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# BMJ Open

## Spironolactone for Adult Female Acne (SAFA): A double-blind, placebo-controlled, phase III randomised study of spironolactone as systemic therapy for acne in adult women: study protocol

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## 1 Title

2 Spironolactone for Adult Female Acne (SAFA): A double-blind, placebo-controlled, phase III randomised  
3 study of spironolactone as systemic therapy for acne in adult women: study protocol

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## Abstract

**Introduction:** Acne is one of the most common inflammatory skin diseases worldwide and can cause significant psychosocial impact and permanent physical scarring. Spironolactone, a potassium-sparing diuretic, has anti-androgenic properties, providing the potential to reduce sebum production and hyperkeratinisation in the intrafollicular duct of acne prone follicles. Dermatologists have prescribed spironolactone for acne in adult women for over 30 years, but robust clinical study data to evidence use are lacking.

**Methods and analysis:** Women ( $\geq 18$  years) with persistent facial acne requiring systemic therapy, are randomised to receive one tablet daily of 50 mg spironolactone or a matched placebo for the first 6 weeks, increasing to up to two tablets daily (total 100 mg spironolactone or matched placebo) until week-24, along with usual topical therapy if desired. Study treatment stops at week-24, participants are informed of their treatment allocation and enter an unblinded follow-up period for up to 6 months (up to 52 weeks after baseline). Primary outcome is the Acne-specific Quality of Life (Acne-QoL) symptom subscale score at week-12. Secondary outcomes include: Acne-QoL total and subscales, participant acne self-assessment recorded on a 6-point Likert scale at 6, 12, 24 weeks and up to 52 weeks, Investigator's Global Assessment (IGA) at weeks 6 and 12, cost and cost effectiveness are assessed over 24 weeks. Aiming to detect a group difference of 2 points on the Acne-QoL symptom subscale (s.d. 5.8, effect size 0.35), allowing for 20% loss to follow-up, gives a sample size of 398 participants. **Ethics and dissemination:** This protocol was approved by Wales Research Ethics Committee (18/WA/0420). Follow-up to be completed in early 2022. Findings will be disseminated to participants, peer-reviewed journals, networks and patient groups, on social media, on the study website and the Southampton Clinical Trials Unit (CTU) website to maximise impact.

**Study registration:** ISRCTN 12892056.

## 57 **Strengths and limitations of this study**

- 58 • First adequately powered randomised placebo-controlled study to provide evidence about the clinical  
59 and cost-effectiveness of spironolactone in the treatment of acne
- 60 • Pragmatic design includes a primary outcome that is a participant-reported outcome measure, broad  
61 eligibility and recruitment strategies via primary care, secondary care, community and social media  
62 advertising
- 63 • Randomisation to either spironolactone or matched placebo, with participants in both groups using  
64 topical treatments as usual (creams, gels, lotions), if desired, in order to reflect the place of oral  
65 treatments in the acne care pathway
- 66 • Dosing regimen was informed by survey amongst health professionals indicating an initial dose of  
67 50mg with an increase up to 150 mg spironolactone depending on response
- 68 • Adaptions during the COVID-19 pandemic included change to remote follow-up visits (via phone or  
69 video call), posting of study tablets/questionnaires to participants and increased social media  
70 advertising from July 2020

## 71 **Keywords**

72 Spironolactone; adult female acne; topical therapy; dermatology; randomised controlled study

## 73 **Background**

74 Acne vulgaris (from here on referred to as acne) is the eighth most common disease worldwide<sup>1</sup> and typically  
75 starts in adolescence with 15-20% of people affected showing moderate or severe acne, often persisting into  
76 adulthood<sup>2</sup>. Facial scarring occurs in approximately 20% of people but the main impact is social, with levels  
77 of psychological disability equivalent to those seen in conditions such as asthma and diabetes<sup>3,4</sup>. Incidence  
78 of acne in adult women is considerable and growing<sup>5-9</sup>.

79 First line treatment for acne is topical treatments either alone or combination preparations, containing  
80 retinoids, benzoyl peroxide and/or antibiotics<sup>3</sup>. However, non-adherence to topical treatments is common,  
81 possibly because of the need to be used consistently for up to 8 weeks and adverse reactions, such as  
82 stinging or redness, are common<sup>10</sup>. People therefore commonly seek second-line therapies, such as oral  
83 antibiotics, co-cyprindiol or combined oral contraceptives<sup>3</sup>. In the UK, oral isotretinoin can be used under the  
84

1  
2  
3 85 supervision of a dermatologist for indications including severe acne or acne that has not responded to an  
4  
5 86 adequate course of a systemic antibiotics. Oral isotretinoin is highly effective, but is contraindicated for some  
6  
7 87 and is teratogenic<sup>2</sup>.

8  
9 88 A third of people who consult with acne are prescribed long courses of oral antibiotics<sup>3,11</sup>. However, acne is a  
10  
11 89 disease of sebogenesis and antibiotics have no effect on sebum production<sup>12,13</sup>. Furthermore, rising rates of  
12  
13 90 antibiotic resistance mean non-antibiotic alternatives are needed<sup>14</sup>.

14  
15 91 Spironolactone, a potassium-sparing diuretic, is widely used in the UK for indications including  
16  
17 92 hypertension<sup>15</sup> and has been used off-license for women with acne for  $\geq 30$  years due to its anti-androgenic  
18  
19 93 properties. US Guidelines suggest a role in the management of female acne<sup>1</sup>. Spironolactone is not used to  
20  
21 94 treat acne in men, because of its feminising side effects<sup>16</sup>.

22 95 There is limited evidence for the effectiveness of spironolactone for treating acne and the need for evidence  
23  
24 96 from randomised controlled trials (RCTs) in this patient group is acknowledged<sup>16</sup>.

25  
26 97 When considering spironolactone as a potential alternative systemic therapy for acne, one study reported  
27  
28 98 treatment success in women who had previously failed isotretinoin<sup>17</sup> and a second study comparing the  
29  
30 99 frequency with which participants switched drug treatment within one year of initiation, demonstrated no  
31  
32 100 significant difference between those taking spironolactone and those taking oral antibiotics for their acne,<sup>18</sup>  
33  
34 101 implying they are equally tolerated by users.

35  
36 102 A James Lind Alliance Priority Setting Partnership, funded by the National Institute for Health Research  
37  
38 103 (NIHR), identified the need to establish the best way to manage acne in women who may or may not have  
39  
40 104 underlying hormonal abnormalities<sup>19</sup>. This informed an NIHR commissioned call (16/13 Persistent acne in  
41  
42 105 adult women) for proposals to answer the research question: 'What is the effectiveness of spironolactone in  
43  
44 106 the treatment of moderate-severe persistent acne in adult women?'

45 107 This study will investigate the addition of spironolactone to usual topical therapy in adult women with  
46  
47 108 persistent facial acne requiring systemic therapy.

## 49 50 109 **Methods**

### 51 52 53 110 **Study design and setting**

54  
55 111 The study is a phase III, multicentre, double-blind, randomised superiority study, to investigate clinical and  
56  
57 112 cost-effectiveness of spironolactone in the treatment of moderate or severe persistent facial acne in adult  
58  
59 113 women compared to placebo, in addition to standard topical treatment. The design is pragmatic in order to  
60



1  
2  
3 114 have strong external validity and to inform real-world decision-making for women with acne and their health  
4  
5 115 professionals. Pragmatic design includes broad eligibility and recruitment strategies, a primary outcome that  
6  
7 116 is relevant to participants, low intensity follow-up and an intention-to-treat (ITT) analysis. 'Moderate to severe  
8  
9 117 acne', in the context of this study, is defined as acne that warrants treatment with oral antibiotics, as judged  
10  
11 118 by the potential participant and study clinician.

12  
13 119 Baseline and follow-up appointments are carried out by UK hospital dermatology centres in order to facilitate  
14  
15 120 blood tests at baseline and clinical assessments. Participants continue on the allocated treatment  
16  
17 121 (spironolactone or placebo) in combination with their usual topical treatment (if desired) for a total duration of  
18  
19 122 24 weeks with assessments at weeks 6 and 12. Primary outcome is assessed at week-12 with the patient-  
20  
21 123 reported Acne-QoL<sup>20,21</sup>. From week-12, participants in both groups may receive 'usual care' from their usual  
22  
23 124 clinical team including oral treatments (oral antibiotics, hormonal treatments), and from week-24 isotretinoin,  
24  
25 125 if the participant and study clinician feel the need for rescue treatment. At week-24, participants stop taking  
26  
27 126 their study treatment, are informed of their treatment group allocation and enter an unblinded observational  
28  
29 127 follow-up period for up to six months (up to 52 weeks after baseline). During this observational final follow-up  
30  
31 128 period, participants can ask their General Practitioner (GP) to be prescribed spironolactone for their acne if  
32  
33 129 they wish, or pursue other acne treatments as part of usual care. The study schema (Figure 1) illustrates the  
34  
35 130 patient pathway through the study with Table 1 summarising the study procedures.

36  
37 131 Adaptations during the COVID-19 pandemic included the option to hold follow-up visits at weeks 6 and 12  
38  
39 132 remotely (phone/video calls) and to post out the study tablets and questionnaires to participants. Participants  
40  
41 133 were also given standardised instructions on how to photograph their face to submit as part of remote follow-  
42  
43 134 up assessments. Baseline visits continued to be face-to-face due to the requirement of a urine pregnancy  
44  
45 135 test and blood test to assess kidney function and serum potassium levels.

46  
47 136 *FIGURE 1: STUDY SCHEMA*

48  
49 137 *TABLE 1: SCHEDULE OF PROCEDURES*

## 50 51 138 **Eligibility**

### 52 53 139 **Inclusion criteria**

54  
55 140 Participants should fulfil all the following criteria:

- 56  
57 141 • Women aged  $\geq 18$  years
- 58  
59 142 • Facial acne vulgaris, symptoms present for at least 6 months

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2  
3 143 • Acne of sufficient severity to warrant treatment with oral antibiotics, as judged by the study clinician.  
4  
5 144 Patients with an IGA $\geq$ 2 are eligible to participate in the study  
6  
7  
8 145 • Women of childbearing potential at risk of pregnancy must be willing to use their usual hormonal or  
9  
10 146 barrier method of contraception for the first 6 months of the study (whilst taking the study  
11  
12 147 investigational medicinal product (IMP)) and for at least 4 weeks afterwards  
13  
14 148 • Willing to be randomised to either study group  
15  
16 149 • Willing and able to give informed consent  
17  
18 150 • Sufficient English to carry out primary outcome Acne-QoL (which has not been validated in other  
19  
20 151 languages)

### 21 152 **Exclusion criteria**

22 153 Individuals meeting any of the following criteria will be excluded:

- 23  
24 154 • Acne grade 0-1 using IGA (i.e. clear or almost clear)  
25  
26 155 • Has ever taken spironolactone  
27  
28 156 • Oral antibiotic treatment (lasting longer than a week) for acne within past month  
29  
30 157 • Oral isotretinoin treatment within past 6 months  
31  
32 158 • Started, stopped or changed long-term (lasting more than 2 weeks) hormonal contraception, co-  
33 159 cyprindiol or other hormonal treatment within past 3 months  
34  
35 160 • Planning to start, stop or change long-term (lasting more than 2 weeks) hormonal contraception, co-  
36 161 cyprindiol or other hormonal treatment within the next 3 months  
37  
38 162 • Pregnant/breastfeeding  
39  
40 163 • Intending to become pregnant in the next 6 months  
41  
42 164 • Contra-indicated to spironolactone:  
43  
44 165 ○ Currently taking potassium-sparing diuretic, ACE inhibitor, angiotensin II receptor blocker or  
45 166 digoxin  
46  
47 167 ○ Hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose  
48 168 malabsorption (as the spironolactone and placebo tablets contain lactose)  
49  
50 169 ○ Androgen-secreting adrenal or ovarian tumour  
51  
52 170 ○ Cushing's syndrome  
53  
54 171 ○ Congenital adrenal hyperplasia  
55  
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- 172 ○ Estimated Glomerular Filtration Rate (eGFR) below 60 ml/min/1.73m<sup>2</sup>
- 173 ○ Serum potassium level above upper limit of reference range for the laboratory processing
- 174 the sample

## 175 **Intervention and control**

176 Study participants receive one tablet daily (50 mg spironolactone or matched placebo) for the first six weeks  
177 of the study. At, or any time after the week-6 visit, the dose is escalated to two tablets daily (total 100 mg  
178 spironolactone or matched placebo) by the study clinician, providing the participant is tolerating any side  
179 effects (see box 1). Participants are instructed to take their total dose once daily in the morning to avoid  
180 diuresis later in the day/evening.

181 Participants may use their usual topical treatments throughout the study but adherence to topicals is not  
182 actively promoted as this may mask differences between the randomised groups. Participants are  
183 discouraged from changing their topical treatments between baseline and week-12.

184 *INSERT BOX 1: RATIONAL FOR DOSING REGIMEN*

## 185 **Intervention adherence**

186 The hospital study team assess participant adherence to treatment at each study visit using pill counts. In  
187 cases where only remote visits are possible, the participant informs the study team of the number of tablets  
188 remaining. However, no additional support or activity is undertaken to encourage daily pill taking, in keeping  
189 with the trial's pragmatic design.

## 190 **Randomisation and assignment to intervention group**

191 Following consent, participants are randomised 1:1 by clinical staff at the hospital site using an independent  
192 web-based system (TENALEA) using varying blocks of size 2 and 4, stratified by centre and by baseline  
193 severity (IGA<3 vs 3 or more). The allocation sequence was generated by a statistician using computer-  
194 generated random numbers. Participants, study staff and investigators are blind to the treatment allocation  
195 until end of the treatment period at week-24. Treatment allocation is revealed prior to week-24 only if there is  
196 a clinical need to do so.

## 197 **Recruitment**

198 Potential participants, identified in primary and secondary care, direct advertising in areas close to recruiting  
199 hospitals and social media advertising, are directed to the study website

1  
2  
3 200 (<https://www.southampton.ac.uk/safa>) or to contact the local study team directly.

4  
5 201 In primary care, recruitment is supported by general practices acting as Participant Identification Centres  
6  
7 202 (PIC) local to the recruiting centres identifying potential participants either opportunistically or via database  
8  
9 203 search based on an acne diagnosis and relevant prescription within the past 6 months and mail-out of  
10  
11 204 invitation pack. In secondary care, potential participants are identified opportunistically in out-patient clinics  
12  
13 205 and through screening new referral letters.

14  
15 206 We use targeted social media advertising to promote the study, build study awareness and interest.

16  
17 207 Participants are free to withdraw consent from the study at any time without providing a reason. They may  
18  
19 208 withdraw from study treatment but remain in follow-up; withdraw from study and follow-up, but give  
20  
21 209 permission for their data to be used in analyses; or completely withdraw from the study and not permit their  
22  
23 210 data to be used.

## 24 25 211 **Primary and secondary outcome measures**

26  
27 212 Clinically, the effectiveness of acne treatments is usually judged at 8-12 weeks, so the primary outcome in  
28  
29 213 the study is assessed at week-12 with the Acne-QoL symptom subscale score<sup>20,21</sup>. The Acne-QoL was  
30  
31 214 developed and validated for use in a clinical study to assess the impact of therapy on quality of life among  
32  
33 215 people with facial acne and the primary outcome at week-12 is the symptom subscale score of the Acne-  
34  
35 216 QoL, because the Acne-QoL was intended to be presented as 4 separate subscale scores. It was not  
36  
37 217 designed or validated to have a total score, however, it has published Minimum Clinically Important  
38  
39 218 Difference (MCID) of 2 points for the subscales and range 0 to 30 for symptom subscale score<sup>20-22</sup>. Other  
40  
41 219 participant-reported outcome measures in acne do not have a published MCID available and have not been  
42  
43 220 found to have advantages in terms of acceptability and validity<sup>23</sup>.

44  
45 221 Secondary outcomes include Acne-QoL at week-24, participant self-assessed overall improvement recorded  
46  
47 222 on a 6-point Likert scale with photographs taken at baseline<sup>24</sup>, IGA<sup>5</sup>, participant global assessment, use of  
48  
49 223 acne medication and participant satisfaction with study treatment. The IGA is a 5-point scale ranging from  
50  
51 224 clear to severe (0 'Clear'; 1 'Almost clear'; 2 'Mild'; 3 'Moderate'; 4 'Severe')<sup>6,25</sup>. The Investigator's Global  
52  
53 225 Assessment (IGA)<sup>5,24</sup> is used to grade the participant's acne as lesion counts are time consuming, with wide  
54  
55 226 inter-assessor variation and give little additional information to global assessments. All outcome measures  
56 227 are shown in Table 2.

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3 228 The safety profile of spironolactone is well established<sup>15,16</sup>. Consequently, we collect information about  
4  
5 229 adverse reactions of special interest, both to inform the dose review decision from week-6 onwards as well  
6  
7 230 as to learn more about incidence of side effects in this population. We also collect and report all serious  
8  
9 231 adverse events (SAEs).

11 232 *TABLE 2: SCHEDULE OF OBSERVATIONS*

13  
14 233 **Pregnancy**

15  
16 234 Spironolactone is considered contraindicated in pregnancy, or a category C drug (i.e. potential benefits may  
17  
18 235 warrant use in pregnant women despite potential risks)<sup>1,15</sup>. The main concern is around possible feminisation  
19  
20 236 of the male foetus in the third trimester of pregnancy<sup>1</sup>. Women of childbearing potential at risk of pregnancy  
21  
22 237 will be asked to use their usual hormonal or barrier method of contraception during the first 24 weeks of the  
23  
24 238 study and for at least 4 weeks (approximately one menstrual cycle) afterwards. A pregnancy test will be  
25  
26 239 conducted for all participants at their baseline visit and documented in their medical notes. At weeks 6 and  
27  
28 240 12, the study nurse/doctor will ask participants to confirm that they are still using contraception and have not  
29  
30 241 changed contraceptive method. Participants who become pregnant will be asked to inform their local site  
31  
32 242 study team as soon as possible and will not be able to continue in the study.

33  
34 243 **Sample size**

35  
36 244 Based on comparison of the Acne-QoL symptom score between groups at week-12, power 90%, alpha 0.05  
37  
38 245 and seeking a difference between groups of 2 points on the symptom subscale (s.d. 5.8, effect size 0.35),  
39  
40 246 346 participants are needed. Allowing for 20% loss to follow up gives a total 434 participants (217 per  
41  
42 247 group). Following discussions with oversight committees post funding award, the sample size was  
43  
44 248 recalculated. Allowing for a correlation with baseline of 0.293 and a deflation factor of  $1-\rho^2$ <sup>26</sup>, gives a total  
45  
46 249 sample size required of 398 participants. A difference of 2 points on the symptom subscale and a standard  
47  
48 250 deviation of 5.8 (equivalent to an effect size 0.35) is in line with that reported in studies in a similar patient  
49  
50 251 group and with the MCID reported for Acne-QoL<sup>20,21</sup>.

51  
52 252 **Data collection methods**

53  
54 253 Participant data are entered into study electronic case report forms (eCRF) via a remote data collection tool  
55  
56 254 (Medidata Rave) by trained hospital research personnel with specific roles on the study and regularly  
57  
58 255 checked for missing or anomalous values by Southampton CTU study staff.

59  
60

## 256 **Data management**

257 Participant data are pseudonymised by assigning each participant a participant identifier code, which is used  
258 to identify the participant during the study and for any participant-specific communication between  
259 Southampton CTU and recruiting sites.

## 260 **Patient and public involvement (PPI)**

261 This study addresses a priority area identified as important to patients and health professionals by the James  
262 Lind Alliance Priority Setting Partnership for Acne<sup>7</sup>. We gained feedback from a virtual acne-specific patient  
263 panel, convened through 'People in Research' (<https://www.peopleinresearch.org>). A patient survey was  
264 carried out with the support of the UK Dermatology Clinical Trials Network (UK DCTN) in order to inform the  
265 study design. Findings suggested that participants would find it difficult to abstain from using topical  
266 treatments for more than 12 weeks and that asking participants to take a placebo for one year would also be  
267 a barrier to recruitment.

268 Two public contributors with experience of acne attend all Trial Management Group (TMG) meetings to  
269 ensure that decisions around study design are informed by their perspective, study procedures are feasible  
270 for participants and study materials are readable and include all the relevant information that participants  
271 would want. Public contributors influenced the trial design and delivery, for instance by advocating use of  
272 social media advertising to improve recruitment, arguing against repeated measures in this patient group and  
273 that an upper age limit of 50 years was arbitrary and could appear discriminatory.

## 274 **Statistical methods**

275 The study will be reported in accordance with CONSORT guidelines. A detailed statistical analysis plan  
276 (SAP) will be written and reviewed prior to the study database being locked.

277 The modified ITT population consists of all participants who have consented and been randomised to a  
278 treatment arm and have complete data for the outcome being analysed. Analyses will be performed  
279 according to the modified ITT principle using a linear regression model. All analyses will be carried out in the  
280 modified ITT population, with the level of missing data reported, unless otherwise stated. The frequency and  
281 pattern of missing data will be examined and a multiple imputation model will be used as a sensitivity  
282 analysis if appropriate.

283 For the primary analyses, descriptive statistics will be obtained for the randomised groups to characterise  
284 recruited participants and assess baseline comparability. For the primary outcome, a linear regression model

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3 285 will be used to analyse Acne-QoL symptom subscale at week-12, adjusting for baseline variables (including  
4  
5 286 baseline Acne-QoL symptom subscale score, use of topical treatments, use of hormonal contraception/co-  
6  
7 287 cyprindiol) and randomisation stratification variables (centre, baseline severity (IGA < 3 versus 3 or more)). A  
8  
9 288 full list of covariates and model specification will be set out in the SAP. A 95% confidence interval for the  
10  
11 289 least squares mean difference between arms in Acne-QoL symptom subscale at week-12 will be calculated.  
12  
13 290 The same analysis methods will be used to summarise Acne-QoL symptom subscale at other time points  
14  
15 291 (weeks 6, 24 and up to 52 weeks after baseline) and for the other Acne-QoL subscales (self-perception, role-  
16  
17 292 emotional and role-social) and total score. IGA and participants' comparison with baseline photo at weeks 6,  
18  
19 293 12 and 24 will be dichotomised as success or failure as recommended by the US Food and Drug  
20  
21 294 Administration (with success for IGA and participants global assessment defined as clear or almost clear  
22  
23 295 (grade 0 or 1) and at least a two-grade improvement from baseline; this represents a clinically meaningful  
24  
25 296 outcome). The dichotomised outcomes will be summarised by frequencies and percentages and compared  
26  
27 297 by group using logistic regression adjusting for baseline assessment, use of hormonal contraception/co-  
28  
29 298 cyprindiol), use of topical treatment and randomisation stratification factors.  
30  
31 299 Adverse reactions of special interest and SAEs will be summarised by group with frequencies and  
32  
33 300 percentages and compared with Pearson's  $\chi^2$  tests. Logistic regression modelling will also be used to adjust  
34  
35 301 for any important differences in topical treatment use by group. Subgroup analyses will investigate how the  
36  
37 302 treatment effect differs by whether participants have symptoms consistent with polycystic ovary syndrome  
38  
39 303 (PCOS) as recorded at the baseline visit. It is acknowledged the study is not powered for this subgroup  
40  
41 304 analysis. The same analysis methods will be applied to the outcomes collected at up to 52 weeks however  
42  
43 305 the interpretation of these results will be assessed with caution as participants will potentially have been off  
44  
45 306 treatment for up to 6 months or started a different acne treatment. All analyses will be carried out using  
46  
47 307 STATA and/or SAS.  
48  
49 308 There are no planned interim analyses or subgroup analyses.

### 50 309 **Health economics analysis**

51  
52 310 If the intervention is found effective, a within-study economic evaluation will be undertaken to assess value for  
53  
54 311 money of spironolactone plus usual care versus placebo plus usual care. The main perspective of the analysis  
55  
56 312 will be that of the NHS over the 24 week treatment period, although a secondary analysis will assess the  
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3 313 importance of a broader perspective by incorporating out of pocket costs related to acne and any  
4  
5 314 productivity/employment impacts for people with persistent acne<sup>27</sup>.

6  
7 315 Costs, including intervention and wider NHS resource use, are being recorded in the study eCRF for the former  
8  
9 316 whilst wider NHS resource use is captured in participant questionnaires at baseline, weeks 6, 12, and 24.

10  
11 317 Costs will be valued using published unit costs for a common recent price year to estimate mean cost per  
12  
13 318 participant in each arm<sup>28-30</sup>.

14  
15 319 Review of the reliability, validity and responsiveness of three generic preference-based measures (EQ-5D,  
16  
17 320 SF-6D and HUI) in skin conditions only found evidence to support the use of the EQ-5D in skin diseases with  
18  
19 321 no studies looking at measurement properties for the Short-Form six-dimensions (SF-6D) or Health Utilities  
20  
21 322 Index (HUI) in skin disease<sup>31</sup>. Problems on the EQ-5D domains were found to be substantially higher in the  
22  
23 323 acne sample receiving specialist care than in an age truncated population sample (aged 20-39 years)

24 324 particularly on the pain/discomfort (42.1% in the acne sample versus 17.7% in an age-truncated population  
25  
26 325 sample) and anxiety/depression domains (52.8% versus 12.5% respectively)<sup>32</sup>. EQ-5D was found to be

27  
28 326 responsive to change, with moderate effect sizes at 4 and 12 months (-0.44 and -0.53 respectively)<sup>32</sup>. We  
29  
30 327 will value the EQ-5D-5L in our primary analysis in line with NICE recommendations at the time of analysis<sup>3,33</sup>.

31  
32 328 Quality Adjusted Life Years (QALYs) (estimated using EQ-5D-5L<sup>31,32</sup>) for the study period will be estimated  
33  
34 329 using linear interpolation and area under the curve with and without baseline adjustment<sup>34</sup>. Clinical measures

35  
36 330 were found to be more responsive to change than the generic measures (shown by larger effect sizes) and  
37  
38 331 combination of generic preference based measures with the use of disease specific measure was concluded

39  
40 332 to be desirable<sup>32</sup>. The primary economic evaluation will be an incremental cost utility analysis to enable the  
41  
42 333 cost effectiveness to be compared across a range of health conditions and interventions such that decision

43 334 makers can use the information to inform prioritisation of health care. A secondary cost effectiveness

44  
45 335 analysis using the disease specific Acne-QoL will be presented as appropriate, though it should be noted

46  
47 336 that this instrument does not have utility weights available and it is unclear what incremental cost per unit of  
48  
49 337 change on the Acne-QoL represents good value for money. All analysis will be conducted and presented

50  
51 338 using established methods<sup>27,35</sup>.

52  
53  
54 339 If spironolactone is not found to be clinically effective a full economic evaluation will not be conducted. Instead,  
55  
56 340 estimates of mean costs and utility per participant will be presented at the various study time points as these

57 341 may be informative for other researchers undertaking future economic studies or economic modelling in this  
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59 342 clinical area.



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343 A detailed Health Economic Analysis Plan will be written prior to the study database being locked.

## 344 **Oversight and monitoring**

345 The TMG includes representatives with expertise in dermatology, primary care research, psychology,  
346 medical statistics and health economics, public contributors, and Southampton CTU staff involved in the day-  
347 to-day running of the study and is responsible for the oversight of the progress of the study. An independent  
348 Trial Steering Committee (TSC) and an independent Data Monitoring and Ethics Committee (DMEC) have  
349 been set up to monitor study progress and safety.

350 Data on adverse reactions will be collected at the baseline and follow-up visits, and participants will be asked  
351 to report any adverse reactions in their week-24 questionnaire. SAEs may be identified by participant report  
352 at any time directly to the hospital study team, at follow-up visits or questionnaires. Participants' GPs will be  
353 informed of their patient's participation in the study and asked to notify the hospital study team of any  
354 potential SAE. The study also has a UK regulatory compliant real-time SAE reporting process to identify  
355 serious adverse reactions and suspected unexpected serious adverse reactions that could suspend or stop  
356 the study if warranted.

357 The Southampton CTU has undertaken a risk assessment for the study which includes the requirements for  
358 monitoring (both central and site). The Southampton CTU undertakes a number of internal audits of its own  
359 systems and processes annually and has routine audits from both its sponsor and the independent Medicine  
360 and Health care products regulatory authority (MHRA) every 2-3 years.

## 361 **Discussion**

362 This is the first adequately powered pragmatic, randomised trial investigating the effect of spironolactone on  
363 acne in adult women in comparison to a matched placebo. If found to be clinically and cost effective, use of  
364 spironolactone will likely become the new standard of care in addition to topical treatments potentially  
365 reducing antibiotic use for women requiring systemic therapy.

366 Respondents to a survey of people with experience with acne reported that they would be unwilling to be  
367 recruited to a study where they remained blinded to the treatment allocation for 52 weeks, due to concerns  
368 about potential worsening of acne over this time. Therefore, the study was designed as blinded treatment  
369 phase of 24 weeks with an observational follow-up period for up to 6 months after. Use of acne treatments,  
370 such as oral isotretinoin or antibiotics, between week-24 and up to 52 weeks are carefully recorded as

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3 371 differences between groups would be important in interpreting week-52 outcomes. Use of topical treatments  
4  
5 372 is allowed in both groups during the 24 week treatment phase as i) women with moderate-severe acne may  
6  
7 373 be unwilling to be randomised to placebo alone, and ii) recruiting women with moderate-severe acne to a  
8  
9 374 placebo-controlled study with no effective treatment for 12 weeks in the control arm may risk worsening of  
10  
11 375 acne and possible scarring.  
12  
13 376 Although others are seeking to evaluate the role of spironolactone in comparison with oral tetracyclines<sup>36</sup>,  
14  
15 377 this is the largest study to date to inform clinical practice over the effectiveness of spironolactone as an  
16  
17 378 alternative treatment for acne in adult women.  
18  
19

## 20 379 **Abbreviations**

21		
22 380	ACE	Angiotensin-converting enzyme
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24		
25 381	CRN	Clinical Research Network
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27 382	CTU	Clinical Trials Unit
28		
29		
30 383	DMEC	Data Monitoring and Ethics Committee
31		
32 384	eCRF	Electronic Case Report Form
33		
34		
35 385	eGFR	Estimated Glomerular Filtration Rate
36		
37		
38 386	EQ-5D-5 L	EuroQoI Five Dimensions Five Level
39		
40 387	GP	General Practitioner
41		
42		
43 388	HUI	Health Utilities Index
44		
45 389	HRA	Health Research Authority
46		
47		
48 390	HTA	Health Technology Assessment
49		
50		
51 391	ICF	Informed Consent Form
52		
53 392	IGA	Investigator's Global Assessment
54		
55		
56 393	IMP	Investigational Medicinal Product
57		
58 394	IPD	Individual Patient Data
59		
60		

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2			
3	395	ITT	Intention-to-treat
4			
5			
6	396	MCID	Minimum Clinically Important Difference
7			
8	397	MHRA	Medicines and Healthcare products Regulatory Agency
9			
10			
11	398	NHS	National Health Service
12			
13			
14	399	NICE	National Institute for Health and Care Excellence
15			
16	400	NIHR	National Institute for Health Research
17			
18			
19	401	PCOS	Polycystic Ovary Syndrome
20			
21	402	PGA	Participant's Global Assessment
22			
23			
24	403	PIC	Participant Identification Centre
25			
26	404	PIS	Participant Information Sheet
27			
28			
29	405	PPI	Patient and Public Involvement
30			
31			
32	406	PSS	Personal Social Services
33			
34	407	QALYs	Quality Adjusted Life Years
35			
36			
37	408	QoL	Quality of Life
38			
39	409	RCT	Randomised Controlled Trial
40			
41			
42	410	REC	Research Ethics Committee
43			
44			
45	411	SAE	Serious Adverse Event
46			
47	412	SF-6D	Short Form Six Dimensions
48			
49			
50	413	SpR	Specialty registrar
51			
52	414	TMG	Trial Management Group
53			
54			
55	415	TSC	Trial Steering Committee
56			
57	416	UHS	University Hospital Southampton NHS Foundation Trust
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3 417 UK DCTN UK Dermatology Clinical Trials Network  
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5

## 6 418 **Declarations**

7  
8

## 9 419 **Acknowledgements**

10  
11

- 12 420 • The virtual patient panel (brought together by NIHR INVOLVE) for their advice on the study design.
- 13  
14 421 • The study was developed with support from the UK Dermatology Clinical Trials Network (UK DCTN).  
15  
16 422 The UK DCTN is grateful to the British Association of Dermatologists and the University of  
17  
18 423 Nottingham for financial support of the Network. UK DCTN conducted surveys among patients with  
19  
20 424 acne and health professionals managing acne to inform the study design, promoting the study and  
21  
22 425 identifying and advising on potential hospital sites delivering the study.  
23
- 24 426 • Wessex CRN for funding the initial social media advertising campaign.
- 25  
26  
27 427 • Jessica Boxall and Liz Allaway for management of the study social media accounts as well as  
28  
29 428 running and coordinating the social media adverts.
- 30  
31 429 • Hospital dermatology centres recruiting for the study: Queen Elizabeth Hospital, Birmingham; Bristol  
32  
33 430 Royal Infirmary Dermatology Centre, Bristol; University Hospital of Wales, Cardiff; General Hospital,  
34  
35 431 Epsom; District Hospital, Harrogate; St Mary's Hospital (Imperial College NHS Healthcare Trust),  
36  
37 432 London; Queen's Medical Centre, Nottingham; General Hospital, Poole; St Mary's General Hospital  
38  
39 433 Dermatology Centre, Portsmouth; Swansea Bay University Health Board, Swansea.
- 40  
41 434 • Participant Identification Centres (PICs) for searching their patient lists and mail outs and Clinical  
42  
43 435 Research Networks (CRNs) for helping to identify potential PICs.  
44

## 46 436 **Authors' contributions**

47

48 437 Research funding was obtained by MS, AL, NF, GG, PL, IM, JN, MJR, TS, IS, LS, BS, KT and KST. All  
49  
50 438 authors have contributed to the development of the protocol and to the management of the study. SR leads  
51  
52 439 on the day-to-day management of the study, overseen by ZE, MS, JN and BS. This paper was drafted by FC  
53  
54 440 and SR with contributions from MS and all authors. All authors read and approved the final manuscript.  
55

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57

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59  
60

1  
2  
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4  
5 444 Southampton CTU. The views expressed are those of the author(s) and not necessarily those of the NIHR  
6  
7 445 or the Department of Health and Social Care. The NIHR HTA funder will play no role in the execution,  
8  
9 446 analysis, interpretation of data, or study publication. The study is registered on the UK NIHR study portfolio  
10  
11 447 meaning there are research nurses based at UK hospitals who help in screening potential patients to identify  
12  
13 448 those eligible for the study.  
14  
15 449 Southampton CTU, a NIHR CTU support funded UK Clinical Research Collaboration registered CTU, is  
16  
17 450 coordinating the study. University of Southampton is the sponsor for the study.  
18

### 19 451 **Trial status**

20  
21  
22 452 This clinical trial was registered on 17-Sep-2018 (EudraCT Number: 2018-003630-33) and on 15-Oct-2018  
23  
24 453 (ISRCTN, registry number: ISRCTN 12892056). The first participant was recruited on 05-Jun-2019 and  
25  
26 454 recruitment is expected to be completed on 31-Aug-2021. The current protocol is version 10, dated 08-Mar-  
27  
28 455 2021. The full protocol v10 08-MAR-2021 is available as supplementary material and on request via  
29  
30 456 [safa@soton.ac.uk](mailto:safa@soton.ac.uk) or on the study website [https://www.southampton.ac.uk/safa/about/researchers-and-](https://www.southampton.ac.uk/safa/about/researchers-and-clinicians.page)  
31  
32 457 [clinicians.page](https://www.southampton.ac.uk/safa/about/researchers-and-clinicians.page). REC/MHRA approved protocol amendments will be communicated to sites via email and  
33  
34 458 updated trial documentation provided centrally via the trial website. Trial registries will be amended where  
35  
36 459 relevant with explanations for these changes. End of study is defined as the date when the last point of data  
37  
38 460 is collected for the last participant from their Final follow-up questionnaire.  
39

### 40 461 **Ethics approval**

41  
42 462 The trial received favourable ethical opinion from Wales Research Ethics Committee (18/WA/0420) and has  
43  
44 463 Health Research Authority (HRA) approval (IRAS 246637).  
45  
46

### 47 464 **Availability of data and materials**

#### 49 465 **Data Management Plan**

50  
51  
52 466 Full details of the data management strategy for the study are available in the SAFA data management plan,  
53  
54 467 available on request via [safa@soton.ac.uk](mailto:safa@soton.ac.uk).  
55

#### 56 468 **Underlying data**

57  
58  
59 469 Pseudonymised individual participant data (IPD) within the clinical study dataset will be available for sharing  
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470 via controlled access by authorised Southampton CTU staff (as delegated to Southampton CTU by the study  
471 sponsor). Data access can be requested via a Southampton CTU Data Release application form (available  
472 from <https://www.southampton.ac.uk/ctu/about/index.page>) after the trial is published. Please email the  
473 completed form to the Southampton CTU Data Release Committee Coordinator at [ctu@soton.ac.uk](mailto:ctu@soton.ac.uk).  
474 Data access requests are reviewed against specific eligibility criteria by the Southampton CTU data  
475 custodian and key members of the study team, including a statistician and chief investigator or by an  
476 external Independent Review Panel. Decisions about requests are made promptly and usually no more than  
477 three months after receipt of request. Responses to all data requests, with a clear rationale for any refusals,  
478 will be sent promptly to the data requester.

### 479 **Extended data**

480 Written informed consent is obtained from participants during the baseline visit by qualified site trial team  
481 members. A copy of the study's Informed Consent Form (v4 05-MAR-2021) is available as supplementary  
482 material or on request via [safa@soton.ac.uk](mailto:safa@soton.ac.uk).

### 483 **Consent for publication**

484 Responsibility for publication has been delegated to Prof Miriam Santer and Prof Alison Layton (co-Chief  
485 Investigators) and Prof Gareth Griffiths (Director of Southampton CTU), who have consented to this  
486 publication.

### 487 **Competing interests**

488 The authors have no competing interests to declare.

### 489 **Authors' information (optional)**

490 Not applicable.

### 491 **Open Access**

492 This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution  
493 (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial  
494 use, provided the original work is properly cited. See: <http://creativecommons.org/licenses/by/4.0/>

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60496 **Tables**

497 Table 1: Schedule of procedures

Observation/procedure	Person undertaking the specified event	Visit				
		Screening/ Baseline	Week 6	Week 12	End of Treatment/ Week 24 contact	End of Study/ Final Follow-up questionnaire (52 weeks or sooner) <sup>3</sup>
<b>ENROLMENT</b>						
Informed Consent	Nurse/ Other clinician <sup>1</sup>	X				
Eligibility evaluation	Other clinician	X				
Participant characteristics	Nurse/Other clinician	X				
Blood pressure	Nurse/Other clinician	X				
Blood tests (serum potassium, eGFR)	Nurse/Other clinician	X				
Pregnancy test	Nurse/Other clinician	X				
<b>RANDOMISATION</b>	Nurse/Other clinician	X				
<b>ASSESSMENTS</b>						
Investigator's Global Assessment (IGA)	Nurse/ Other clinician	X	X	X		
Medical history	Participant	X				
Self-assessment - Participants Global Assessment (adapted IGA)	Participant	X	X	X	X	X
Acne Medication Use	Nurse/Other clinician/Participant	X	X	X	X	X
Other Medication Use	Nurse/Other clinician/Participant	X				
Acne-QoL	Participant	X	X	X	X	X
EQ-5D-5L	Participant	X	X	X	X	X
Resource use questionnaire	Participant	X	X	X	X	X
Self-assessment – comparison with baseline photo - 6 Point Likert Scale	Participant		X	X	X	X
Collection of ARs of special interest: Headache Dizziness/vertigo/ Light headedness Tingling Indigestion/heartburn/ Dyspepsia Diarrhoea Polyuria (passing much more urine than normal) Nausea/feeling sick Vomiting/being sick Tenderness of the breasts Breast enlargement Irregular menstrual periods Abdominal pain Weight gain Reduced libido (reduced interest in sex) Fatigue/tiredness Drowsiness/sleepiness	Participant/ Other clinician		X	X	X	

Observation/procedure	Person undertaking the specified event	Visit				
		Screening/ Baseline	Week 6	Week 12	End of Treatment/ Week 24 contact	End of Study/ Final Follow-up questionnaire (52 weeks or sooner) <sup>3</sup>
Serious Adverse Events	Other clinician (PI or delegate)		X	X	X	
Assessment of treatment response to determine dose adjustment <sup>2</sup>	Participant / Other clinician		X	X		
Satisfaction with study treatment	Participant				X	
<b>OTHER ACTIVITIES</b>						
Discuss use of contraception	Nurse/Other clinician	X	X	X		
Photographs of face taken	Nurse/Other clinician	X				
Photographs given to participant	Nurse/Other Clinician	X		X (If a set was stored at site)		
Letter to participant's GP (patient participation)	Nurse/Other clinician	X				
Check participant is not using oral acne treatment	Nurse/Other clinician/Participant		X	X		
Return excess IMP to clinic	Participant		X	X	X (return via post)	
Spirolactone/Placebo pill count	Nurse/Other clinician/Participant		X	X	X	
Letter to participant's GP (if dose is change)	Nurse/Other clinician		X	X		
Reminder to participant to report any subsequent adverse event(s) that might reasonably be related to participation in this study (up to 52 weeks)	Nurse/Other clinician			X		
Ask participant if they would like to receive a summary of the study results, when available	Nurse/Other clinician			X		
Letter to participant (unblinding)					X (after 24 weeks)	
Letter to participant's GP (unblinding)					X (after 24 weeks)	

<sup>1</sup> Dermatologist or Clinical Research Fellow, in line with local procedures with demonstrable and appropriate level of training. Specific duties delegated by the PI and listed on the delegation log.

<sup>2</sup> Dose escalated to 2 tablets per day if participant is tolerating side effects.

<sup>3</sup> The follow-up questionnaire will be sent out 6 months or sooner after the 24-week timepoint.



Table 2: Schedule of observations

Outcome measure	6 weeks	12 weeks (primary endpoint)	24 weeks (end of treatment)	Unblinded Follow-up ( 52 weeks or sooner) <sup>h</sup>
<b>Primary outcome measure</b>				
Acne-QoL symptom subscale score		X		
<b>Secondary outcome measures</b>				
Acne-QoL symptom subscale score	X	X	X	X
Acne-QoL other subscales <sup>a</sup>	X	X	X	X
Acne-QoL total score	X	X	X	X
Participant self-assessed overall improvement <sup>b</sup>	X	X	X	X
Investigator's Global Assessment (IGA) <sup>c</sup>	X	X		
Participant's Global Assessment (PGA) <sup>d</sup>	X	X	X	X
Participant satisfaction with study treatment <sup>e</sup>			X	
Health-related quality of life using EQ-5D-5L <sup>f</sup>	X	X	X	X
Costs incurred	X	X	X	X
Cost-effectiveness <sup>g</sup>			X	

<sup>a</sup> Self-perception, role-emotional and role-social; <sup>b</sup> recorded on a 6-point Likert scale with photographs taken at the baseline visit to aid recall<sup>37</sup>; <sup>c</sup> 5-point scale ranging from clear to severe (0 - Clear; 1 - Almost clear; 2 - Mild; 3 - Moderate; 4 - Severe)<sup>38</sup>;

<sup>d</sup> Same scale as the IGA, but written in Plain English for participants' use; <sup>e</sup> Asked prior to revealing treatment allocation after 24 weeks;

<sup>f</sup> The EQ-5D-5 L assesses five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression; <sup>g</sup> Using EQ-5D-5L and data on health resource use during the study; <sup>h</sup> The follow-up questionnaire will be sent out 6 months or sooner after the 24-week timepoint.

**BOX 1*****Rationale for the dosing regimen***

We conducted a survey of health professionals to inform the spironolactone dose regimen (unpublished).

Responses were received from 41 Dermatology consultants, 10 Dermatology nurses and 3 Dermatology SpRs.

Of these 54 Dermatology health professionals, 22 prescribed spironolactone (9 rarely, 10 sometimes and 3 often). Most of those who responded stated that they would start at 50mg and increase up to 100-150mg depending on response. Several noted that this would depend on the patient's weight, with the starting dose lowered to 25mg if needed and allowing the dosage to increase up to 200mg. There was no consistency on the timeframe for these increases with 4 weeks, 6 weeks, 12 weeks and 6 months all being mentioned as review points.

A previous HTA study examining common treatments in the management of acne suggested that assessing efficacy at 6 weeks was ideal<sup>24</sup> – this informed the timing of follow-up assessments and dose escalation. US guidelines note that studies have been carried out using spironolactone doses ranging from 50mg to 200mg daily.<sup>1</sup> No specific dose is recommended but it is noted that side effects are dose-related.<sup>1</sup>

A recent hybrid systematic review of RCTs and case series identified some very low-quality evidence which showed that a daily dose of 200mg was statistically significantly more effective than placebo versus inflamed lesions, but it also confirmed that this dose is associated with a significantly greater risk of adverse side effects than lower doses.<sup>17</sup>

Hence, there would appear to be no merit in using these higher doses for managing acne. Data from the multiple case series suggested that any future RCT examining lower doses is likely to generate results that confirm the effectiveness and better safety profile of doses  $\leq 100$  mg per day, which informed the dosage regimen.

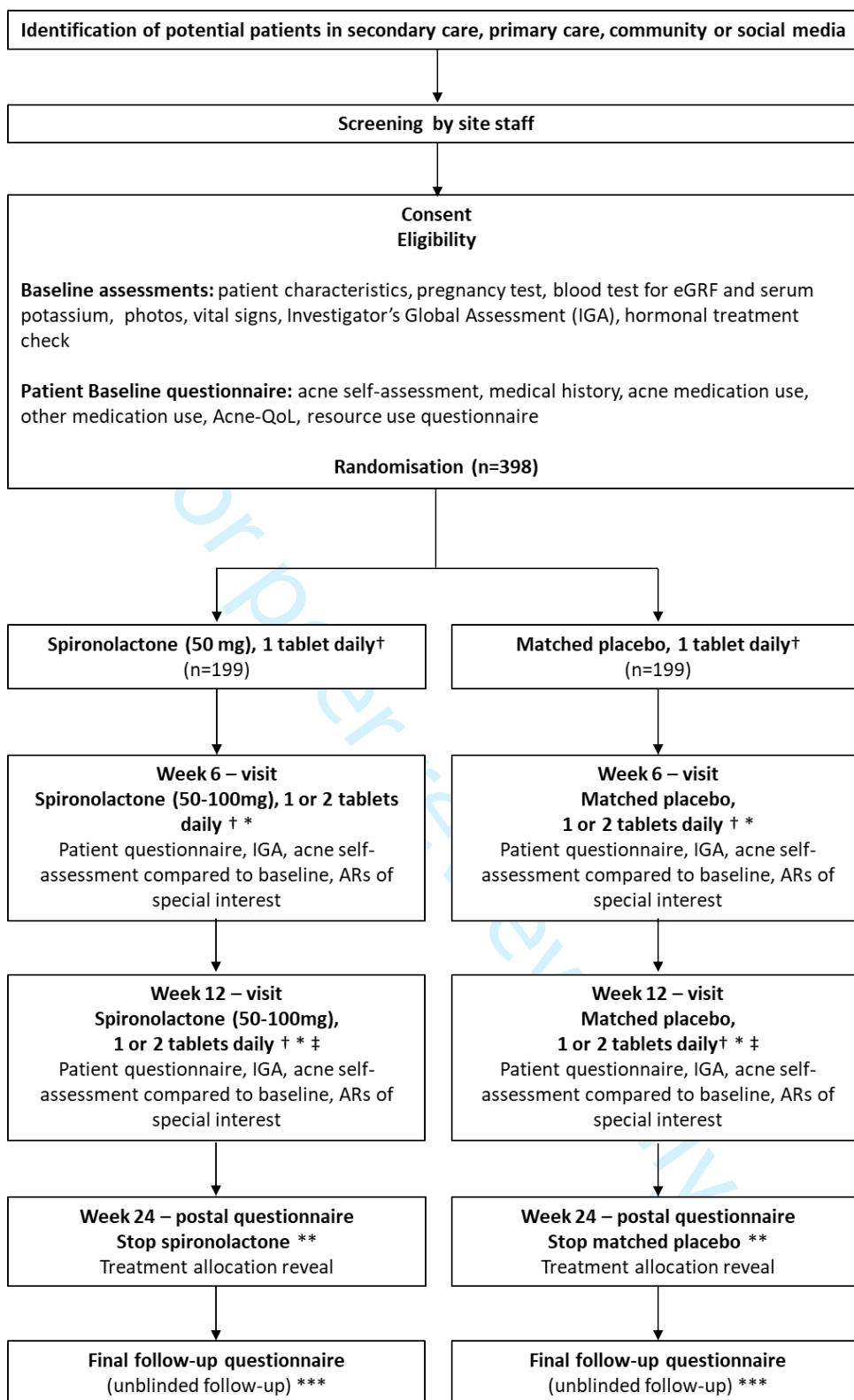
For most licensed indications for spironolactone, the British National Formulary states a starting dose of 100mg, titrated as required. Therefore, a starting dose of 50mg in the SAFA study seems conservative.

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† Allow use of topical therapy (creams/lotions/gels)

\*Escalate dose if study tablet is tolerated, otherwise maintain on 1 tablet

‡ Add antibiotic taken by mouth/change topical therapy if response to study tablet is inadequate

\*\*Participants in either arm may seek to use spironolactone after this time.

\*\*\*The follow-up questionnaire will be sent out 6 months or sooner after the 24-week timepoint.



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	ItemNo	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 17
	2b	All items from the World Health Organization Trial Registration Data Set	Included throughout manuscript
Protocol version	3	Date and version identifier	17
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 16
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

**Introduction**

1				
2	Background and	6a	Description of research question and justification	3-4
3	rationale		for undertaking the trial, including summary of	
4			relevant studies (published and unpublished)	
5			examining benefits and harms for each intervention	
6				
7		6b	Explanation for choice of comparators	5
8				
9	Objectives	7	Specific objectives or hypotheses	4
10				
11	Trial design	8	Description of trial design including type of trial (eg,	5
12			parallel group, crossover, factorial, single group),	
13			allocation ratio, and framework (eg, superiority,	
14			equivalence, noninferiority, exploratory)	
15				
16				
17				
18	<b>Methods: Participants, interventions, and outcomes</b>			
19	Study setting	9	Description of study settings (eg, community clinic,	4-5
20			academic hospital) and list of countries where data	
21			will be collected. Reference to where list of study	
22			sites can be obtained	
23				
24				
25	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If	5-7
26			applicable, eligibility criteria for study centres and	
27			individuals who will perform the interventions (eg,	
28			surgeons, psychotherapists)	
29				
30				
31	Interventions	11a	Interventions for each group with sufficient detail to	7
32			allow replication, including how and when they will	
33			be administered	
34				
35		11b	Criteria for discontinuing or modifying allocated	9, 5
36			interventions for a given trial participant (eg, drug	
37			dose change in response to harms, participant	
38			request, or improving/worsening disease)	
39				
40				
41		11c	Strategies to improve adherence to intervention	7
42			protocols, and any procedures for monitoring	
43			adherence (eg, drug tablet return, laboratory tests)	
44				
45		11d	Relevant concomitant care and interventions that	5
46			are permitted or prohibited during the trial	
47				
48				
49	Outcomes	12	Primary, secondary, and other outcomes, including	8, 9
50			the specific measurement variable (eg, systolic	
51			blood pressure), analysis metric (eg, change from	
52			baseline, final value, time to event), method of	
53			aggregation (eg, median, proportion), and time	
54			point for each outcome. Explanation of the clinical	
55			relevance of chosen efficacy and harm outcomes	
56			is strongly recommended	
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2	Participant	13	Time schedule of enrolment, interventions	7, Figure 1,
3	timeline		(including any run-ins and washouts),	Table 2
4			assessments, and visits for participants. A	
5			schematic diagram is highly recommended (see	
6			Figure)	
7				
8	Sample size	14	Estimated number of participants needed to	9
9			achieve study objectives and how it was	
10			determined, including clinical and statistical	
11			assumptions supporting any sample size	
12			calculations	
13				
14				
15	Recruitment	15	Strategies for achieving adequate participant	7, 8
16			enrolment to reach target sample size	
17				
18				

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

21				
22				
23	Sequence	16a	Method of generating the allocation sequence (eg,	9
24	generation		computer-generated random numbers), and list of	
25			any factors for stratification. To reduce	
26			predictability of a random sequence, details of any	
27			planned restriction (eg, blocking) should be	
28			provided in a separate document that is	
29			unavailable to those who enrol participants or	
30			assign interventions	
31				
32				
33	Allocation	16b	Mechanism of implementing the allocation	9
34	concealment		sequence (eg, central telephone; sequentially	
35	mechanism		numbered, opaque, sealed envelopes), describing	
36			any steps to conceal the sequence until	
37			interventions are assigned	
38				
39				
40	Implementation	16c	Who will generate the allocation sequence, who	9
41			will enrol participants, and who will assign	
42			participants to interventions	
43				
44				
45	Blinding	17a	Who will be blinded after assignment to	9
46	(masking)		interventions (eg, trial participants, care providers,	
47			outcome assessors, data analysts), and how	
48				
49		17b	If blinded, circumstances under which unblinding is	9
50			permissible, and procedure for revealing a	
51			participant's allocated intervention during the trial	
52				
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### Methods: Data collection, management, and analysis



1				
2	Data collection	18a	Plans for assessment and collection of outcome,	9
3	methods		baseline, and other trial data, including any related	
4			processes to promote data quality (eg, duplicate	
5			measurements, training of assessors) and a	
6			description of study instruments (eg,	
7			questionnaires, laboratory tests) along with their	
8			reliability and validity, if known. Reference to where	
9			data collection forms can be found, if not in the	
10			protocol	
11				
12				
13		18b	Plans to promote participant retention and	4, 7
14			complete follow-up, including list of any outcome	
15			data to be collected for participants who	
16			discontinue or deviate from intervention protocols	
17				
18				
19	Data	19	Plans for data entry, coding, security, and storage,	10
20	management		including any related processes to promote data	
21			quality (eg, double data entry; range checks for	
22			data values). Reference to where details of data	
23			management procedures can be found, if not in the	
24			protocol	
25				
26				
27	Statistical	20a	Statistical methods for analysing primary and	10, 11
28	methods		secondary outcomes. Reference to where other	
29			details of the statistical analysis plan can be found,	
30			if not in the protocol	
31				
32				
33		20b	Methods for any additional analyses (eg, subgroup	11, 12
34			and adjusted analyses)	
35				
36		20c	Definition of analysis population relating to protocol	10, 11
37			non-adherence (eg, as randomised analysis), and	
38			any statistical methods to handle missing data (eg,	
39			multiple imputation)	
40				
41				
42	<b>Methods: Monitoring</b>			
43				
44	Data monitoring	21a	Composition of data monitoring committee (DMC);	13
45			summary of its role and reporting structure;	
46			statement of whether it is independent from the	
47			sponsor and competing interests; and reference to	
48			where further details about its charter can be	
49			found, if not in the protocol. Alternatively, an	
50			explanation of why a DMC is not needed	
51				
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53		21b	Description of any interim analyses and stopping	10, 11
54			guidelines, including who will have access to these	
55			interim results and make the final decision to	
56			terminate the trial	
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2	Harms	22	Plans for collecting, assessing, reporting, and	13
3			managing solicited and spontaneously reported	
4			adverse events and other unintended effects of	
5			trial interventions or trial conduct	
6				
7	Auditing	23	Frequency and procedures for auditing trial	13
8			conduct, if any, and whether the process will be	
9			independent from investigators and the sponsor	
10				
11				
12	<b>Ethics and dissemination</b>			
13				
14	Research ethics	24	Plans for seeking research ethics	2, 17
15	approval		committee/institutional review board (REC/IRB)	
16			approval	
17				
18	Protocol	25	Plans for communicating important protocol	17
19	amendments		modifications (eg, changes to eligibility criteria,	
20			outcomes, analyses) to relevant parties (eg,	
21			investigators, REC/IRBs, trial participants, trial	
22			registries, journals, regulators)	
23				
24				
25	Consent or	26a	Who will obtain informed consent or assent from	18, Table 1
26	assent		potential trial participants or authorised surrogates,	
27			and how (see Item 32)	
28				
29				
30		26b	Additional consent provisions for collection and use	n/a
31			of participant data and biological specimens in	
32			ancillary studies, if applicable	
33				
34	Confidentiality	27	How personal information about potential and	17, 18
35			enrolled participants will be collected, shared, and	
36			maintained in order to protect confidentiality	
37			before, during, and after the trial	
38				
39				
40	Declaration of	28	Financial and other competing interests for	18
41	interests		principal investigators for the overall trial and each	
42			study site	
43				
44	Access to data	29	Statement of who will have access to the final trial	18
45			dataset, and disclosure of contractual agreements	
46			that limit such access for investigators	
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49	Ancillary and	30	Provisions, if any, for ancillary and post-trial care,	n/a
50	post-trial care		and for compensation to those who suffer harm	
51			from trial participation	
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2	Dissemination	31a	Plans for investigators and sponsor to	2
3	policy		communicate trial results to participants,	
4			healthcare professionals, the public, and other	
5			relevant groups (eg, via publication, reporting in	
6			results databases, or other data sharing	
7			arrangements), including any publication	
8			restrictions	
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11		31b	Authorship eligibility guidelines and any intended	16
12			use of professional writers	
13				
14		31c	Plans, if any, for granting public access to the full	17
15			protocol, participant-level dataset, and statistical	
16			code	
17				
18				
19	<b>Appendices</b>			
20				
21	Informed consent	32	Model consent form and other related	Additional
22	materials		documentation given to participants and authorised	File 2
23			surrogates	
24				
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26	Biological	33	Plans for collection, laboratory evaluation, and	n/a
27	specimens		storage of biological specimens for genetic or	
28			molecular analysis in the current trial and for future	
29			use in ancillary studies, if applicable	
30				

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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

## Spironolactone for Adult Female Acne (SAFA): A double-blind, placebo-controlled, phase III randomised study of spironolactone as systemic therapy for acne in adult women: study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-053876.R1
Article Type:	Protocol
Date Submitted by the Author:	14-Jul-2021
Complete List of Authors:	<p>Renz, Susanne; University of Southampton, Southampton Clinical Trials Unit</p> <p>Chinnery, Fay; University of Southampton, Southampton Clinical Trials Unit</p> <p>Stuart, Beth; University of Southampton, Primary Care Research Centre, Faculty of Medicine, School of Primary Care, Population Sciences and Medical Education ; University of Southampton, Southampton Clinical Trials Unit</p> <p>Day, Laura; University of Southampton, Southampton Clinical Trials Unit</p> <p>Muller, Ingrid; University of Southampton, Primary Care Research Centre, Faculty of Medicine, School of Primary Care, Population Sciences and Medical Education</p> <p>Soulsby, Irene; PPI representative</p> <p>Nuttall, Jacqui; University of Southampton, Southampton Clinical Trials Unit</p> <p>Thomas, Karen ; PPI representative, Acne Support</p> <p>Thomas, Kim; University of Nottingham, School of Medicine, Centre of Evidence Based Dermatology</p> <p>Sach, Tracey; University of East Anglia, Health Economics Group, Norwich Medical School</p> <p>Stanton, Louise; University of Southampton, Southampton Clinical Trials Unit</p> <p>Ridd, Matthew; University of Bristol Faculty of Health Sciences, Population Health Sciences</p> <p>Francis, Nick; University of Southampton, Primary Care Research Centre, Faculty of Medicine, School of Primary Care Population Sciences and Medical Education</p> <p>Little, Paul; University of Southampton, Primary Care Research Centre, Faculty of Medicine, School of Primary Care, Population Sciences and Medical Education</p> <p>Eminton, Zina; University of Southampton, Southampton Clinical Trials Unit</p> <p>Griffiths, Gareth; University of Southampton, Southampton Clinical Trials Unit</p> <p>Layton, Alison M; University of York, Hull York Medical School</p> <p>Santer, Miriam; University of Southampton, Primary Care Research Centre, Faculty of Medicine, School of Primary Care, Population Sciences and Medical Education</p>

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<b>Primary Subject Heading:</b>	Dermatology
<b>Secondary Subject Heading:</b>	Dermatology
<b>Keywords:</b>	DERMATOLOGY, Acne < DERMATOLOGY, Adult dermatology < DERMATOLOGY

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Manuscripts



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## 1 Title

2 Spironolactone for Adult Female Acne (SAFA): A double-blind, placebo-controlled, phase III randomised  
3 study of spironolactone as systemic therapy for acne in adult women: study protocol

## 5 Names protocol contributors

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## Abstract

**Introduction:** Acne is one of the most common inflammatory skin diseases worldwide and can have significant psychosocial impact and cause permanent scarring. Spironolactone, a potassium-sparing diuretic, has anti-androgenic properties, potentially reducing sebum production and hyperkeratinisation in acne prone follicles. Dermatologists have prescribed spironolactone for acne in women for over 30 years, but robust clinical study data are lacking. This study seeks to evaluate whether spironolactone is clinically and cost-effective in treating acne in women.

**Methods and analysis:** Women ( $\geq 18$  years) with persistent facial acne requiring systemic therapy, are randomised to receive one tablet daily of 50 mg spironolactone or a matched placebo until week-6, increasing to up to two tablets daily (total 100 mg spironolactone or matched placebo) until week-24, along with usual topical therapy if desired. Study treatment stops at week-24, participants are informed of their treatment allocation and enter an unblinded observational follow-up period for up to 6 months (up to week-52 after baseline). Primary outcome is the Acne-specific Quality of Life (Acne-QoL) symptom subscale score at week-12. Secondary outcomes include: Acne-QoL total and subscales, participant acne self-assessment recorded on a 6-point Likert scale at 6, 12, 24 weeks and up to 52 weeks, Investigator's Global Assessment (IGA) at weeks 6 and 12, cost and cost effectiveness are assessed over 24 weeks. Aiming to detect a group difference of 2 points on the Acne-QoL symptom subscale (s.d. 5.8, effect size 0.35), allowing for 20% loss to follow-up, gives a sample size of 398 participants. **Ethics and dissemination:** This protocol was approved by Wales Research Ethics Committee (18/WA/0420). Follow-up to be completed in early 2022. Findings will be disseminated to participants, peer-reviewed journals, networks and patient groups, on social media, on the study website and the Southampton Clinical Trials Unit (CTU) website to maximise impact.

**Study registration:** ISRCTN 12892056.



## 57 **Strengths and limitations of this study**

- 58 • Pragmatic design to inform real-world decision making for women with acne includes a primary  
59 outcome that is a participant-reported outcome measure, broad eligibility and recruitment strategies  
60 via primary care, secondary care, community and social media advertising
- 61 • Randomisation to either spironolactone or matched placebo, with participants in both groups using  
62 topical treatments as usual (creams, gels, lotions), if desired, in order to reflect the place of oral  
63 treatments in the acne care pathway
- 64 • Adaptions during the COVID-19 pandemic included inevitable limitations, including remote follow-up  
65 visits (via phone or video call), limiting collection of secondary outcomes such as investigator-  
66 assessed acne severity

## 67 **Keywords**

68 Spironolactone; adult female acne; topical therapy; dermatology; randomised controlled study

## 69 **Background**

70 Acne vulgaris (from here on referred to as acne) is the eighth most common disease worldwide<sup>1</sup> and typically  
71 starts in adolescence with 15-20% of people affected showing moderate or severe acne, often persisting into  
72 adulthood<sup>2</sup>. Facial scarring occurs in approximately 20% of people but the main impact is social, with levels  
73 of psychological disability equivalent to those seen in conditions such as asthma and diabetes<sup>3,4</sup>. Incidence  
74 of acne in adult women is considerable and growing<sup>5-9</sup>.

75 First line treatment for acne is topical treatments either alone or combination preparations, containing  
76 retinoids, benzoyl peroxide and/or antibiotics<sup>3</sup>. However, non-adherence to topical treatments is common,  
77 possibly because of the need to be used consistently for up to 8 weeks and adverse reactions, such as  
78 stinging or redness, are common<sup>10</sup>. People therefore commonly seek second-line therapies, such as oral  
79 antibiotics, ethinylestradiol/cyproterone acetate (co-cyprindiol) or combined oral contraceptives<sup>3</sup>. In the UK,  
80 oral isotretinoin can be used under the supervision of a dermatologist for indications including severe, cystic,  
81 nodular or recalcitrant acne. Oral isotretinoin is highly effective, but is not suitable for all patients and is  
82 teratogenic<sup>2</sup>, therefore needing careful pregnancy prevention management.

83 A third of people who consult with acne are prescribed long courses of oral antibiotics<sup>3,11</sup>. However, acne is a  
84 disease of sebogenesis and antibiotics have no effect on sebum production<sup>12,13</sup>. Furthermore, rising rates of  
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3 86 antibiotic resistance mean non-antibiotic alternatives are needed<sup>14</sup>.

4  
5 87 Spironolactone, a potassium-sparing diuretic, is widely used in the UK for indications including  
6  
7 88 hypertension<sup>15</sup> and has been used off-license for women with acne for  $\geq 30$  years due to its anti-androgenic  
8  
9 89 properties. US Guidelines suggest a role in the management of female acne<sup>1</sup>. Spironolactone is not used to  
10  
11 90 treat acne in men, because of its feminising side effects<sup>16</sup>.

12  
13 91 There is limited evidence for the effectiveness of spironolactone for treating acne and the need for evidence  
14  
15 92 from randomised controlled trials (RCTs) in this patient group is acknowledged<sup>16</sup>.

16  
17 93 When considering spironolactone as a potential alternative systemic therapy for acne, one study reported  
18  
19 94 treatment success in women who had previously failed isotretinoin<sup>17</sup> and a second study comparing the  
20  
21 95 frequency with which participants switched drug treatment within one year of initiation, demonstrated no  
22  
23 96 significant difference between those taking spironolactone and those taking oral antibiotics for their acne,<sup>18</sup>  
24  
25 97 implying they are equally tolerated by users. A further database study has shown that spironolactone may  
26  
27 98 have superior drug usage survival compared to oral antibiotics for women with acne, giving a suggestion of  
28  
29 99 greater perceived effectiveness and tolerability<sup>19</sup>.

30 100 A James Lind Alliance Priority Setting Partnership, funded by the National Institute for Health Research  
31  
32 101 (NIHR), identified the need to establish the best way to manage acne in women who may or may not have  
33  
34 102 underlying hormonal abnormalities<sup>20</sup>. This informed an NIHR commissioned call (16/13 Persistent acne in  
35  
36 103 adult women) for proposals to answer the research question: 'What is the effectiveness of spironolactone in  
37  
38 104 the treatment of moderate-severe persistent acne in adult women?'

39  
40 105 This study aims to answer whether spironolactone in addition to standard topical therapy is able to improve  
41  
42 106 acne-related quality of life in adult women with moderate-severe persistent facial acne compare to placebo  
43  
44 107 plus standard topical therapy.

## 45 46 108 **Methods**

### 47 48 49 109 **Study design and setting**

50  
51 110 The study is a phase III, multicentre, double-blind, randomised superiority study, to investigate clinical and  
52  
53 111 cost-effectiveness of spironolactone in the treatment of moderate or severe persistent facial acne in adult  
54  
55 112 women compared to placebo, in addition to standard topical treatment. The design is pragmatic in order to  
56  
57 113 have strong external validity and to inform real-world decision-making for women with acne and their health  
58  
59 114 professionals. Pragmatic design includes broad eligibility and recruitment strategies, a primary outcome that  
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3 115 is relevant to participants, low intensity follow-up and an intention-to-treat (ITT) analysis. 'Moderate to severe  
4  
5 116 acne', in the context of this study, is defined as acne that warrants treatment with oral antibiotics, as judged  
6  
7 117 by the potential participant and study clinician.

8  
9 118 Baseline and follow-up appointments are carried out by UK hospital dermatology centres in order to facilitate  
10  
11 119 blood tests at baseline and clinical assessments. Participants continue on the allocated treatment  
12  
13 120 (spironolactone or placebo) in combination with their usual topical treatment (if desired) for a total duration of  
14  
15 121 24 weeks with assessments at weeks 6 and 12. Primary outcome is assessed at week-12 with the patient-  
16  
17 122 reported Acne-QoL<sup>21,22</sup>. From week-12, participants in both groups may receive 'usual care' from their usual  
18  
19 123 clinical team including oral treatments (oral antibiotics, hormonal treatments), and from week-24 isotretinoin,  
20  
21 124 if the participant and study clinician feel the need for rescue treatment. Trial participants receive shopping  
22  
23 125 vouchers at baseline, 6 and 12 weeks (total £40). At week-24, participants stop taking their study treatment,  
24  
25 126 are informed of their treatment group allocation and enter an unblinded observational follow-up period for up  
26  
27 127 to six months (up to week-52 after baseline). During this observational final follow-up period, participants can  
28  
29 128 ask their General Practitioner (GP) to be prescribed spironolactone for their acne if they wish, or pursue  
30  
31 129 other acne treatments as part of usual care. Figure 1 illustrates the patient pathway through the study with  
32  
33 130 Table 1 summarising the study procedures.

34  
35 131 Adaptations during the COVID-19 pandemic included the option to hold follow-up visits at weeks 6 and 12  
36  
37 132 remotely (phone/video calls) and to post out the study tablets and questionnaires to participants. Participants  
38  
39 133 were also given standardised instructions on how to photograph their face to submit as part of remote follow-  
40  
41 134 up assessments. Baseline visits continued to be face-to-face due to the requirement of a urine pregnancy  
42  
43 135 test and blood test to assess kidney function and serum potassium levels.

44  
45 136 *FIGURE 1: STUDY SCHEMA*

46  
47 137 *TABLE 1: SCHEDULE OF PROCEDURES*

## 48 49 138 **Eligibility**

### 50 51 139 **Inclusion criteria**

52  
53 140 Participants should fulfil all the following criteria:

- 54  
55 141
- 56 142 • Women aged  $\geq 18$  years
  - 57 143 • Facial acne vulgaris, symptoms present for at least 6 months
  - 58 144 • Acne of sufficient severity to warrant treatment with oral antibiotics, as judged by the study clinician.
- 59  
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3 144 Patients with an IGA $\geq$ 2 are eligible to participate in the study  
4  
5

- 6 145 • Women of childbearing potential at risk of pregnancy must be willing to use their usual hormonal or  
7  
8 146 barrier method of contraception for the first 6 months of the study (whilst taking the study  
9  
10 147 investigational medicinal product (IMP)) and for at least 4 weeks afterwards  
11  
12 148 • Willing to be randomised to either study group  
13  
14 149 • Willing and able to give informed consent  
15  
16 150 • Sufficient English to carry out primary outcome Acne-QoL

17  
18 151 **Exclusion criteria**

19  
20 152 Individuals meeting any of the following criteria will be excluded:

- 21  
22 153 • Acne grade 0-1 using IGA (i.e. clear or almost clear)  
23  
24 154 • Has ever taken spironolactone  
25  
26 155 • Oral antibiotic treatment (lasting longer than a week) for acne within past month  
27  
28 156 • Oral isotretinoin treatment within past 6 months  
29  
30 157 • Started, stopped or changed long-term (lasting more than 2 weeks) hormonal contraception,  
31  
32 158 ethinylestradiol/cyproterone acetate (co-cyprindiol) or other hormonal treatment within past 3 months  
33  
34 159 • Planning to start, stop or change long-term (lasting more than 2 weeks) hormonal contraception,  
35  
36 160 ethinylestradiol/cyproterone acetate (co-cyprindiol) or other hormonal treatment within the next 3  
37  
38 161 months  
39  
40 162 • Pregnant/breastfeeding  
41  
42 163 • Intending to become pregnant in the next 6 months  
43  
44 164 • Contra-indicated to spironolactone:  
45  
46 165 ○ Currently taking potassium-sparing diuretic, ACE inhibitor, angiotensin II receptor blocker or  
47  
48 166 digoxin  
49  
50 167 ○ Hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose  
51  
52 168 malabsorption (as the spironolactone and placebo tablets contain lactose)  
53  
54 169 ○ Androgen-secreting adrenal or ovarian tumour  
55  
56 170 ○ Cushing's syndrome  
57  
58 171 ○ Congenital adrenal hyperplasia  
59  
60 172 ○ Estimated Glomerular Filtration Rate (eGFR) below 60 ml/min/1.73m<sup>2</sup>

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3 173                   ○ Serum potassium level above upper limit of reference range for the laboratory processing  
4  
5 174                   the sample  
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7

## 8 175 **Intervention and control**

9  
10 176 Study participants receive one tablet daily (50 mg spironolactone or matched placebo) for the first six weeks  
11  
12 177 of the study. At, or any time after the week-6 visit, the dose is escalated to two tablets daily (total 100 mg  
13  
14 178 spironolactone or matched placebo) by the study clinician, providing the participant is tolerating any side  
15  
16 179 effects (see box 1). Participants are instructed to take their total dose once daily in the morning to avoid  
17  
18 180 diuresis later in the day/evening. All known adverse effects of spironolactone are detailed in the Patient  
19  
20 181 Information Sheet and trial participants have the opportunity to discuss the trial with the site team and  
21  
22 182 discuss any questions before consenting to enter the trial.

23 183 Participants may use their usual topical treatments throughout the study but adherence to topicals is not  
24  
25 184 actively promoted as this may mask differences between the randomised groups. Participants are  
26  
27 185 discouraged from changing their topical treatments between baseline and week-12.

28  
29 186 *INSERT BOX 1: RATIONAL FOR DOSING REGIMEN*  
30

## 31 187 **Intervention adherence**

32  
33 188 The hospital study team assess participant adherence to treatment at each study visit using pill counts. In  
34  
35 189 cases where only remote visits are possible, the participant informs the study team of the number of tablets  
36  
37 190 remaining. However, no additional support or activity is undertaken to encourage daily pill taking, in keeping  
38  
39 191 with the study's pragmatic design.  
40

## 41 42 192 **Randomisation and assignment to intervention group**

43  
44  
45 193 Following consent, participants are randomised 1:1 by clinical staff at the hospital site using an independent  
46  
47 194 web-based system (TENALEA) using varying blocks of size 2 and 4, stratified by centre and by baseline  
48  
49 195 severity (IGA<3 vs 3 or more). The allocation sequence was generated by a statistician using computer-  
50  
51 196 generated random numbers. Participants, study staff and investigators are blind to the treatment allocation  
52  
53 197 until end of the treatment period at week-24. Treatment allocation is revealed prior to week-24 only if there is  
54  
55 198 a clinical need to do so.  
56

## 57 199 **Recruitment**

58  
59 200 Potential participants, identified in primary and secondary care, direct advertising in areas close to recruiting  
60

201 hospitals and social media advertising, are directed to the study website

202 (<https://www.southampton.ac.uk/safa>) or to contact the local study team directly.

203 In primary care, recruitment is supported by general practices acting as Participant Identification Centres  
204 (PIC) local to the recruiting centres identifying potential participants either opportunistically or via database  
205 search based on an acne diagnosis and relevant prescription within the past 6 months and mail-out of  
206 invitation pack. In secondary care, potential participants are identified opportunistically in out-patient clinics  
207 and through screening new referral letters.

208 We use targeted social media advertising to promote the study, build study awareness and interest.

209 Participants are free to withdraw consent from the study at any time without providing a reason. They may  
210 withdraw from study treatment but remain in follow-up; withdraw from study and follow-up, but give  
211 permission for their data to be used in analyses; or completely withdraw from the study and not permit their  
212 data to be used.

### 213 **Primary and secondary outcome measures**

214 Clinically, the effectiveness of acne treatments is usually judged at 8-12 weeks, so the primary outcome in  
215 the study is assessed at week-12 with the Acne-QoL symptom subscale score<sup>21,22</sup>. The Acne-QoL was  
216 developed and validated for use in a clinical study to assess the impact of therapy on quality of life among  
217 people with facial acne and the primary outcome at week-12 is the symptom subscale score of the Acne-  
218 QoL, because the Acne-QoL was intended to be presented as 4 separate subscale scores. It was not  
219 designed or validated to have a total score, however, it has published Minimum Clinically Important  
220 Difference (MCID) of 2 points for the subscales and range 0 to 30 for symptom subscale score<sup>21-23</sup>. Other  
221 participant-reported outcome measures in acne do not have a published MCID available and have not been  
222 found to have advantages in terms of acceptability and validity<sup>24</sup>.

223 Secondary outcomes include Acne-QoL at week-24, participant self-assessed overall improvement recorded  
224 on a 6-point Likert scale with photographs taken at baseline<sup>25</sup>, IGA<sup>5</sup>, participant global assessment, use of  
225 acne medication and participant satisfaction with study treatment. Trial participants are at each time point  
226 asked which topical or oral treatments were used in the period since the previous time point (if any) and have  
227 the option to add more information of the treatments for their acne in a free text box of the participant  
228 questionnaires. The IGA is a 5-point scale ranging from clear to severe (0 'Clear'; 1 'Almost clear'; 2 'Mild'; 3  
229 'Moderate'; 4 'Severe')<sup>6,26</sup>. The IGA<sup>5,25</sup> is used to grade the participant's acne as lesion counts are time

1  
2  
3 230 consuming, with wide inter-assessor variation and give little additional information to global assessments. All  
4  
5 231 outcome measures are shown in Table 2.  
6  
7 232 The safety profile of spironolactone is well established<sup>15,16</sup>. Consequently, we collect information about  
8  
9 233 adverse reactions of special interest, both to inform the dose review decision from week-6 onwards as well  
10  
11 234 as to learn more about incidence of side effects in this population. We also collect and report all serious  
12  
13 235 adverse events (SAEs).

14  
15 236 *TABLE 2: SCHEDULE OF OBSERVATIONS*

16  
17  
18 237 **Pregnancy**

19  
20 238 Spironolactone is considered contraindicated in pregnancy, or a category C drug (i.e. potential benefits may  
21  
22 239 warrant use in pregnant women despite potential risks)<sup>1,15</sup>. The main concern is around possible feminisation  
23  
24 240 of the male foetus in the third trimester of pregnancy<sup>1</sup>. Women of childbearing potential at risk of pregnancy  
25  
26 241 will be asked to use their usual hormonal or barrier method of contraception during the first 24 weeks of the  
27  
28 242 study and for at least 4 weeks (approximately one menstrual cycle) afterwards. A pregnancy test will be  
29  
30 243 conducted for all participants at their baseline visit and documented in their medical notes. At weeks 6 and  
31  
32 244 12, the study nurse/doctor will ask participants to confirm that they are still using contraception and have not  
33  
34 245 changed contraceptive method. Participants who become pregnant will be asked to inform their local site  
35  
36 246 study team as soon as possible and will not be able to continue in the study.

37  
38 247 **Sample size**

39  
40 248 Based on comparison of the Acne-QoL symptom score between groups at week-12, power 90%, alpha 0.05  
41  
42 249 and seeking a difference between groups of 2 points on the symptom subscale (s.d. 5.8, effect size 0.35),  
43  
44 250 346 participants are needed. Allowing for 20% loss to follow up gives a total 434 participants (217 per  
45  
46 251 group). Following discussions with oversight committees post funding award, the sample size was  
47  
48 252 recalculated. Allowing for a correlation with baseline of 0.293 and a deflation factor of  $1-\rho^{227}$ , gives a total  
49  
50 253 sample size required of 398 participants. A difference of 2 points on the symptom subscale and a standard  
51  
52 254 deviation of 5.8 (equivalent to an effect size 0.35) is in line with that reported in studies in a similar patient  
53  
54 255 group and with the MCID reported for Acne-QoL<sup>21,22</sup>.

55  
56 256 **Data collection methods**

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257 Participant data are entered into study electronic case report forms (eCRF) via a remote data collection tool  
258 (Medidata Rave) by trained hospital research personnel with specific roles on the study and regularly  
259 checked for missing or anomalous values by Southampton CTU study staff.

## 260 Data management

261 Participant data are pseudonymised by assigning each participant a participant identifier code, which is used  
262 to identify the participant during the study and for any participant-specific communication between  
263 Southampton CTU and recruiting sites. The site retains a participant identification code list which is only  
264 available to site staff and stored in a secure location at site.

## 265 Patient and public involvement (PPI)

266 This study addresses a priority area identified as important to patients and health professionals by the James  
267 Lind Alliance Priority Setting Partnership for Acne<sup>7</sup>. We gained feedback from a virtual acne-specific patient  
268 panel, convened through 'People in Research' (<https://www.peopleinresearch.org>). A patient survey was  
269 carried out with the support of the UK Dermatology Clinical Trials Network (UK DCTN) in order to inform the  
270 study design. Findings suggested that participants would find it difficult to abstain from using topical  
271 treatments for more than 12 weeks and that asking participants to take a placebo for one year would also be  
272 a barrier to recruitment.

273 Two public contributors with experience of acne attend all Trial Management Group (TMG) meetings to  
274 ensure that decisions around study design are informed by their perspective, study procedures are feasible  
275 for participants and study materials are readable and include all the relevant information that participants  
276 would want. Public contributors influenced the trial design and delivery, for instance by advocating use of  
277 social media advertising to improve recruitment, arguing against repeated measures in this patient group and  
278 that an upper age limit of 50 years was arbitrary and could appear discriminatory.

## 279 Statistical methods

280 The study will be reported in accordance with CONSORT guidelines. A detailed statistical analysis plan  
281 (SAP) will be written and reviewed prior to the study database being locked.

282 The modified ITT population consists of all participants who have consented and been randomised to a  
283 treatment arm and have complete data for the outcome being analysed. Analyses will be performed  
284 according to the modified ITT principle using a linear regression model. All analyses will be carried out in the  
285 modified ITT population, with the level of missing data reported, unless otherwise stated. The frequency and



1  
2  
3 286 pattern of missing data will be examined and a multiple imputation model will be used as a sensitivity  
4  
5 287 analysis if appropriate.  
6  
7 288 For the primary analyses, descriptive statistics will be obtained for the randomised groups to characterise  
8  
9 289 recruited participants and assess baseline comparability. For the primary outcome, a linear regression model  
10  
11 290 will be used to analyse Acne-QoL symptom subscale at week-12, adjusting for baseline variables (including  
12  
13 291 baseline Acne-QoL symptom subscale score, use of topical treatments, use of hormonal contraception/  
14  
15 292 ethinylestradiol/cyproterone acetate (co-cyprindiol) and randomisation stratification variables (centre,  
16  
17 293 baseline severity (IGA < 3 versus 3 or more)). A full list of covariates and model specification will be set out  
18  
19 294 in the SAP. A 95% confidence interval for the least squares mean difference between arms in Acne-QoL  
20  
21 295 symptom subscale at week-12 will be calculated.  
22  
23 296 The same analysis methods will be used to summarise Acne-QoL symptom subscale at other time points  
24  
25 297 (weeks 6, 24 and up to week-52weeks after baseline) and for the other Acne-QoL subscales (self-perception,  
26  
27 298 role-emotional and role-social) and total score. IGA and participants' comparison with baseline photo at  
28  
29 299 weeks 6, 12 and 24 will be dichotomised as success or failure as recommended by the US Food and Drug  
30  
31 300 Administration (with success for IGA and participants global assessment defined as clear or almost clear  
32  
33 301 (grade 0 or 1) and at least a two-grade improvement from baseline; this represents a clinically meaningful  
34  
35 302 outcome). The dichotomised outcomes will be summarised by frequencies and percentages and compared  
36  
37 303 by group using logistic regression adjusting for baseline assessment, use of hormonal contraception/  
38  
39 304 ethinylestradiol/cyproterone acetate (co-cyprindiol), use of topical treatment and randomisation stratification  
40  
41 305 factors.  
42  
43 306 Adverse reactions of special interest and SAEs will be summarised by group with frequencies and  
44  
45 307 percentages and compared with Pearson's  $\chi^2$  tests. Logistic regression modelling will also be used to adjust  
46  
47 308 for any important differences in topical treatment use by group. Subgroup analyses will investigate how the  
48  
49 309 treatment effect differs by whether participants have symptoms consistent with polycystic ovary syndrome  
50  
51 310 (PCOS) as recorded at the baseline visit. It is acknowledged the study is not powered for this subgroup  
52  
53 311 analysis. The same analysis methods will be applied to the outcomes collected at up to 52 weeks however  
54  
55 312 the interpretation of these results will be assessed with caution as participants will potentially have been off  
56  
57 313 treatment for up to 6 months or started a different acne treatment. All analyses will be carried out using  
58  
59 314 STATA and/or SAS.  
60  
61 315 There are no planned interim analyses or subgroup analyses.

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## 316 **Health economics analysis**

317 If the intervention is found effective, a within-study economic evaluation will be undertaken to assess value for  
318 money of spironolactone plus usual care versus placebo plus usual care. The main perspective of the analysis  
319 will be that of the NHS over the 24 week treatment period, although a secondary analysis will assess the  
320 importance of a broader perspective by incorporating out of pocket costs related to acne and any  
321 productivity/employment impacts for people with persistent acne<sup>28</sup>.

322 Costs, including intervention and wider NHS resource use, are being recorded in the study eCRF for the former  
323 whilst wider NHS resource use is captured in participant questionnaires at baseline, weeks 6, 12, and 24.

324 Costs will be valued using published unit costs for a common recent price year to estimate mean cost per  
325 participant in each arm<sup>29-31</sup>.

326 Review of the reliability, validity and responsiveness of three generic preference-based measures (EQ-5D,  
327 SF-6D and HUI) in skin conditions only found evidence to support the use of the EQ-5D in skin diseases with  
328 no studies looking at measurement properties for the Short-Form six-dimensions (SF-6D) or Health Utilities

329 Index (HUI) in skin disease<sup>32</sup>. Problems on the EQ-5D domains were found to be substantially higher in the  
330 acne sample receiving specialist care than in an age truncated population sample (aged 20-39 years)

331 particularly on the pain/discomfort (42.1% in the acne sample versus 17.7% in an age-truncated population  
332 sample) and anxiety/depression domains (52.8% versus 12.5% respectively)<sup>33</sup>. EQ-5D was found to be

333 responsive to change, with moderate effect sizes at 4 and 12 months (-0.44 and -0.53 respectively)<sup>33</sup>. We  
334 will value the EQ-5D-5L in our primary analysis in line with NICE recommendations at the time of analysis<sup>3,34</sup>.

335 Quality Adjusted Life Years (QALYs) (estimated using EQ-5D-5L<sup>32,33</sup>) for the study period will be estimated  
336 using linear interpolation and area under the curve with and without baseline adjustment<sup>35</sup>. Clinical measures

337 were found to be more responsive to change than the generic measures (shown by larger effect sizes) and  
338 combination of generic preference based measures with the use of disease specific measure was concluded

339 to be desirable<sup>33</sup>. The primary economic evaluation will be an incremental cost utility analysis to enable the  
340 cost effectiveness to be compared across a range of health conditions and interventions such that decision

341 makers can use the information to inform prioritisation of health care. A secondary cost effectiveness  
342 analysis using the disease specific Acne-QoL will be presented as appropriate, though it should be noted

343 that this instrument does not have utility weights available and it is unclear what incremental cost per unit of  
344 change on the Acne-QoL represents good value for money. All analysis will be conducted and presented

345 using established methods<sup>28,36</sup>.

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3 346 If spironolactone is not found to be clinically effective a full economic evaluation will not be conducted. Instead,  
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5 347 estimates of mean costs and utility per participant will be presented at the various study time points as these  
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7 348 may be informative for other researchers undertaking future economic studies or economic modelling in this  
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9 349 clinical area.

10  
11 350 A detailed Health Economic Analysis Plan will be written prior to the study database being locked.

## 13 351 **Oversight and monitoring**

15 352 The TMG includes representatives with expertise in dermatology, primary care research, psychology,  
16  
17 353 medical statistics and health economics, public contributors, and Southampton CTU staff involved in the day-  
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19 354 to-day running of the study and is responsible for the oversight of the progress of the study. An independent  
20  
21 355 Trial Steering Committee (TSC) and an independent Data Monitoring and Ethics Committee (DMEC) have  
22  
23 356 been set up to monitor study progress and safety.

25 357 Data on adverse reactions will be collected at the baseline and follow-up visits, and participants will be asked  
26  
27 358 to report any adverse reactions in their week-24 questionnaire. SAEs may be identified by participant report  
28  
29 359 at any time directly to the hospital study team, at follow-up visits or questionnaires. Participants' GPs will be  
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31 360 informed of their patient's participation in the study and asked to notify the hospital study team of any  
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33 361 potential SAE. The study also has a UK regulatory compliant real-time SAE reporting process to identify  
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35 362 serious adverse reactions and suspected unexpected serious adverse reactions that could suspend or stop  
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37 363 the study if warranted.

39 364 The Southampton CTU has undertaken a risk assessment for the study which includes the requirements for  
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41 365 monitoring (both central and site). The Southampton CTU undertakes a number of internal audits of its own  
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43 366 systems and processes annually and has routine audits from both its sponsor and the independent Medicine  
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45 367 and Health care products regulatory authority (MHRA) every 2-3 years.

## 48 368 **Discussion**

51 369 This is the first adequately powered pragmatic, randomised trial investigating the effect of spironolactone on  
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53 370 acne in adult women in comparison to a matched placebo. If found to be clinically and cost effective, use of  
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55 371 spironolactone will likely become the new standard of care in addition to topical treatments potentially  
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57 372 reducing antibiotic use for women requiring systemic therapy.

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3 373 Respondents to a survey of people with experience with acne reported that they would be unwilling to be  
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5 374 recruited to a study where they remained blinded to the treatment allocation for 52 weeks, due to concerns  
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7 375 about potential worsening of acne over this time. Therefore, the study was designed as blinded treatment  
8  
9 376 phase of 24 weeks with an observational follow-up period for up to 6 months after. Use of acne treatments,  
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11 377 such as oral isotretinoin or antibiotics, between week-24 and up to week-52 are carefully recorded as  
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13 378 differences between groups and would be important in interpreting week-52 outcomes. Use of topical  
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15 379 treatments is allowed in both groups during the 24 week treatment phase as i) women with moderate-severe  
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17 380 acne may be unwilling to be randomised to placebo alone, and ii) recruiting women with moderate-severe  
18  
19 381 acne to a placebo-controlled study with no effective treatment for 12 weeks in the control arm may risk  
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21 382 worsening of acne and possible scarring.  
22  
23 383 Although others are seeking to evaluate the role of spironolactone in comparison with oral tetracyclines<sup>37</sup>,  
24  
25 384 this is the largest study to date to inform clinical practice over the effectiveness of spironolactone as an  
26  
27 385 alternative treatment for acne in adult women.

## 29 386 Abbreviations

31	32 387	ACE	Angiotensin-converting enzyme
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34	388	CRN	Clinical Research Network
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37	389	CTU	Clinical Trials Unit
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39	390	DMEC	Data Monitoring and Ethics Committee
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42	391	eCRF	Electronic Case Report Form
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45	392	eGFR	Estimated Glomerular Filtration Rate
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47	393	EQ-5D-5 L	EuroQol Five Dimensions Five Level
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49			
50	394	GP	General Practitioner
51			
52	395	HUI	Health Utilities Index
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55	396	HRA	Health Research Authority
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58	397	HTA	Health Technology Assessment
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3	398	ICF	Informed Consent Form
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6	399	IGA	Investigator's Global Assessment
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8	400	IMP	Investigational Medicinal Product
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11	401	IPD	Individual Patient Data
12			
13	402	ITT	Intention-to-treat
14			
15			
16	403	MCID	Minimum Clinically Important Difference
17			
18			
19	404	MHRA	Medicines and Healthcare products Regulatory Agency
20			
21	405	NHS	National Health Service
22			
23			
24	406	NICE	National Institute for Health and Care Excellence
25			
26	407	NIHR	National Institute for Health Research
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28			
29	408	PCOS	Polycystic Ovary Syndrome
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31			
32	409	PGA	Participant's Global Assessment
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34	410	PIC	Participant Identification Centre
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37	411	PIS	Participant Information Sheet
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39	412	PPI	Patient and Public Involvement
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42	413	PSS	Personal Social Services
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44	414	QALYs	Quality Adjusted Life Years
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47	415	QoL	Quality of Life
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50	416	RCT	Randomised Controlled Trial
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52	417	REC	Research Ethics Committee
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55	418	SAE	Serious Adverse Event
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57	419	SF-6D	Short Form Six Dimensions
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59			
60	420	SpR	Specialty registrar

3	421	TMG	Trial Management Group
6	422	TSC	Trial Steering Committee
8	423	UHS	University Hospital Southampton NHS Foundation Trust
11	424	UK DCTN	UK Dermatology Clinical Trials Network

## Declarations

## Acknowledgements

- The virtual patient panel (brought together by NIHR INVOLVE) for their advice on the study design.
- The study was developed with support from the UK Dermatology Clinical Trials Network (UK DCTN).  
The UK DCTN is grateful to the British Association of Dermatologists and the University of Nottingham for financial support of the Network. UK DCTN conducted surveys among patients with acne and health professionals managing acne to inform the study design, promoting the study and identifying and advising on potential hospital sites delivering the study.
- Wessex CRN for funding the initial social media advertising campaign.
- Jessica Boxall and Liz Allaway for management of the study social media accounts as well as running and coordinating the social media adverts.
- Hospital dermatology centres recruiting for the study: Queen Elizabeth Hospital, Birmingham; Bristol Royal Infirmary Dermatology Centre, Bristol; University Hospital of Wales, Cardiff; General Hospital, Epsom; District Hospital, Harrogate; St Mary's Hospital (Imperial College NHS Healthcare Trust), London; Queen's Medical Centre, Nottingham; General Hospital, Poole; St Mary's General Hospital Dermatology Centre, Portsmouth; Swansea Bay University Health Board, Swansea.
- Participant Identification Centres (PICs) for searching their patient lists and mail outs and Clinical Research Networks (CRNs) for helping to identify potential PICs.

## Authors' contributions

Research funding was obtained by MS, AL, NF, GG, PL, IM, JN, MJR, TS, IS, LS, BS, KT and KST. All authors have contributed to the development of the protocol and to the management of the study. SR leads on the day-to-day management of the study, overseen by ZE, MS, JN and BS. This paper was drafted by FC

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447 and SR with contributions from LD, MS and all authors. All authors read and approved the final manuscript.

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450 (HTA) programme (Grant Reference Number: 16/13/02) and supported by NIHR CTU support funding at  
451 Southampton CTU. The views expressed are those of the author(s) and not necessarily those of the NIHR  
452 or the Department of Health and Social Care. The NIHR HTA funder will play no role in the execution,  
453 analysis, interpretation of data, or study publication. The study is registered on the UK NIHR study portfolio  
454 meaning there are research nurses based at UK hospitals who help in screening potential patients to identify  
455 those eligible for the study.  
456 Southampton CTU, a NIHR CTU support funded UK Clinical Research Collaboration registered CTU, is  
457 coordinating the study. University of Southampton is the sponsor for the study.

## 458 **Trial status**

459 This clinical trial was registered on 17-Sep-2018 (EudraCT Number: 2018-003630-33) and on 15-Oct-2018  
460 (ISRCTN, registry number: ISRCTN 12892056). The first participant was recruited on 05-Jun-2019 and  
461 recruitment is expected to be completed on 31-Aug-2021. The current protocol is version 10, dated 08-Mar-  
462 2021. The full protocol v10 08-MAR-2021 is available as supplementary material and on request via  
463 [safa@soton.ac.uk](mailto:safa@soton.ac.uk) or on the study website [https://www.southampton.ac.uk/safa/about/researchers-and-](https://www.southampton.ac.uk/safa/about/researchers-and-clinicians.page)  
464 [clinicians.page](https://www.southampton.ac.uk/safa/about/researchers-and-clinicians.page). REC/MHRA approved protocol amendments will be communicated to sites via email and  
465 updated trial documentation provided centrally via the trial website. Trial registries will be amended where  
466 relevant with explanations for these changes. End of study is defined as the date when the last point of data  
467 is collected for the last participant from their Final follow-up questionnaire.

## 468 **Ethics approval**

469 The trial received favourable ethical opinion from Wales Research Ethics Committee (18/WA/0420) and has  
470 Health Research Authority (HRA) approval (IRAS 246637).

## 471 **Availability of data and materials**

### 472 **Data Management Plan**

473 Full details of the data management strategy for the study are available in the SAFA data management plan,  
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3 474 available on request via [safa@soton.ac.uk](mailto:safa@soton.ac.uk).  
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### 5 475 **Underlying data**

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8 476 Pseudonymised individual participant data (IPD) within the clinical study dataset will be available for sharing  
9  
10 477 via controlled access by authorised Southampton CTU staff (as delegated to Southampton CTU by the study  
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12 478 sponsor). Data access can be requested via a Southampton CTU Data Release application form (available  
13  
14 479 from <https://www.southampton.ac.uk/ctu/about/index.page>) after the trial is published. Please email the  
15  
16 480 completed form to the Southampton CTU Data Release Committee Coordinator at [ctu@soton.ac.uk](mailto:ctu@soton.ac.uk).

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18 481 Data access requests are reviewed against specific eligibility criteria by the Southampton CTU data  
19  
20 482 custodian and key members of the study team, including a statistician and chief investigator or by an  
21  
22 483 external Independent Review Panel. Decisions about requests are made promptly and usually no more than  
23  
24 484 three months after receipt of request. Responses to all data requests, with a clear rationale for any refusals,  
25  
26 485 will be sent promptly to the data requester.  
27

### 28 486 **Extended data**

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31 487 Written informed consent is obtained from participants during the baseline visit by qualified site trial team  
32  
33 488 members. A copy of the study's Informed Consent Form (v4 05-MAR-2021) is available as supplementary  
34  
35 489 material or on request via [safa@soton.ac.uk](mailto:safa@soton.ac.uk) .  
36

### 37 490 **Consent for publication**

38  
39 491 Responsibility for publication has been delegated to Prof Miriam Santer and Prof Alison Layton (co-Chief  
40  
41 492 Investigators) and Prof Gareth Griffiths (Director of Southampton CTU), who have consented to this  
42  
43 493 publication.  
44

### 45 494 **Competing interests**

46  
47  
48 495 The authors have no competing interests to declare.  
49

### 50 496 **Authors' information (optional)**

51  
52  
53 497 Not applicable.  
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### 55 498 **Tables**

56  
57 499 Table 1: Schedule of procedures  
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Observation/procedure	Person undertaking the specified event	Visit				
		Screening/ Baseline	Week 6	Week 12	End of Treatment/ Week 24 contact	End of Study/ Final Follow-up questionnaire (52 weeks or sooner) <sup>3</sup>
<b>ENROLMENT</b>						
Informed Consent	Nurse/ Other clinician <sup>1</sup>	X				
Eligibility evaluation	Other clinician	X				
Participant characteristics	Nurse/Other clinician	X				
Blood pressure	Nurse/Other clinician	X				
Blood tests (serum potassium, eGFR)	Nurse/Other clinician	X				
Pregnancy test	Nurse/Other clinician	X				
<b>RANDOMISATION</b>	Nurse/Other clinician	X				
<b>ASSESSMENTS</b>						
Investigator's Global Assessment (IGA)	Nurse/ Other clinician	X	X	X		
Medical history	Participant	X				
Self-assessment - Participants Global Assessment (adapted IGA)	Participant	X	X	X	X	X
Acne Medication Use	Nurse/Other clinician/Participant	X	X	X	X	X
Other Medication Use	Nurse/Other clinician/Participant	X				
Acne-QoL	Participant	X	X	X	X	X
EQ-5D-5L	Participant	X	X	X	X	X
Resource use questionnaire	Participant	X	X	X	X	X
Self-assessment – comparison with baseline photo - 6 Point Likert Scale	Participant		X	X	X	X
Collection of ARs of special interest: Headache Dizziness/vertigo/ Light headedness Tingling Indigestion/heartburn/ Dyspepsia Diarrhoea Polyuria (passing much more urine than normal) Nausea/feeling sick Vomiting/being sick Tenderness of the breasts Breast enlargement Irregular menstrual periods Abdominal pain Weight gain Reduced libido (reduced interest in sex) Fatigue/tiredness Drowsiness/sleepiness	Participant/ Other clinician		X	X	X	
Serious Adverse Events	Other clinician (PI or delegate)		X	X	X	

Observation/procedure	Person undertaking the specified event	Visit				
		Screening/ Baseline	Week 6	Week 12	End of Treatment/ Week 24 contact	End of Study/ Final Follow-up questionnaire (52 weeks or sooner) <sup>3</sup>
Assessment of treatment response to determine dose adjustment <sup>2</sup>	Participant / Other clinician		X	X		
Satisfaction with study treatment	Participant				X	
<b>OTHER ACTIVITIES</b>						
Discuss use of contraception	Nurse/Other clinician	X	X	X		
Photographs of face taken	Nurse/Other clinician	X				
Photographs given to participant	Nurse/Other Clinician	X		X (If a set was stored at site)		
Letter to participant's GP (patient participation)	Nurse/Other clinician	X				
Check participant is not using oral acne treatment	Nurse/Other clinician/Participant		X	X		
Return excess IMP to clinic	Participant		X	X	X (return via post)	
Spironolactone/Placebo pill count	Nurse/Other clinician/Participant		X	X	X	
Letter to participant's GP (if dose is change)	Nurse/Other clinician		X	X		
Reminder to participant to report any subsequent adverse event(s) that might reasonably be related to participation in this study (up to 52 weeks)	Nurse/Other clinician			X		
Ask participant if they would like to receive a summary of the study results, when available	Nurse/Other clinician			X		
Letter to participant (unblinding)					X (after 24 weeks)	
Letter to participant's GP (unblinding)					X (after 24 weeks)	

<sup>1</sup> Dermatologist or Clinical Research Fellow, in line with local procedures with demonstrable and appropriate level of training. Specific duties delegated by the PI and listed on the delegation log.

<sup>2</sup> Dose escalated to 2 tablets per day if participant is tolerating side effects.

<sup>3</sup> The follow-up questionnaire will be sent out 6 months or sooner after the 24-week timepoint.

Table 2: Schedule of observations

Outcome measure	6 weeks	12 weeks (primary endpoint)	24 weeks (end of treatment)	Unblinded Follow-up ( 52 weeks or sooner) <sup>h</sup>
<b>Primary outcome measure</b>				
Acne-QoL symptom subscale score		X		
<b>Secondary outcome measures</b>				
Acne-QoL symptom subscale score	X	X	X	X
Acne-QoL other subscales <sup>a</sup>	X	X	X	X
Acne-QoL total score	X	X	X	X
Participant self-assessed overall improvement <sup>b</sup>	X	X	X	X
Investigator's Global Assessment (IGA) <sup>c</sup>	X	X		
Participant's Global Assessment (PGA) <sup>d</sup>	X	X	X	X
Participant satisfaction with study treatment <sup>e</sup>			X	
Health-related quality of life using EQ-5D-5L <sup>f</sup>	X	X	X	X
Costs incurred	X	X	X	X
Cost-effectiveness <sup>g</sup>			X	

<sup>a</sup> Self-perception, role-emotional and role-social; <sup>b</sup> recorded on a 6-point Likert scale with photographs taken at the baseline visit to aid recall<sup>37</sup>; <sup>c</sup> 5-point scale ranging from clear to severe (0 - Clear; 1 - Almost clear; 2 - Mild; 3 - Moderate; 4 - Severe)<sup>38</sup>;

<sup>d</sup> Same scale as the IGA, but written in Plain English for participants' use; <sup>e</sup> Asked prior to revealing treatment allocation after 24 weeks;

<sup>f</sup> The EQ-5D-5 L assesses five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression; <sup>g</sup> Using EQ-5D-5L and data on health resource use during the study; <sup>h</sup> The follow-up questionnaire will be sent out 6 months or sooner after the 24-week timepoint.

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### 518 **Rationale for the dosing regimen**

519 We conducted a survey of health professionals to inform the spironolactone dose regimen (unpublished).

520 Responses were received from 41 Dermatology consultants, 10 Dermatology nurses and 3 Dermatology  
521 SpRs.

522 Of these 54 Dermatology health professionals, 22 prescribed spironolactone (9 rarely, 10 sometimes and 3  
523 often). Most of those who responded stated that they would start at 50mg and increase up to 100-150mg  
524 depending on response. Several noted that this would depend on the patient's weight, with the starting dose  
525 lowered to 25mg if needed and allowing the dosage to increase up to 200mg. There was no consistency on  
526 the timeframe for these increases with 4 weeks, 6 weeks, 12 weeks and 6 months all being mentioned as  
527 review points.

528 A previous HTA study examining common treatments in the management of acne suggested that assessing  
529 efficacy at 6 weeks was ideal<sup>25</sup> – this informed the timing of follow-up assessments and dose escalation. US  
530 guidelines note that studies have been carried out using spironolactone doses ranging from 50mg to 200mg  
531 daily.<sup>1</sup> No specific dose is recommended but it is noted that side effects are dose-related.<sup>1</sup>

532 A recent hybrid systematic review of RCTs and case series identified some very low-quality evidence which  
533 showed that a daily dose of 200mg was statistically significantly more effective than placebo versus inflamed  
534 lesions, but it also confirmed that this dose is associated with a significantly greater risk of adverse side  
535 effects than lower doses.<sup>17</sup>

536 Hence, there would appear to be no merit in using these higher doses for managing acne. Data from the  
537 multiple case series suggested that any future RCT examining lower doses is likely to generate results that  
538 confirm the effectiveness and better safety profile of doses  $\leq 100$  mg per day, which informed the dosage  
539 regimen.

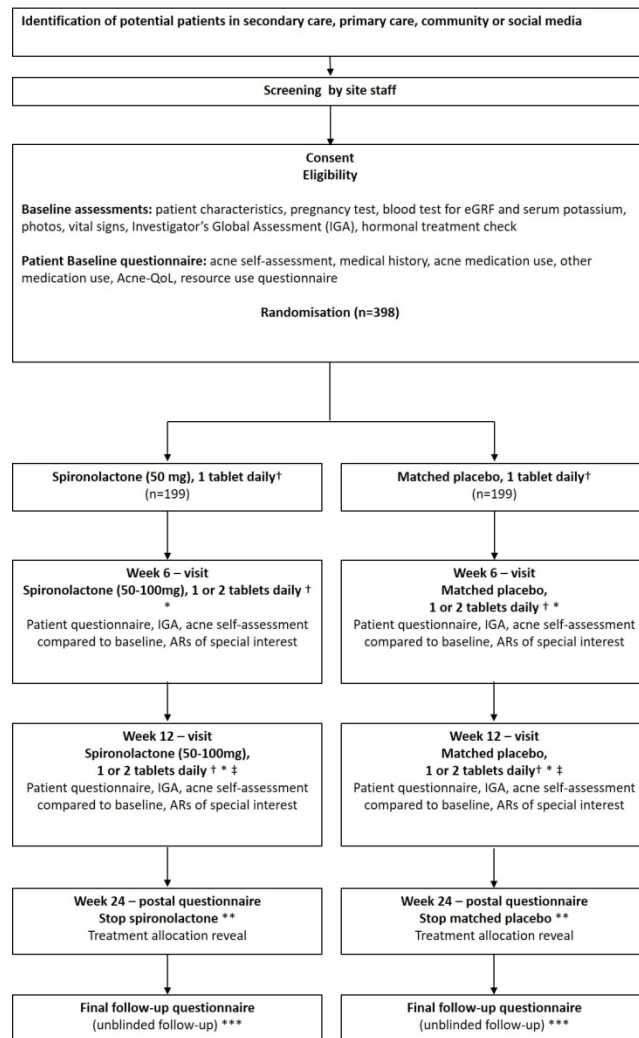
540 For most licensed indications for spironolactone, the British National Formulary states a starting dose of  
541 100mg, titrated as required. Therefore, a starting dose of 50mg in the SAFA study seems conservative.

## 547 **References**

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## Study schema

95x177mm (300 x 300 DPI)

(Print on local headed paper)



**REC Number: 18/WA/0420**

**IRAS ID: 246637**

**SAFA INFORMED CONSENT FORM**

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

**Participant Identification Number for this trial:**

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Name of Researcher:

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**Please initial each box**

1. I confirm that I have read the participant information sheet (version \_\_ dated DD-MMM-YYYY) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care or legal rights being adversely affected.
3. I give permission for a copy of my consent form to be sent to the Southampton Clinical Trials Unit (where it will be stored securely), to allow confirmation of my consent.
4. I agree for my contact details to be shared with the Southampton Clinical Trials Unit (where stored securely), to allow the study team to contact me if needed in an emergency situation (e.g. during a pandemic).
5. I understand that relevant sections of my medical records, and data collected during the study, may be looked at by individuals from the Sponsor or their delegates, from Regulatory Authorities, or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
6. I understand that the information collected about me may be used to support other ethically approved research in the future, and may be shared in a pseudonymised form with other researchers.
7. I agree to my General Practitioner being informed of my participation in the study and to receiving information critical to my care.
8. I agree to not donate blood during the first 6 months of the study.

INITIAL
INITIAL
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INITIAL





9. I agree to photographs of my facial acne being taken at the first clinic visit.

10. I agree to give a blood sample at the first clinic visit.

11. **WOMEN OF CHILD BEARING POTENTIAL AT RISK OF PREGNANCY:**

- I agree to take a pregnancy test at the first clinic visit
- I agree to use my usual hormonal or barrier method of contraception as detailed in the patient information sheet
- I agree to refrain from donation of eggs during the first 6 months of the study

12. I understand that my pseudonymised data will be held on servers located within and outside of the EU, and that access to data managed by Southampton Clinical Trials Unit (SCTU) will be strictly controlled and applicable Data Protection Legislation will be abided by.

13. I agree to take part in the SAFA study.

YES

NO

14. **OPTIONAL:** If I withdraw from the study, I give permission for the study team to still use my pseudonymised data that has been collected.



15. **OPTIONAL:** I agree that the hospital may store photographs of my facial acne taken at my first clinic visit.



16. **OPTIONAL:** I agree to being informed of the results of the SAFA study.



\_\_\_\_\_  
Name of Participant

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date (DD-MMM-YYYY)

\_\_\_\_\_  
Name of researcher  
taking consent

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date (DD-MMM-YYYY)

**Reminder for Research Team:**

- Original signed consent form to be kept in the Investigator Site File
- 1 photocopy given to the participant
- 1 photocopy filed in the participant's medical records
- 1 scanned copy to be emailed to the Southampton CTU via secure nhs.net email account, for central monitoring purposes



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	ItemNo	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 17
	2b	All items from the World Health Organization Trial Registration Data Set	Included throughout manuscript
Protocol version	3	Date and version identifier	17
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 16
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

**Introduction**

1				
2	Background and	6a	Description of research question and justification	3-4
3	rationale		for undertaking the trial, including summary of	
4			relevant studies (published and unpublished)	
5			examining benefits and harms for each intervention	
6				
7		6b	Explanation for choice of comparators	5
8				
9	Objectives	7	Specific objectives or hypotheses	4
10				
11	Trial design	8	Description of trial design including type of trial (eg,	5
12			parallel group, crossover, factorial, single group),	
13			allocation ratio, and framework (eg, superiority,	
14			equivalence, noninferiority, exploratory)	
15				
16				
17				
18	<b>Methods: Participants, interventions, and outcomes</b>			
19	Study setting	9	Description of study settings (eg, community clinic,	4-5
20			academic hospital) and list of countries where data	
21			will be collected. Reference to where list of study	
22			sites can be obtained	
23				
24				
25	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If	5-7
26			applicable, eligibility criteria for study centres and	
27			individuals who will perform the interventions (eg,	
28			surgeons, psychotherapists)	
29				
30				
31	Interventions	11a	Interventions for each group with sufficient detail to	7
32			allow replication, including how and when they will	
33			be administered	
34				
35		11b	Criteria for discontinuing or modifying allocated	9, 5
36			interventions for a given trial participant (eg, drug	
37			dose change in response to harms, participant	
38			request, or improving/worsening disease)	
39				
40				
41		11c	Strategies to improve adherence to intervention	7
42			protocols, and any procedures for monitoring	
43			adherence (eg, drug tablet return, laboratory tests)	
44				
45		11d	Relevant concomitant care and interventions that	5
46			are permitted or prohibited during the trial	
47				
48				
49	Outcomes	12	Primary, secondary, and other outcomes, including	8, 9
50			the specific measurement variable (eg, systolic	
51			blood pressure), analysis metric (eg, change from	
52			baseline, final value, time to event), method of	
53			aggregation (eg, median, proportion), and time	
54			point for each outcome. Explanation of the clinical	
55			relevance of chosen efficacy and harm outcomes	
56			is strongly recommended	
57				
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2	Participant	13	Time schedule of enrolment, interventions	7, Figure 1,
3	timeline		(including any run-ins and washouts),	Table 2
4			assessments, and visits for participants. A	
5			schematic diagram is highly recommended (see	
6			Figure)	
7				
8	Sample size	14	Estimated number of participants needed to	9
9			achieve study objectives and how it was	
10			determined, including clinical and statistical	
11			assumptions supporting any sample size	
12			calculations	
13				
14				
15	Recruitment	15	Strategies for achieving adequate participant	7, 8
16			enrolment to reach target sample size	
17				
18				

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

21				
22				
23	Sequence	16a	Method of generating the allocation sequence (eg,	9
24	generation		computer-generated random numbers), and list of	
25			any factors for stratification. To reduce	
26			predictability of a random sequence, details of any	
27			planned restriction (eg, blocking) should be	
28			provided in a separate document that is	
29			unavailable to those who enrol participants or	
30			assign interventions	
31				
32				
33	Allocation	16b	Mechanism of implementing the allocation	9
34	concealment		sequence (eg, central telephone; sequentially	
35	mechanism		numbered, opaque, sealed envelopes), describing	
36			any steps to conceal the sequence until	
37			interventions are assigned	
38				
39				
40	Implementation	16c	Who will generate the allocation sequence, who	9
41			will enrol participants, and who will assign	
42			participants to interventions	
43				
44				
45	Blinding	17a	Who will be blinded after assignment to	9
46	(masking)		interventions (eg, trial participants, care providers,	
47			outcome assessors, data analysts), and how	
48				
49		17b	If blinded, circumstances under which unblinding is	9
50			permissible, and procedure for revealing a	
51			participant's allocated intervention during the trial	
52				
53				

### Methods: Data collection, management, and analysis

1				
2	Data collection	18a	Plans for assessment and collection of outcome,	9
3	methods		baseline, and other trial data, including any related	
4			processes to promote data quality (eg, duplicate	
5			measurements, training of assessors) and a	
6			description of study instruments (eg,	
7			questionnaires, laboratory tests) along with their	
8			reliability and validity, if known. Reference to where	
9			data collection forms can be found, if not in the	
10			protocol	
11				
12				
13		18b	Plans to promote participant retention and	4, 7
14			complete follow-up, including list of any outcome	
15			data to be collected for participants who	
16			discontinue or deviate from intervention protocols	
17				
18				
19	Data	19	Plans for data entry, coding, security, and storage,	10
20	management		including any related processes to promote data	
21			quality (eg, double data entry; range checks for	
22			data values). Reference to where details of data	
23			management procedures can be found, if not in the	
24			protocol	
25				
26				
27	Statistical	20a	Statistical methods for analysing primary and	10, 11
28	methods		secondary outcomes. Reference to where other	
29			details of the statistical analysis plan can be found,	
30			if not in the protocol	
31				
32				
33		20b	Methods for any additional analyses (eg, subgroup	11, 12
34			and adjusted analyses)	
35				
36		20c	Definition of analysis population relating to protocol	10, 11
37			non-adherence (eg, as randomised analysis), and	
38			any statistical methods to handle missing data (eg,	
39			multiple imputation)	
40				
41				
42	<b>Methods: Monitoring</b>			
43				
44	Data monitoring	21a	Composition of data monitoring committee (DMC);	13
45			summary of its role and reporting structure;	
46			statement of whether it is independent from the	
47			sponsor and competing interests; and reference to	
48			where further details about its charter can be	
49			found, if not in the protocol. Alternatively, an	
50			explanation of why a DMC is not needed	
51				
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53		21b	Description of any interim analyses and stopping	10, 11
54			guidelines, including who will have access to these	
55			interim results and make the final decision to	
56			terminate the trial	
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2	Harms	22	Plans for collecting, assessing, reporting, and	13
3			managing solicited and spontaneously reported	
4			adverse events and other unintended effects of	
5			trial interventions or trial conduct	
6				
7	Auditing	23	Frequency and procedures for auditing trial	13
8			conduct, if any, and whether the process will be	
9			independent from investigators and the sponsor	
10				
11				
12	<b>Ethics and dissemination</b>			
13				
14	Research ethics	24	Plans for seeking research ethics	2, 17
15	approval		committee/institutional review board (REC/IRB)	
16			approval	
17				
18	Protocol	25	Plans for communicating important protocol	17
19	amendments		modifications (eg, changes to eligibility criteria,	
20			outcomes, analyses) to relevant parties (eg,	
21			investigators, REC/IRBs, trial participants, trial	
22			registries, journals, regulators)	
23				
24				
25	Consent or	26a	Who will obtain informed consent or assent from	18, Table 1
26	assent		potential trial participants or authorised surrogates,	
27			and how (see Item 32)	
28				
29				
30		26b	Additional consent provisions for collection and use	n/a
31			of participant data and biological specimens in	
32			ancillary studies, if applicable	
33				
34	Confidentiality	27	How personal information about potential and	17, 18
35			enrolled participants will be collected, shared, and	
36			maintained in order to protect confidentiality	
37			before, during, and after the trial	
38				
39				
40	Declaration of	28	Financial and other competing interests for	18
41	interests		principal investigators for the overall trial and each	
42			study site	
43				
44	Access to data	29	Statement of who will have access to the final trial	18
45			dataset, and disclosure of contractual agreements	
46			that limit such access for investigators	
47				
48				
49	Ancillary and	30	Provisions, if any, for ancillary and post-trial care,	n/a
50	post-trial care		and for compensation to those who suffer harm	
51			from trial participation	
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2	Dissemination	31a	Plans for investigators and sponsor to	2
3	policy		communicate trial results to participants,	
4			healthcare professionals, the public, and other	
5			relevant groups (eg, via publication, reporting in	
6			results databases, or other data sharing	
7			arrangements), including any publication	
8			restrictions	
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11		31b	Authorship eligibility guidelines and any intended	16
12			use of professional writers	
13				
14		31c	Plans, if any, for granting public access to the full	17
15			protocol, participant-level dataset, and statistical	
16			code	
17				
18				
19	<b>Appendices</b>			
20				
21	Informed consent	32	Model consent form and other related	Additional
22	materials		documentation given to participants and authorised	File 2
23			surrogates	
24				
25				
26	Biological	33	Plans for collection, laboratory evaluation, and	n/a
27	specimens		storage of biological specimens for genetic or	
28			molecular analysis in the current trial and for future	
29			use in ancillary studies, if applicable	
30				

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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.