will be presented at the various study time points, as these may be informative for other researchers undertaking future economic studies or economic modelling in this clinical area. This section needs to be read with this in mind.

5.1 Analysis population

In line with the statistical analysis plan, the economic base-case analysis will be performed based on a modified Intention-to-treat (ITT) population, which includes all participants who have been randomised to a treatment arm, regardless of compliance, and have completed data for the costs and outcomes being analysed (complete case analysis). The level of missing data will be reported.

5.2 Timing of analyses

The final analysis will be a within-trial analysis, taking a 24-week time horizon in the base case analysis.

5.3 Discount rates for costs and benefits

As the time horizon being evaluated is 24 weeks (less than 1 year) in the base case, costs and benefits will not be discounted (NICE, 2013).

5.4 Cost-effectiveness threshold(s)

The main base case analysis will be a cost utility analysis, combining estimated mean costs and QALYs for each intervention group in an incremental analysis to compare it to the decision makers threshold willingness to pay (ʎ) per QALY. The reported economic analysis will use a cost-effectiveness threshold (ʎ) of £30,000 (£20,000) per QALY (NICE 2013).

The secondary analysis is a cost effectiveness analysis, where decision makers will need to make a value judgement about the acceptable value per unit change on Acne-QOL.

5.5 Statistical decision rule(s)

As appropriate, all statistical tests will be two-sided with the statistical significance level set at 5%.

5.6 Analysis of resource Use

Mean (standard deviation [SD]) resource use per participant will be estimated for each randomised group. Mean difference (95% confidence interval [CI]) in mean resource use between arms (spironolactone compared to standard care) will also be presented.

5.7 Analysis of costs

Mean (SD) cost per participant will be estimated for each randomised group. Mean difference (95% CI) in mean cost between arms (spironolactone compared to standard care) will also be estimated unadjusted.

5.8 Analysis of outcomes

The primary outcome for the economic evaluation will be quality-adjusted life years (QALYs) of participants over 24 weeks in the base case. Mean (SD) utility and mean (SD) QALYS per participant per randomised group will be presented and mean difference (95% CI) in utility and QALYs between arms (spironolactone compared to standard care) will be estimated unadjusted.

The secondary outcome for the economic evaluation will be unit change on the Acne-QoL symptom subscale score unadjusted. Mean (SD) Acne-QoL symptom subscale score per participant per randomised group will be estimated along with the unadjusted mean difference (95% CI) in Acne-QoL symptom subscale score between groups.

For both the primary base case and the secondary analysis an adjusted analysis will also be reported where randomised groups will be compared using a regression-based approach (such as seemingly unrelated regression equations if appropriate) (Willan et al 2004) adjusted by randomisation stratification variables (centre, baseline severity [IGA < 3 versus 3 or more]) and baseline variables (including baseline Acne-QoL symptom subscale score, use of topical treatments (Y/N)).

5.9 Data cleaning for analysis

Before carrying out analyses, plausibility checks will be performed on the relevant data fields, such as resource use and reported outcome measures, such as quality of life. Where problems are identified, the health economist will contact the data manager of the trial for clarification.

5.10 Missing data

The primary analysis will be of complete cases (complete case analysis). However, Trial data will be examined for any missing data, in particular the amount of missing data and the likely mechanism of missingness. We will present a sensitivity analysis based on data imputed using a chained equations multiple imputation models, assuming missing at random is a reasonable assumption. The imputation models would include the outcome measure (cost or utility), baseline value of the outcome (cost or utility), randomisation group, and all covariates (randomisation stratification variables (centre, baseline severity [IGA < 3 versus 3 or more]) and baseline variables (including baseline Acne-QoL symptom subscale score, , use of topical treatments (Y/N)) included in the analysis model.

5.11 Analysis of cost-effectiveness

If spironolactone is not found to be clinically effective then costs and outcomes will not be combined in a full economic evaluation. Instead 5.7 and 5.8 will be presented for the benefit of future researchers working in this area, who may wish to develop an economic model for acne.

If spironolactone is found to be clinically effective in the clinical trial, then cost and QALY data will be combined to estimate an incremental cost-effectiveness ratio (ICER), if appropriate, from an NHS perspective, comparing spironolactone with standard care to standard care alone, unadjusted and adjusted. A regression-based approach (such as seemingly unrelated regression equations if appropriate) (Willan et al 2004) will be used in primary base case cost utility analyses. Adjustment will take account of randomisation stratification variables (centre, baseline severity [IGA < 3 versus 3 or more]) and baseline variables (including baseline Acne-QoL symptom subscale score, use of topical treatments (Y/N)).

The primary clinical outcome measure of the SAFA trial, as described above, will be used in the secondary cost-effectiveness analysis. Incremental cost per unit change on the Acne-QoL symptom subscale score will be estimated unadjusted and adjusted.

5.12 Sampling uncertainty

It is likely that costs and outcomes will be skewed, therefore non-parametric bootstrapping will be used to determine the level of sampling uncertainty surrounding the mean ICERs by generating 10,000 estimates of incremental costs and benefits. These estimates will be plotted on a cost-effectiveness plane. In addition, Cost-Effectiveness Acceptability Curves (CEAC) will be produced, which will show the probability that spironolactone is cost effective at different values of willingness to pay.

5.13 Subgroup analysis/Analysis of heterogeneity

Exploratory subgroup analyses are planned as part of the statistical analysis plan to investigate how the treatment effect differs by whether participants have symptoms consistent with PCOS as recorded at the baseline visit, by age (below 25 years and 25 years and over) and by the use of hormonal co-treatments (yes/no). If any of these suggest effectiveness differs significantly between groups, we will consider the merits of running a subgroup cost utility analysis.

5.14 Sensitivity analyses

Sensitivity analyses will be undertaken to explore key uncertainties around important parameters in the primary economic evaluation:

1. A cost utility analysis based on data imputed using a chained equations multiple imputation model will be undertaken. The imputation models will include the outcome measure (cost and utility), baseline value of the outcome (cost and utility), randomisation group, and all covariates included in the adjusted analysis model.

2. Taking a wider cost perspective – including the costs (if any) incurred by participants and their families and friends in terms of out-of-pocket costs into the cost-utility analysis.

3. If the clinical analysis finds that level of compliance influences effectiveness, we will undertake a sensitivity analysis to compare the cost effectiveness given different levels of compliance. This will be informed by the findings of the clinical analysis.

4. A cost utility analysis will be undertaken using a per protocol approach to costing the intervention resource use. That is the intervention will be costed as if accessed via secondary care rather than primary care.

5. A cost utility analysis will be undertaken comparing Spironolactone to oral antibiotics rather than placebo. Clinicians tell us that it is unusual for women with persistent acne to receive no active oral treatment. It will be assumed that all women in the placebo arm

received oral antibiotics (lymecycline or doxycycline, 1 tablet daily for 24 weeks) in addition to topical treatment. QALYs will be assumed to be the same as those measured within the trial but a threshold analysis will be conducted in order to estimate what value of QALYs would switch the cost-effectiveness result given it is likely the difference between groups would be lower if both were on active treatments.

The cost of spironolactone will not be tested in sensitivity analyses given the NHS indicative/drug tariff price is currently around £2 per 28 tablets of Spironolactone 100mg tablets (https://bnf.nice.org.uk/medicinal-forms/spironolactone.html).

SECTION 6: MODELLING AND VALUE OF INFORMATION ANALYSES

6.1 Extrapolation or Decision analytic modelling

The within-trial base case time horizon will be 24 weeks. We will not be developing a decision-analytic model taking a longer time horizon given the lack of data on effectiveness and resource use/costs beyond 24 weeks. We will have some high-level resource use data and utility data at 52 weeks which we will present as means (95% CI) per patient per arm.

SECTION 7: REPORTING/PUBLISHING

7.1 Reporting standards

The CHEERS reporting quality guidelines will be followed when writing up the health economic evaluation (Husereau et al 2022).

7.2 Reporting deviations from the HEAP

Any deviations necessary from the HEAP will be described and justified in the main study report (HTA monograph).

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SECTION 8: Appendices

Appendix 1: Example Unit cost table

Unit Costs Table (UK£ sterling, Price Year)

Cost Item	Unit Cost (£)	Source
Intervention		
Spironolactone		
GP visits related to intervention		
Blood test		
Primary Care		
GP visits unrelated to intervention		
Practice Nurse		
Pharmacist		
Hospital Doctor		
Hospital Nurse		
Therapist (assume psychologist)		
Other		
Medication		

Appendix 2: Examples of tables for mean resource use and costs

Example of the "Mean (Standard Deviation) Resource Use and Mean Difference in Resource Use per Patient (95% Confidence Interval) over the 24-week treatment period for the Intervention arm compared to usual care arm" table

	Spironolactone + topicals (n=)		**Placebo + topicals (n=)**		**Mean difference**
	Mean	**Std dev**	**Mean**	**Std dev**	**(95% CI)**
Spironolactone (number)					
GP visits related to intervention (number of visits)*					
Blood tests (number)					
GP (number of visits)					
Practice Nurse (number of visits)					
Pharmacist (number of visits)					
Hospital Doctor (number of visits)					
Hospital Nurse (number of visits)					
A&E (number of visits)					
Therapist (number of visits)					
Medication – Prescriptions items (number)					

This table is for illustrative purposes only.

*Assumes that if spironolactone is found effective it would be prescribed in primary care.

Example of the "Mean (Standard Deviation) Cost and Cost Difference (95% Confidence Interval) Per Patient over the 24-week treatment period for the Intervention arm compared to usual care arm (in 2021 UK pounds sterling)" table

	Spironolactone + topicals (n=)		**Placebo + topicals (n=)**		**Mean difference**
	Mean	**Std dev**	**Mean**	**Std dev**	**(95% CI) £'s**
Intervention					
Spironolactone					
GP visits related to intervention*					
Blood tests					
Primary Care and Community					
GP visits unrelated to intervention					
Practice Nurse					
Pharmacist					
Secondary Care					
Hospital Doctor					
Hospital Nurse					
A&E					
Therapist					
Other					
Medication					
Total health care costs					

This table is for illustrative purposes only.

*Assumes that if spironolactone is found effective it would be prescribed in primary care.

Appendix 3: Examples of tables reporting outcomes

Utility and QALYs for base case

	Spironolactone + topicals (n=)		Placebo + topicals (n=)	
	Mean	**Std dev**	**Mean**	**Std dev**
Participants aged 11 years and over (n=)				
EQ-5D-5L Baseline				
EQ-5D-5L 6 weeks				
EQ-5D-5L 12 weeks				
EQ-5D-5L 24 weeks				
QALYs at 24 weeks				
EQ-5D-5L 52 weeks				
QALYs at 52 weeks				

Appendix 4: Content Areas of Acne-QoL Domains

Self Perception		**Role-emotional**	
1	Feel unattractive	5	Spending time treating face
3	Feel self-concious	9	Need to have meds or cover-up available
10	Self-confidence affected	8	Meds won't clear face fast enough
2	Feel embarrassed	7	Not looking your best
6	Dissatisfied with self appearance	4	Feel upset
Role-Social		**Acne Symptoms**	
12	Going out in public	15	Bumps on face
11	Meeting new people	16	Bumps full of pus
14	Interacting with opposite sex (or same sex if gay) a problem	17	Scabbing from acne
13	Socializing with people a problem	18	Concerned with scarring
		19	Oily skin

Source: p.7, Acne-specific Quality of Life Questionnaire (Acne-QoL) Manual & Interpretation Guide (2003)