Acne Care Online:

feasibility and full-scale RCT of an online intervention to support acne self-management

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Protocol Information

This protocol describes the Acne Care Online study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non- study participants; every care was taken in its drafting, but corrections or amendments may be necessary.

Compliance

This study will adhere to the principles of Good Clinical Practice (GCP). It will be conducted in compliance with the protocol, in accordance with current Data Protection Regulations and all other regulatory requirements, as appropriate.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Acne-QoL	Acne-Specific Quality of Life questionnaire
Acne vulgaris	Acne
CEAC	Cost Effectiveness Acceptability Curves
CONSORT	Consolidated Standards of Reporting Trials
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
GP	General Practice or General Practitioner
HEAP	Health economics analysis plan
ICER	Incremental Cost-Effectiveness Ratio
IPQ	Illness Perceptions Questionnaire
MCID	Minimum Clinically Important Difference
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NIHR	NHS Institute for Health & Care Research
PEI	Patient Enablement Instrument
PETS	Problematic Experiences of Therapy Scale
PHQ-4	Patient Health Questionnaire
REC	Research Ethics Committee
PMG	Programme Management Group
PSC	Programme Steering Committee
QALY	Quality Adjusted Life Years
QoL	Quality of life
RCT	Randomised Controlled Trial
SAP	Statistical analysis plan
SWEMWBS	Short Warwick Edinburgh Mental Well-being Scale
UoS	University of Southampton

KEYWORDS

Acne, primary care, community care, pharmacy, schools, digital intervention, adherence, self-management, randomised controlled trial, process evaluation, economic evaluation

1 TRIAL SYNOPSIS

Short title/Acronym:	Acne Care Online
Full title:	Acne Care Online: feasibility and full-scale RCT of an online intervention to support acne self-management

Population:	Young people with acne (aged 13-25 years)
Objective:	To determine the feasibility and effectiveness of an online behavioural intervention aimed at supporting self-management, improving outcomes and reducing antibiotic use in acne
Study Designs:	A multi-centre randomised controlled trial with a feasibility trial and full-scale randomised trial with internal pilot, nested health economic evaluations and mixed-methods process evaluation studies
Sample sizes:	Feasibility study: 60 participants Feasibility qualitative process interviews: up to 10 participants from each trial arm (20 maximum) Full-scale trial: 908 participants (including 85 in internal pilot) Full scale trial qualitative process interviews: 20-25 participants
Intervention:	Access to online behavioural intervention for people with acne to support effective acne self-management, in addition to usual care
Control group:	Usual care, including signposting to NHS advice from baseline and access to the intervention after 52 weeks follow-up
Follow up duration:	52 weeks
Recruitment sites	Feasibility trial, internal pilot and full-scale trial will recruit through general practices, community pharmacies, social media and other community recruitment, such as schools and colleges. **Feasibility study:** We anticipate needing 8-12 GP sites for the feasibility trial to randomise 30 participants (half of total as the remainder to be recruited through social media and community advertising). The exact number of sites will be determined by recruitment rates. **Full-scale study with internal pilot:** We anticipate needing around 100 GP sites for the full-scale trial to randomise 450 participants (half of total as the remainder to be recruited through social media and other sources). The exact number of sites will be determined by recruitment rates.

URL for randomisation:	www.lifeguideonline.org
Outcome measures	**Both feasibility trial and full-scale trial will include the following measures:** **Primary outcome** Acne severity measured using the Acne-QoL symptoms subscale at 12 weeks, compared with baseline **Other measures (including secondary outcomes, process measures and economic measures)** Acne severity evaluated over 12 months using Acne-QoL symptom subscale, using repeated measures analysis over 12 weeks, 24 weeks, 36 weeks and 52 weeks, controlled for baseline Acne-QoL other subscales (self-perception, role-emotional and role-social) and total score evaluated over 12 months using Acne-QoL symptom subscale using repeated measures analysis over 12 weeks, 24 weeks, 36 weeks and 52 weeks, controlled for baseline Use of topical treatment for acne at baseline, 12 weeks, 24 weeks, 36 weeks and 52 weeks (self-report and treatment adherence) Use of acne-related antibiotics and other oral acne treatment use at baseline, 12 weeks, 24 weeks, 36 weeks and 52 weeks, including frequency of use (self-report) Past use of topical and oral treatments for acne Problematic Experiences of Therapy Scale (PETS) will be asked prior to adherence questions at baseline,12 weeks and 52 weeks. Patient Enablement Instrument (PEI) at baseline, 12 weeks and 52 weeks Brief Illness Perceptions Questionnaire (IPQ) at baseline, 12 weeks and 52 weeks Patient Health Questionnaire (PHQ–4) for Anxiety and Depression at baseline, 12 weeks and 52 weeks EQ-5D-5L at baseline, 12 weeks, 24 weeks, 36 weeks and 52 weeks Short Warwick Edinburgh Mental Well-being Scale (SWEMWBS) at baseline, 12 weeks, 24 weeks, 36 weeks and 52 weeks Resource use will be measured at baseline, 12 weeks, 24 weeks, 36 weeks and 52 weeks (self-report)

	Prior belief in effectiveness of online interventions will be asked at baseline and use and type of online resources previously used for acne will be asked at baseline, 12 weeks and 52 weeks Demographics Age of onset and duration of acne **We will assess questionnaire burden in the feasibility trial and if this is not acceptable to participants we will consider not including the Brief IPQ and SWEMWBS in the full-scale trial and internal pilot**
Statistical methods	**Feasibility trial:** Descriptive statistics will describe recruitment and retention rates, completion of questionnaire items and characteristics of participants. All outcome measures will be included in the feasibility trial to assess acceptability of trial processes and questionnaire burden. **Full-scale trial sample size:** Based on comparison of the Acne-QoL symptoms subscale at 12 weeks, power 90%, alpha 0.05 and a mean difference of 2 points (standard deviation 5.8), 356 participants are needed. Allowing for 30% non-adherence and 20% loss to follow up gives a total 908 participants (454 per arm). **Full-scale trial analysis:** The primary analysis will be a linear regression model to analyse Acne-QoL symptom subscale at 12 weeks, adjusting for key baseline covariates and stratification factors. As a secondary analysis we will also assess Acne-QoL symptom subscale and other Acne-QoL subscales with a repeated measures approach, using a multilevel mixed model and adjusting for the same covariates as the primary analysis. Secondary outcomes will be modelled using a regression modelling approach with a distribution appropriate to the outcome. All analyses will be on an intention to treat basis.
Process evaluation	**Feasibility trial:** We will conduct up to 10 qualitative interviews with participants in the intervention group and up to 10 participants in the control group to explore facilitators and barriers to trial recruitment and retention and to inform programme theory for design of the process evaluation in the full-scale trial. **Full-scale trial:**

	Qualitative interviews will be carried out with 20-25 trial participants to provide in-depth understanding of experiences and factors that influence engagement with the intervention. This will include approximately 15-20 people in the intervention group and approximately 5 people in the control group. Quantitative process evaluation will assess baseline data (age, gender, acne severity) to examine moderator effects on intervention engagement (automated intervention usage data and self-reported treatment adherence) and outcomes. We will assess potential mediators of intervention adherence with outcomes; changes in questionnaire items on beliefs about treatment (PETS) and enablement (PEI), as well as intervention usage.
Economic evaluation	**Feasibility trial:** All economic measures will be included in the feasibility trial to assess completion rates and acceptability of trial processes. **Full-scale trial:** A within-trial cost utility analysis comparing the online intervention to usual care will be undertaken from an NHS perspective. Resource use will be collected via self-report questionnaires at baseline, 12 weeks, 24 weeks, 36 weeks and 52 weeks. Health-related quality of life will be measured using EQ-5D-5L scores at the same timepoints, which will be converted to utility scores to estimate Quality-Adjusted Life years for the trial period. Cost utility analyses using regression analysis will estimate the incremental cost, incremental benefit and incremental cost effectiveness of the online intervention compared to usual care alone. Sensitivity analyses will be undertaken to explore key uncertainties. If the inclusion of the Short Warwick Edinburgh Mental Well-being Scale (SWEMWBS) proves acceptable in the feasibility study we will estimate Mental Well-being Adjusted Life Years (MWALY).

2 SCHEDULE OF OBSERVATIONS AND PROCEDURES

Outcomes collected	Baseline	12 weeks	24 weeks	36 weeks	52 Weeks (end of study)
Sign up information required	x				
Screening questions	x				
Demographics	x				
Age of onset and duration of acne	x				
Acne-QoL	x	x	x	x	x
Current use of topical acne treatments (which one)	x	x	x	x	x
Past use of topical acne treatments (which one)	x				
Problematic Experiences of Therapy Scale (PETS)	x	x			x
Adherence to topical acne treatments (frequency of application)	x	x	x	x	x
Current use of oral acne treatments (which one)	x	x	x	x	x
Past use of oral acne treatments (which one)	x				
Patient Enablement Instrument (PEI)	x	x			x
Prior belief about effectiveness of intervention	x				
Use of online resources	x	x			x
Patient Health Questionnaire (PHQ–4)	x	x			x
EQ-5D-5L	x	x	x	x	x
Short Warwick Edinburgh Mental Well-being Scale (SWEMWBS)	x	x	x	x	x
Brief Illness Perceptions Questionnaire	x	x			x
Resource use	x	x	x	x	x

Data collection during intervention period is kept to a minimum to reduce participant burden and reduce chance of regular monitoring over-shadowing intervention effects. Total questionnaire duration is 10 minutes and has been assessed as acceptable by public contributors in the target age range.

3 LAY SUMMARY

Background

Acne is very common, frequently causes distress or low self-confidence, and may lead to permanent scarring, long-lasting dark marks, or depression. Treatment of acne is a major cause of antibiotic use amongst young people, leading to antibiotic resistance. Evidence and guidelines suggest that topical treatments (creams or gels applied directly to the skin) should be the main treatments for acne. Effective topical treatments are available from pharmacies without a prescription, but many people are unaware of these and buy cosmetic products that don't help instead. People often give up on topical treatments because they are not given full advice on how to use them. For example, they don't know how to reduce the risk of stinging and redness or that it takes several weeks for treatments to start working.

We have developed a new website to help young people with acne to manage acne more effectively, including information on how to obtain effective treatments, promote regular treatment use and advice on how to avoid side effects.

Aims

We will test the new website in a randomised trial to see whether it improves outcomes for people with acne and reduces the use of long-term oral antibiotics.

Methods

People with acne (aged 13-25 years) will be invited to take part in the study through a variety of sources including from GP practices, pharmacies, community and social media advertising, and through schools and other partner organisations. Participants will be asked to register online and complete an online consent form and questionnaire before being allocated by chance (randomly) to either the new study website, or to the control group. All participants will be able to access their usual health care or acne treatments during the study. Participants will be asked to complete questionnaires at 12 weeks, 24 weeks, 36 weeks and 52 weeks asking about their acne, quality of life and their use of acne treatments.

Participants in the control group will be signposted to standard NHS advice about acne. They will also be offered access to the new website after 52 weeks follow-up.

We will also explore how the new website works, by talking to those that have used it and analysing how they used it, and explore the costs to the NHS and for patients of using the website and estimate its value for money.

Dissemination

We will publish this work in peer-reviewed journals, at conferences and via patient organisations. If effective, we will aim to make the new website freely available and ensure widespread uptake by working with young people and health care providers to signpost and endorse its use.

4 BACKGROUND AND RATIONALE

Acne vulgaris (hereon acne) is extremely common, affecting over 90% of teenagers.[1] It is primarily a condition affecting the pilosebaceous unit (hair follicles in the skin and associated oil glands), leading to inflammatory and non-inflammatory lesions and scarring,[2] most commonly affecting the face. The aetiology remains unclear but research into dietary, hygiene or other lifestyle causes have shown these to have little influence.[2]

Acne can cause significant distress, decreased self-confidence and increased rates of depression and suicidal ideation.[2] Distress about the appearance of acne appears to be particularly high amongst women and people identifying as non-white.[3] The majority of acne is classed as mild, with moderate or severe acne combined making up less than 15% of acne.[4, 5] Acne persists in 40-60% of people into their twenties and is thought to lead to some degree of scarring in approximately 20% of the population.[2, 4]

As well as limiting quality of life, acne makes a major contribution to antibiotic use amongst young people,[6] results in substantial health service use[7] as well as causing skin changes that can be permanent, such as skin pigment changes and scarring.[2] Skin conditions account for 18% of antibiotics prescribed outside hospitals[8] and, although data are scarce, antibiotic resistance arising from acne treatment is a major and increasing concern.[9] Health service use for acne is substantial with approximately 3% of people aged 13-25 visiting their GP for acne each year[7] (10k consultations per year in the UK), of whom 8% are referred to secondary care.[7] The majority of people attending secondary care are prescribed isotretinoin and require frequent review (monthly for women).[10]

There is high-quality evidence supporting use of topical treatments for acne, which are recommended as first line treatment for mild-to-moderate acne in UK guidelines.[11] However, treatment adherence is low, mainly due to limited understanding, with insufficient motivation and support necessary to engage effectively with treatments (regular use is needed over several weeks) and the barrier of skin irritation unless mitigating advice is emphasised.[12] These problems can be overcome with better support.[13]

Another major barrier to the use of effective treatment is a perception that acne is not a problem that warrants medical attention, even where the condition has considerable emotional and social impact.[14, 15] People with acne often have little awareness of effective topical treatments available via pharmacy or on prescription and instead use ineffective cosmetic products.[16] They frequently consult late, and at a point when they are disillusioned with topical treatments and are keen for oral treatments, commonly antibiotics, which are incorrectly perceived as being more effective than topical treatments.[16] GPs prescribe oral antibiotics during 31% of first consultations for acne,[17] with median duration 4 months,[6] partly due to perception of high patient demand for antibiotics.[18]

NHS England describes acne as a condition appropriate for self-management with pharmacy advice and use of over-the-counter medicine.[19] Accessible support is needed for people with acne to gain early control of the condition through helping them obtain effective treatment, use this regularly and avoid side effects. Early treatment of acne is a priority in order to avoid oral antibiotic use, lessen psychosocial impact and reduce risk of severe acne or scarring that

may lead to further treatment, referral and psychological consequences,[9] as early treatment can minimise subsequent scarring and associated referrals.[20]

Although there have been many calls for improved education and information for people with acne,[2, 12, 13] there is little research evaluating behavioural interventions to date, and education and information are insufficient to change behaviour effectively: the most recent review identified four RCTs of interventions; two used emails or text messaging (both small and inconclusive) and two used increased follow-up visits.[21]

A recent study of an instructional video on how to use topical treatments for acne, delivered via a pharmaceutical company app, found weak evidence of increased treatment adherence, but there were methodological limitations and the app is not widely used.[22] An industry-funded guideline has been developed for pharmacists but not widely used.[23]

Digital interventions change health-related behaviours when based on robust development supported by theory and multiple behaviour techniques.[24] A Cochrane review has shown that digital interventions improve outcomes in long-term conditions.[25] Given the evidence above for behavioural barriers to treatment (i.e. low awareness of effective topical treatments, low adherence and insufficient management of side effects), there is a good case for the development of a robust intervention to support effective self-management of acne. We focus on young people aged 13-25 years with mild and moderate acne, as this is the largest group, most likely to benefit and because acne in people over the age of 25 and severe acne can be more difficult to manage.

An intervention to improve self-management for acne is likely to have the following potential benefits:

- Effective early management of acne may reduce the emotional, psychological, and social burden of acne;
- Effective early management of acne may reduce the risk of sequelae such as skin pigment changes or scarring, for which there are few effective treatments;
- Improved use of topical treatments is likely to reduce oral antibiotic use, reducing the risks from antimicrobial resistance.

5 AIM AND OBJECTIVES

Aim

To improve outcomes for acne through an online behavioural intervention to help people self-manage acne effectively, including by promoting appropriate treatment use and reducing overuse of long-term oral antibiotics

Objectives

- Assess the feasibility of conducting a randomised trial of an online self-management intervention for acne.
- Evaluate clinical effectiveness of online self-management intervention for acne in improving acne outcomes

- Explore mechanisms underlying effectiveness of the intervention through process evaluation
- Undertake an economic evaluation to estimate cost-effectiveness of the intervention compared with usual care from NHS and patient perspectives

6 STUDY DESIGN

This study is part of a programme of work which has developed an online intervention to support self-management for acne to be evaluated in a feasibility and full-scale, 52 week randomised controlled trial (RCT) with nested health economic and process evaluation studies.

The intervention includes online information and support for young people with help-seeking from healthcare professionals for acne treatments and advice, including a simple patient-held 'decision tool' that people with acne can take to consultations with GP or community pharmacy professionals, in order to support communication within the consultation. Participants will be recruited via GPs, community pharmacies, social media and other community recruitment, such as schools and colleges. We will recruit via all these routes for both feasibility trial and full-scale trial, as assessing rates of recruitment and diversity of recruitment is a key feasibility outcome.

Participants in both feasibility trial and full-scale trial will be randomised to one of two groups:

1. Usual care plus immediate access to the online intervention
2. Usual care with signposting to NHS advice and access to the online intervention after 52 weeks of follow-up

6.1 OUTCOME MEASURES

All participant-reported outcome measures and intervention usage data will be collected online for both the feasibility and full-scale trials. This will be collected using LifeGuide software (www.lifeguideonline.org), which is a unique set of open source software used to develop and trial online behavioural interventions.

Feasibility trial will include the following measures as it is anticipated that these will all be required for the full-scale trial in order to allow for process evaluation and economic evaluation, and acceptability of completion needs to be assessed at feasibility stage. Preliminary public contributor input has suggested that questionnaire length is acceptable (approximately 10 minutes). However, we will assess questionnaire burden in the feasibility trial and if this is not acceptable to participants we will consider reducing these for the full-scale trial and internal pilot.

6.1.1 Primary outcome measure

The primary clinical outcome measure is acne severity measured using the Acne-QoL symptoms subscale at 12 weeks. Although our previous research shows there are several acceptable participant-reported outcome measures for acne,[26] Acne-QoL is the most extensively validated.[27-29] There is not yet a core outcome set developed for acne, although the Acne-QoL is compatible with current developments.[30, 31]

The effect of acne treatments is seen around 6-12 weeks,[32] hence our choice of primary timepoint at 12 weeks. Longer term follow-up to 52 weeks will also be important in order assess the impact of the intervention on maintenance as well as initial control of acne, as relapse in acne following discontinuing treatment is thought to contribute to consulting and lack of acne control.

6.1.2 Other data and outcomes

The further measures to be completed by online questionnaire are as follows. Some are both secondary outcomes and process measures (such as adherence to topical treatments) while some are both process measures and measures to inform cost utility (such as Short Warwick Edinburgh Mental Well-being Scale) so we therefore list them as 'other measures' rather than separating by secondary outcome, process measure or economic outcome.

- Acne severity will be assessed over 12 months by measuring Acne-QoL symptom subscale, using repeated measures analysis over 12 weeks, 24 weeks, 36 weeks and 52 weeks, controlled for baseline
- Acne-QoL other subscales (self-perception, role-emotional and role-social) and total score, using repeated measures analysis over 12 weeks, 24 weeks, 36 weeks and 52 weeks, controlled for baseline
- Demographics will be asked at baseline: age, gender, ethnicity, postcode, occupation of main household earner
- Prior belief in effectiveness of online interventions for acne will be asked at baseline
- Use and type of online resources previously used for acne will be asked at baseline, 12 weeks and 52 weeks
- Age at onset of acne and duration of acne will be asked at baseline
- Current use of topical and oral treatments for acne will be asked at baseline, 12 weeks, 24 weeks, 36 weeks and 52 weeks
- Past use of topical and oral treatments for acne will be asked at baseline
- Adherence to topical acne treatments (frequency of application) will be asked at baseline, 12 weeks, 24 weeks, 36 weeks and 52 weeks
- Problematic Experiences of Therapy Scale (PETS)[33] will be asked prior to adherence questions at baseline, 12 weeks and 52 weeks. The PETS asks participants to what extent they had been prevented from carrying out the intervention by socially acceptable reasons in order to explore barriers to adherence and promote reporting of non-adherence (e.g. "Lack of time prevented me from carrying out the treatment")
- Patient Enablement Instrument (PEI)[34] will be measured at baseline, 12 weeks and 52 weeks to assess the extent to which usual care or intervention use has enabled participants to understand and self-manage their acne
- Brief Illness Perceptions Questionnaire (IPQ)[35] will be measured at baseline, 12 weeks and 52 weeks to explore participants beliefs about their acne that are expected to be important determinants of adherence to treatments (e.g. perceived impact, severity, control, treatability, timeline)
- Patient Health Questionnaire (PHQ–4) for Anxiety and Depression[36] will be measured at baseline, 12 weeks and 52 weeks

- EQ-5D-5L [37] will be used as a measure of generic quality of life (QoL) at baseline, 12 weeks, 24 weeks, 36 weeks and 52 weeks
- The Short Warwick Edinburgh Mental Well-being Scale (SWEMWBS) will be elicited at baseline, 12 weeks, 24 weeks, 36 weeks and 52 weeks, and valued using a UK preference-based value set to estimate Mental Well-being Adjusted Life Years (MWALY). [38] In a previous acne trial (SAFA),[39] a large proportion of the participants started the trial in perfect health according to the EQ-5D (46% in the intervention group and 43% in the control group) and thus the EQ-5D had no capacity to measure any benefit that might occur from the intervention. There has also been some debate about how well the EQ-5D captures mental well-being given 4 of the 5 domains measure physical health. Since acne can significantly affect mental-wellbeing we aim to test and compare the performance of SWEMWBS to EQ-5D as a generic measure of quality of life for people with acne.
- Healthcare resource use will be measured at baseline, 12 weeks, 24 weeks, 36 weeks and 52 weeks – data collection will be kept minimal, and the online format will allow for skipping of sections where no resources have been used. We intend to collect this information every 3 months, with a simple diary prompt, in order to avoid asking participants to recall over longer periods. Self-reported health care resource use has been found to provide acceptable data across other studies.[40, 41]

We will ask about the primary outcome, treatment use, resource use and generic QoL at all time points. We will ask about intervention effects, i.e., treatment adherence and barriers to adherence (PETS), enablement (PEI) and other secondary outcomes (PHQ-4) just at primary timepoint (12 weeks) and 52 weeks, to assess whether there has been maintenance of intervention effect.

6.2 DEFINITION OF END OF STUDY

End of full-scale RCT is defined as the date when the last point of data is collected for the last participant from their follow-up questionnaire.

7 SELECTION AND ENROLMENT OF PARTICIPANTS

7.1 INVITATION TO PARTICIPATE

Recruitment and enrolment procedures, and inclusion criteria will be the same for both feasibility and full-scale trials, so that feasibility of recruitment can be assessed prior to full-scale trial, and necessary adaptations made.

Young people aged 13-25 with acne will be recruited through a variety of sources including mail-out and opportunistic recruitment from general practices, opportunistic recruitment in pharmacies, community and social media advertising, and through schools, colleges, pharmacies and other partner organisations. We will develop age-appropriate recruitment materials to explain what is involved for potential participants.

7.1.1 General practice recruitment

Invitations will be sent through SMS text and/or postal mail out, poster advertising (16-25s only) and/or opportunistic recruitment by participating GP practices.

SMS/postal mailout:

Database searches will identify patients aged 13 to 25 years who either:

- Have been prescribed a topical treatment for acne or co-cyprindiol in the previous 12 months or
- have a diagnostic code for acne on their electronic record over the previous 12 months either with or without having been prescribed an oral tetracycline or erythromycin in that period.

Following close monitoring of our sample recruited within the first 6 months, we propose testing a slightly revised search strategy for recruiting 16-25 year olds from primary care, initially in a limited number of practices. This would involve broadening the search to ALL 16-25 year olds registered at the practice, subject to the same screening checks for unsuitability for invitation outlined below. The rationale for this proposal is as follows:

- To date, many of the participants recruited from primary care report currently using topical treatments. Given that our intervention has been developed primarily to support the effective use of topical treatments, we are concerned that we are not reaching individuals who stand to benefit most from the intervention.
- Given the very high prevalence of acne in the teenage and young adult population (90% affected), and the fact that our SMS wording does not presume or imply prior consultation or treatment for acne (please see amended primary care SMS wording), it would seem reasonable to send this invitation to all 16-25s registered at the practice in order to give those who may have acne, but who have not yet consulted about this, the opportunity to participate.

Given the substantially higher anticipated number of matches, and associated costs, we will ask these test practices to invite individuals matching these broader searches via SMS only, not via postal mail-out. Given the previously documented uncertainty about contact phone numbers of under 16s on medical records (i.e. cannot be sure it is a parent's phone number), we are proposing to test this change only in the 16-25 age group; there are no proposed changes to how primary care practices invite 13-15 year olds.

Decisions about our primary care search strategy for 16-25 year olds beyond these limited number of test practices will be informed by how effective this revised strategy proves to be – i.e. whether it increases the proportion of primary care recruited participants who are not currently using topical treatments. If not successful, we will retain the existing strategy and continue trying to seek more treatment naïve participants from other routes.

GPs will be asked to screen the lists to check for patients who it may be inappropriate to invite, such as known opposition to taking part in research. Patients aged 16 and over will be

contacted directly whereas for those under the age of 16, initial contact will be made with their parent/guardian.

Potential participants (or their parent/guardian where under 16) will be sent the following: 1) SMS text message to their registered mobile number with a link to the study website; and/or 2) postal mail out pack including a summary participant information sheet (PIS) and details of how to access the study website. The study website will include full participant information and parental information, in both accessible (summary PIS) and detailed formats (full PIS), who to contact for further information or discussion, information on eligibility and how to proceed to provide online consent prior to participating in study activities.

Discussions with public contributors have suggested that their parent/carer may not remember to forward messages on so it would be preferable for the invitation to be sent by more than one method, such as by text and by post. We therefore propose to use both routes, inviting participants by text or post or both if necessary. We will not send more than one text invite or more than one postal invite to each potential participant (or their parent/guardian where under 16).

Discussions with GP practices indicate that is not always possible to ascertain whose mobile phone number or email address is linked to GP records. Both public contributors and GP practices have said that, for young people aged over 16, it is often the parent/carer's mobile number still listed as the patient's 'preferred' mobile number, as they have not yet changed this. In these instances, the initial invitation may go to the parent rather than the young person in error, although subsequent links will request the parent/carer to forward the text to the young person so that they can access the participant information sheet and find out how to proceed to provide online consent prior to participating in study activities.

Opportunistic recruitment in general practice will also be offered to potential participants (or their parent/guardian where under 16). The health professional seeing the patient will then send an SMS text message to their mobile number with a link to the study website.

7.1.2 Opportunistic recruitment in pharmacies

Potential participants, or their parent/carer if under 16, will be given a link (via advertisement on screens (16-25 only) or by summary participant information sheet given by the pharmacy professional) directing them to the study website. The study website will include full participant information sheet, who to contact for further information or discussion, information on eligibility and how to proceed to provide online consent prior to participating in study activities.

7.1.3 Recruitment through schools/colleges

We will engage with teaching, pastoral or school nursing staff to plan opportunities to raise awareness of the research, including the possibility of research participation and how to take part. This may include invitations to take part in the study via letter, SMS text or email from the school or college directing interested individuals to the study website. All potential participants invited via this route will be contacted initially via their parent/carer given that many are likely to be under the age of 16.

7.1.4 Community or social media advertising

Community or social media advertising will be targeted at potential participants aged 16 or over. Posters will be displayed in locations such as GP surgeries, hospitals, community pharmacies, post-16 education colleges, University campuses, local newspapers or social media inviting potential participants, directing them towards the study website, which will include full participant information, who to contact for further information or discussion, information on eligibility and how to proceed to provide online consent prior to participating in study activities.

7.2 INCLUSION CRITERIA

Participants will be eligible for inclusion if:

- They are aged 13-25 years with self-defined acne with current active lesions (i.e. mild or worse on self-assessment scale)
- Have internet access

7.3 EXCLUSION CRITERIA

Potential participants will be excluded if:

- Their acne is currently clear or almost clear, i.e. if they answer 'no' to the following question asked online at baseline screening: *"Do you have spots or acne on your face at the moment? This could include whiteheads or more red spots or bumps."*
- They are unable to give informed consent or their parent does not provide consent (for participants aged 13-15 recruited via community or social media advertising)
- They are unable to read and write English as the intervention content and outcome measures are in English
- They are currently taking oral isotretinoin or have taken it within the previous 3 months, as advice about topical acne treatments may be inappropriate in this case
- They took part in interviews as part of Acne Care Online intervention development. (Qualitative interviewees who did not view intervention materials will NOT be excluded)
- Participants in the feasibility trial will be excluded from the full-scale trial
- Only one person per household will be able to take part in the study. If someone from that household has already joined the study then they will be excluded from the study

7.4 CONSENT

Participants will complete informed consent online through study software, prior to completion of baseline questionnaires and randomisation. The right of the participant to refuse to participate without giving reasons will be respected. All participants are free to withdraw at any time from the trial without giving reasons and without prejudicing further treatment. The consent form will include a question requesting explicit consent to access relevant data on intervention usage.

Our procedures are aimed at striking a balance between enabling young people to take part in research, as young people are currently underserved in acne research, vs ensuring informed age-appropriate consent to participate in research.

Participants aged 16 or over

Consent to enter the trial will be sought online from each participant only after they have received full study details and study team contact information (telephone number and email address), to allow time for consideration and the opportunity to ask questions.

Participants aged 13 to 15 recruited via their registered general practice or school

The initial invitation for young people aged 13 to 15 will be sent to their parent/carer, either through their registered practice or their school. They will be provided with a parental information sheet, or link to the study website where they can review this information. This will advise them what the study would involve for their child and will provide the opportunity to contact the research team to ask any questions. If they choose to pass this invitation on to the young person this will mean that 'implied consent' has been given. This would mean that a young person under the age of 16 would not receive materials inviting them to participate in the study unless their parents choose to pass on this information. The young person will then have access to the study website where they can review full study details and study team contact information (telephone number and email address), read the PIS, and will have the opportunity to request further information/ have questions answered. Online informed consent will then be obtained from participants aged 13-15.

In previous studies, where the parent/carer has provided consent and provided contact details for the young person there has been a very high drop-off in number of people engaging with the study. It is unknown whether this is because the young people are not interested in the study, or whether they are uninterested in research presented to them by their parents, but the result is under-representation of under-16s in research. Including this process of 'implied consent' from parents/carers promotes accessibility to research participation for young people. This is particularly appropriate for a low risk study where all trial procedures are online and the decision to be randomised only relates to choice between new online information and standard NHS information.

Participants aged 13 to 15 recruited via community advertising, social media or pharmacy
Community or social media advertising will be targeted at potential participants aged 16 or over only. However, if a young person aged 13-15 wishes to participate (for instance having been given the link by a friend or sibling), then they will receive an explanation that their parent/carer needs to provide consent for them to participate. They will be asked to direct their parent/carer to the study website, which includes full parent information sheet, who to contact for further information or discussion, information on eligibility and how to take part. If a parent provides consent for their young person aged 13-15 to take part then the young person will also be asked to provide consent.

This differs from the process of 'implied consent' for schools and GPs, where it can be ensured that the initial invitation goes to the parent/carer, who then passes it on to the young person, thus forming implied consent. This process cannot be ensured for social media and community advertising, hence the need for parent/carer consent.

Process evaluation interviews

For both feasibility and full-scale trials, participants will be invited to take part in a qualitative study (as part of the process evaluation), and will be asked at baseline whether they consent to be contacted about the interviews. When the interviews are due, participants will be contacted by phone, text message or email to give them further information about the interview study and the opportunity to ask questions. They will then be asked to login to give their consent online or provide written consent prior to the interview, or if they do not manage to complete either of these but attend for an interview then verbal consent will be recorded at the start of the interview. Where face-to-face interviews are carried out written informed consent will be sought in person. Participants will be free to withdraw at any time by contacting the research team.

Interviews will be carried out by experienced qualitative interviewers, either face-to-face or remotely via videoconferencing (Teams) or telephone. Face-to-face interviews will be held in participants' homes, but if they would prefer to meet elsewhere, alternative arrangements may be made for the meeting to be held on University Premises. Encrypted audio-recorders will be used for any interviews that do not take place on Microsoft Teams. Audio recordings will be professionally transcribed, anonymised and checked.

For process evaluation interviews with participants aged 13-15, consent from their parent/carer will be obtained prior to seeking consent from the young person. Feedback from public contributors suggests that 'implied consent' for the trial is acceptable for a low risk trial carried out entirely online, but that parental consent should be obtained in order for the researcher to speak to a research participant aged under 16.

7.5 CONFIDENTIALITY AND DATA PROTECTION

The confidentiality of all participants taking part in the study will be preserved. The study team will ensure that participants' anonymity is maintained and that their identities are protected from unauthorised parties. They will not be identified by their names, but by an identification code. Transcribers of the qualitative process evaluation interviews will sign a confidentiality agreement. The encrypted audio-recorders will be stored in locked offices at the University of Southampton.

Participant data will be collected online via LifeGuide software and stored securely on servers hosted by the University of Southampton. The participant data is pseudo anonymised by assigning each participant a participant identification number which will adapted for use in LifeGuide. Any follow-up data collected by telephone will be entered remotely at site. For qualitative interviews, all electronic data will be stored on a secure server until the transcriptions have been completed. Once these have been carried out and unique identifiers have been assigned then the digital audio recordings will be destroyed. All data will be retained in accordance with current Data Protection Regulations.

7.6 RANDOMISATION AND MASKING

Participants will complete informed consent/assent and baseline questionnaires online within LifeGuide software. Eligible participants will then be randomised to the intervention group or control group by the software.

Blinding of participants is not possible. Participants will be informed online as to which group they have been allocated to immediately. The trial statisticians will remain masked to treatment allocation until all analysis code has been written and checked. It will not be possible for all members of the study team to remain masked to treatment allocation, particularly those carrying out process evaluation interviews and those assisting with identifying participants for these interviews. Randomisation will be carried out in blocks of 4 and 6 and stratified by gender, age (13 to 15 years vs. 16 to 25 years) and recruitment source (general practice or social media/pharmacy/schools/colleges/community recruitment).

8 SAFETY

No specific therapeutic intervention is proposed. This programme consists of online information to support acne self-management. We will not collect adverse events. If serious adverse events are reported by study participants and are judged to be related to using the intervention these will be reported to the Sponsor and HRA.

8.1 SAFEGUARDING

Steps have been taken to ensure safeguarding for both the participants and the researchers. A lone worker policy is in place for the interviewers to follow prior to fieldwork. A safeguarding policy is in place and researchers will have a copy in their interview pack to follow in case of concern arising during interviews with participants.

The participant information sheet advises potential participants that confidentiality may have to be breached if there is a disclosure relating to serious harm, abuse and/or other safeguarding concerns.

9 FEASIBILITY TRIAL

During the feasibility trial all aspects of the protocol will be assessed. This will include (but may not be limited to): recruitment, retention and completion of questionnaires, randomisation, and participant engagement in accessing the intervention. The feasibility trial will allow for any necessary changes to the intervention to be addressed, and to build programme theory to test in the process evaluation of the full-scale trial.

If no changes are made to the intervention or to any trial procedures then data from the participants in the feasibility trial may be included in numbers for the full-scale trial, to avoid recruiting more participants than necessary overall, using established methods for decision-making on whether feasibility or pilot data can be carried forward without compromising trial integrity. [42]

10 INTERNAL PILOT AND FULL-SCALE TRIAL

If the feasibility trial shows that no changes are needed to the intervention or to trial procedures then we will progress straight to full scale trial. However, if substantial changes are needed to the intervention or trial procedures (for instance recruitment strategy) then relevant changes will be made and submitted for amendment to ethics approval if necessary. Once the full scale trial commences, no further changes will be made to the intervention.

11 STUDY PROCEDURES

11.1 STUDY PROCEDURES AND FOLLOW UP

Study procedures for both feasibility and full-scale trials will be carried out online through the online interventions (LifeGuide software). Participants wishing to take part in the study will provide consent and complete an online baseline questionnaire as indicated in the schedule of observations before being randomised to either the intervention group or the control group. Participants in the intervention group will then have access to the intervention. Participants in the control group will be signposted to the NHS advice page on acne and given access to the intervention website after 52 week follow-up. All participants will then have access to the website for 6 months after the trial has ended. As a minimum, the website will also be maintained by the study team until at least the end of the grant funding.

All participants will be asked to complete questionnaires as described above. Automated emails and text messages will be sent to notify participants when their follow-up questionnaires are available for completion.

Reminder emails and messages will be sent to non-responders (no more than 3 messages), followed by reminder telephone calls to invite participants to complete follow-up questions over the phone (no more than 3 calls).

11.2 DEVIATIONS AND SERIOUS BREACHES

Any study protocol deviations, non-compliance, or breaches are departure from the approved protocol. These will be adequately documented in the deviation log and reported to the Chief Investigator and Sponsor immediately. The Sponsor will then advise of and/or undertake any corrective and preventative actions as required. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

All serious protocol deviations, non-compliance or serious breaches of Good Clinical Practice and /or the study protocol will immediately be reported to the relevant Research Ethics Committee (REC).

11.3 WITHDRAWAL

The participant or legal representative is free to withdraw consent from the study at any time without providing a reason. If a participant initially consents but subsequently withdraws from the trial, a clear distinction will be made where possible as to what aspect of the trial the participant is withdrawing from. These aspects could be:

1. Withdrawal from trial intervention
2. Withdrawal from further study follow-up
3. Withdrawal from entire study and does not want data to be used.

The study team will explain the value of remaining in study follow-up and allowing this data to be used for trial purposes. Where possible, participants who have withdrawn from the study will remain in follow-up as per the trial schedule. If participants additionally withdraw consent for further follow up, they will not be followed up further.

Details of study discontinuation (date, reason if known) will be recorded in the trial management database.

12 INTERVENTION AND GROUP DETAILS

Participants will be randomised to either

1) online intervention plus usual care or
2) signposting to NHS information plus usual care, plus access to the intervention after 52 week follow-up

Participants in both groups will continue to receive their usual medical advice and prescriptions provided by their GP surgery and other healthcare services. They will not be prevented from seeking additional online support.

13 STATISTICS AND DATA ANALYSES

13.1 METHOD OF RANDOMISATION

Participants will complete informed consent, baseline questionnaires online and then will be randomised within the software. It will not be possible to blind participants to their allocation group, and it will not be possible to blind research team carrying out process evaluation interviews, but the trial statisticians will remain blinded. Randomisation will be carried out in random permuted blocks of 4 and 6 and stratified by gender, age (13 to 15 years vs. 16 to 25 years) and recruitment source (general practice or social media /pharmacy /schools /colleges /community recruitment).

13.2 SAMPLE SIZE

Updated sample size

Due to lower than anticipated engagement with the intervention, we propose to increase our sample size as follows. Based on comparison of the Acne-QoL symptoms subscale at 12 weeks,

power 90%, alpha 0.05, mean difference 2 points and standard deviation 5.8, 356 participants are needed. Allowing for 30% nonadherence would require 356/0.7^2=727, and allowing for 20% loss to follow up would require 908 participants in total.

Original sample size

Based on comparison of the Acne-QoL symptoms subscale at 12 weeks, power 90%, alpha 0.05 and seeking a standardised effect size of 0.30 (standard deviation 5.8), 470 participants are needed. Allowing for 20% loss to follow up gives a total 588 participants (294 per arm). An effect size of 0.30 equates to a difference in Acne-QoL symptoms subscale between arms of 1.74 points, meaning we would be conservatively powered to detect the published minimal clinically reported difference for Acne-QoL, which is a difference of 2 points on the symptom subscale.[28, 29] A standard deviation 5.8 aligns with trials with a similar patient group.[29] Based on recruitment to SAFA (HTA16/13/02) this sample size is achievable in the proposed timescale.

For the full-scale trial, we anticipate that we will need to recruit up to 100 practices to randomise 450 participants (half of total as the remainder to be recruited through social media and other sources), although this will be reviewed based on ongoing recruitment rates.

13.3 STATISTICAL ANALYSIS PLAN (SAP)

A detailed statistical analysis plan will be developed prior to the final analysis of the trial, however, the main features of the plan are discussed below. Data will be reported and presented according to the revised CONSORT (Consolidated Standards of Reporting Trials) Statement. All results will be reported with 95% confidence intervals and all models will control for the baseline covariates set out in the primary analysis. Any subgroup analyses will be planned and pre-specified in the statistical analysis plan.

Feasibility trial

The analysis of the feasibility study data will be descriptive, focusing on the recruitment and retention rates, as well as participant characteristics to ensure we are recruiting a diverse sample. We will explore the levels of missing data both at the questionnaire and individual questionnaire item levels to explore the acceptability of the outcome measures. We will estimate the standard deviation for our primary outcome and revisit our sample size assumptions for the full-scale trial with oversight committees. If no substantial changes to intervention, recruitment or questionnaires are needed following the feasibility trial then data from feasibility trial participants will contribute to internal pilot trial and full-scale trial analyses.

Internal pilot

The analysis of the internal pilot will be descriptive and again discussed with oversight committees. If no substantial changes to recruitment are needed following the internal pilot then data from these participants will contribute to the full-scale trial analyses. We propose the following progression criteria from internal pilot to full-scale trial:

- Green: if recruitment exceeds 70% of the recruitment predicted the full-scale trial will continue unchanged.
- Amber: if recruitment is 50-70% of the recruitment predicted this will be discussed with oversight committees to consider altering recruitment strategy then proceed with monthly recruitment updates.
- Red: if recruitment is less than 50% predicted this will be discussed with oversight committees and funder. Unless there is a credible plan to increase recruitment, progression to the full-scale trial should be halted.

Full-scale trial

For our primary outcome, we will use a linear regression model to analyse Acne-QoL symptom subscale at 12 weeks. All analyses will control for key baseline covariates and stratification factors. The full model will be set out in the statistical analysis plan prior to database lock. A 95% confidence interval for the mean difference between arms in Acne-QoL symptom subscale at 12 weeks will be calculated and reported. The frequency and pattern of missing data will be examined and a multiple imputation model will be used as a sensitivity analysis if appropriate.

As a secondary analysis we will also assess Acne-QoL symptom subscale and other Acne-QoL subscales with a repeated measures approach, using a multilevel mixed model allowing for observations (level 1) at all timepoints (12 weeks, 24 weeks, 36 weeks and 52 weeks) nested within participants (level 2) and adjusting for the same covariates as the primary analysis.

We will also use the same analysis method as the primary outcome to summarise Acne-QoL symptom subscale at each of the other time points and for the other Acne-QoL subscales (self-perception, role-emotional and role-social) and total score.

Secondary outcomes will be modelled using a regression modelling approach with a distribution appropriate to the outcome: linear regression for continuous outcomes or quantile regression if the assumptions for linear modelling are not met, logistic regression for binary outcomes, and a suitable count distribution such as Poisson or negative binomial for count data. All results will be reported with 95% confidence intervals and all models will control for the baseline covariates set out in the primary analysis. No pre-specified subgroup analyses are planned.

14 NESTED HEALTH ECONOMIC EVALUATION

The economic evidence base for acne is under-researched, particularly in the UK context.[43] This programme grant will provide an opportunity to test and apply resource use data collection tools and preference-based measures with people with acne.

Feasibility trial

Within the feasibility trial phase the focus will be on:

- Testing the use of an (online) aide memoire diary to help capture resource use and self-report questionnaire for collection of resource use data. Completion rates will be assessed and potentially important resource items identified.
- Seeking participants' thoughts on the preference-based measures (EQ-5D-5L[44] and Short Warwick Edinburgh Mental Well-being Scale (SWEMWBS)[38]) and their relevance in acne to help inform how to measure outcomes for use in the economic evaluation to be conducted alongside the full-scale trial.

It is important to explore the most appropriate way to measure outcome for use in the economic evaluation. Despite limited published evidence suggesting support for the use of the EQ-5D in acne,[44, 45] a recent acne trial [39] found a large proportion of the participants started the trial in perfect health on the EQ-5D (46% in the intervention group and 43% in the control group) and thus the EQ-5D had no capacity to measure any benefit that might arise from the intervention. Four of the five dimensions on the EQ-5D measure physical health and so the applicability of the EQ-5D and SWEMWBS will depend, in part, on the importance of mental well-being as opposed to physical health when valuing outcomes for acne.

Full-scale trial

The economic aims within the full-scale trial are:

- Describe the types of resource used for acne within the study sample.
- Estimate resource use and costs in people with acne in the intervention group compared to the usual care group.
- Estimate the Quality-Adjusted Life Years (QALYs)/Mental Wellbeing-Adjusted Life Years (mWALYs) in people living with acne in both arms.
- Undertake a cost-utility analysis to inform decision-making about whether the online intervention should be promoted for acne care in the NHS.

A within trial economic evaluation will estimate whether the online intervention is cost-effective compared to usual care from an NHS and personal social services perspective, and separately from a participant/family perspective as appropriate. We will estimate cost of the intervention and wider health care costs. Data on intervention resource use will be collected by the trial team whilst wider health resource use, in particular acne-related prescriptions, service use and out of pocket costs and productivity costs incurred by participants (or their family) will be collected through self-complete online questionnaires at baseline, 12, 24, 36 and 52 weeks with participants also given (online) resource use aide memoire diaries to use between data collection points to aid recall. Data collection will be kept minimal, and the online format will allow for skipping of sections where no resources have been used.

Depending on the outcome of the feasibility work with respect to outcome measurement we will measure either EQ-5D-5L and/or Short Warwick Edinburgh Mental Well-being Scale (SWEMWBS) at baseline, 12, 24, 36 and 52 weeks in the full-scale trial. Health-related quality of life if measured using EQ-5D will be done so in line with NICE recommendations.[37] EQ-5D-5L scores will be converted to utility scores in line with current recommendations and will be used to estimate Quality-Adjusted Life Years (QALYs) for the trial period.[46] The Short Warwick Edinburgh Mental Well-being Scale (SWEMWBS) consists of seven questions and for

which a UK preference-based value set has been published enabling the estimation of Mental Well-being Adjusted Life Years (MWALY).[38]

If the EQ-5D is used in the full-scale trial, this data will be used to explore the measurement properties (validity, responsiveness, practicality) of the EQ-5D for mild and moderate acne in order to inform future studies and the core outcome set for acne.[30] A cost utility analysis will be performed using accepted methods to inform judgements about the value for money afforded by the online intervention. Using information on costs and benefits, regression analysis will estimate the incremental cost, incremental benefit and incremental cost effectiveness of the online intervention compared to usual care alone. If one arm is clearly dominant (less costly and more effective) a recommendation can be made on this basis. If non-dominance occurs (costs are greater and the intervention more effective or if the intervention is cheaper and less effective), an incremental cost-effectiveness ratio (ICER) will be estimated so that a judgement about value for money can be made[47, 48] Sensitivity analyses will be undertaken to explore the impact of key uncertainties in the analysis. These will be specified in advance in the Health Economics Analysis Plan (HEAP) which will be written and reviewed before the trial data base is locked.

The value of undertaking long-term modelling will be assessed with a view to seeking further funding opportunities to undertake such work should such an approach seem useful. This is likely should the intervention prove effective in the trial but not cost-effective as the long-term cost-effectiveness may be different if establishing effective early acne treatment avoids sequelae, such as scarring, and reduces referrals to secondary care.

15 NESTED PROCESS EVALUATION STUDY

A mixed-methods process evaluation study will explore how participants engage with, and experience, the Acne Care Online trial and intervention and will provide an understanding of the mechanisms through which outcomes are achieved. Participants from both intervention and control arms of the trial will be included in all process analyses to provide comparative insight into the experiences and outcomes of those managing their acne without the Acne Care Online intervention.

Feasibility trial

Within the feasibility trial phase the focus will be on using the insights from these process analyses to:

- Identify any further changes required to intervention content and/or trial processes
- Ensure data collection measures are feasible, accessible and sufficient to provide the data required
- Refine the intervention logic model to inform hypotheses to test about anticipated mechanisms of action within the full-scale trial

Full-scale trial

Within the fully-powered trial, the focus will be on using the insights from these process analyses to:

- Understand how participants engage with, and experience, the trial and intervention
- Understand factors that mediate and moderate outcomes for participants
- Provide further contextual understanding of the trial outcomes

15.1 QUANTITATIVE PROCESS STUDY

15.1.1 Data collection

Quantitative process data will be collected from all participants in each phase of the study via LifeGuide software. This data will be collected via self-report questionnaires and by measures of intervention usage automatically recorded in the software (with informed participant consent).

Self-reported measures of intervention use that participants are asked to complete at baseline, 12 weeks, 24, weeks, 36 weeks and 52 weeks as part of the trial data collection will allow exploration of key constructs in the quantitative process evaluation: beliefs about acne and acne treatments, perceptions of self-efficacy, outcome expectations, psychosocial impact of acne, adherence to treatments and perceived barriers to this and treatment/advice-seeking behaviours. The specific measures and their collection time-points are shown in the 'Schedule of Observations and Procedures'.

Objective measures of intervention use automatically recorded in LifeGuide software, with participant consent, will allow evaluations of intervention usage patterns, such as time spent on intervention, number of visits to the intervention website and pages visited.

15.1.2 Data analysis

Descriptive and inferential statistics will be used to describe the quantitative process data and to examine relationships between key variables of interest. During the feasibility trial we will refine our logic model and anticipated mechanisms of change to identify the specific relationships between variables that we plan to analyse in the full-scale trial, and the appropriate statistical methods to apply.

We will use baseline data to examine potential predictors and moderator effects of participant characteristics (eg., age, acne severity, baseline attitudes) on intervention engagement (objectively recorded detailed website usage and self-reported treatment adherence) and outcome. We will also assess and analyse hypothesised mediators of treatment adherence and intervention outcomes; specifically changes in beliefs about treatment (PETS) as well as intervention usage.

15.2 QUALITATIVE PROCESS STUDY

15.2.1 Data collection

Qualitative process data will be collected from a sub-sample of participants from each phase of the trials. In the feasibility trial, we aim to interview up to 10 participants from each trial arm. In the full-scale trial, we aim to interview approximately 15-20 people in the intervention group and approximately 5 people in the control group (20-25 in total). We aim to conduct

interviews with all participants within three months of them being randomised into the trial. We will try to achieve a maximum variation sample of included participants with regards to characteristics such as age, gender, ethnicity, acne duration and perceived severity, level of usage of the online intervention (for intervention group).

Participants will be identified and invited via their participation in the trial. As part of the trial consent process all participants signing up will be asked if they are willing to be recontacted about later participation in a qualitative interview. When the interviews are due, we will select our maximum variation sample from those participants indicating their willingness to be recontacted. These individuals will then be contacted by phone, text message or email for the study team to provide further information about the interview study and the opportunity to ask questions. They will then be asked to give informed consent online prior to the interview, or if they do not manage to complete online consent but attend for an interview then verbal consent will be recorded at the start of the interview. Where face-to-face interviews are carried out written informed consent will be sought in person. Participants will be free to withdraw at any time by contacting the research team.

For process evaluation interviews with participants aged 13-15, written consent from parent/carer will be obtained prior to seeking assent from the young person.

15.2.2 Data analysis

Data from the qualitative process study will be analysed, firstly, using reflexive thematic analysis to construct themes grounded in the data. This will ensure that these represent participant perspectives and have the potential to challenge or extend our understanding of the factors and mechanisms involved in intervention outcomes. Following this, we will also examine the ways in which these inductively derived themes may map onto, elaborate or diverge from our theoretical frameworks, so as to relate our context-specific insights to generalisable theoretical constructs (where possible and appropriate). The findings will be discussed and interpretations agreed between the co-investigators (including PPI representatives).

15.3 PROCESS EVALUATION ANALYSIS

We will triangulate findings from the quantitative and qualitative process analyses to explore and test the causal mechanisms proposed, to help inform interpretation of trial results, and determine how the interventions could be improved and how implementation into clinical practice could be facilitated.

16 REGULATORY

16.1 CLINICAL TRIAL AUTHORISATION

This trial is not considered to be a clinical trial of a medicinal product or a medical device, so clinical trial authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA) is not applicable.

17 ETHICAL CONSIDERATIONS

17.1 ETHICAL APPROVAL

The trial protocol has received the favourable opinion of a Research Ethics Committee - (North West - Greater Manchester East Research Ethics Committee.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

Within one year after the end of trial, the Chief Investigator will submit a final report with the results, including any publication/abstracts, to the REC.

18 SPONSOR

The University of Southampton is acting as Sponsor for this trial.

18.1 INDEMNITY

The University of Southampton's public and professional indemnity insurance policy provides an indemnity to UoS employees for their potential liability for harm to participants during the conduct of the research. This does not in any way affect an NHS' Trust's responsibility for any clinical negligence on the part of its staff.

18.2 FUNDING

This study is funded by the National Institute for Health and Care Research Programme Grants for Applied Research NIHR202852. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

GP practices

GP practices will be reimbursed through service support payments from the NIHR CRN and research costs from the Acne Care Online study.

Participants

For the trial, participants will be entered into a prize draw to win one of four £50 vouchers at 12 weeks, one of four £50 vouchers at 24 weeks and one of four £50 vouchers at 52 weeks. This will be advertised to participants after they have completed baseline processes as it is an incentive for completing the trial, rather than for signing up to the trial. Participants taking part in the nested qualitative study interviews will receive a £15 gift voucher for their time.

18.3 AUDITS AND INSPECTIONS

The study may be participant to inspection and audit by the University of Southampton (under their remit as Sponsor) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

19 STUDY OVERSIGHT GROUPS

The day-to-day management of the study will be co-ordinated through the trial management team in Southampton, and oversight will be maintained by the Programme Management Group and the Programme Steering Committee.

19.1 PROGRAMME MANAGEMENT GROUP (PMG)

The PMG is responsible for overseeing progress of the study, including both the clinical and practical aspects. The Acne Care Online Programme Management Group (PMG) will be the PMG for the RCT. MS and IM are the Chief Investigators for this trial and will chair the PMG. The PMG includes three public contributors with experience of acne.

The Acne Care Online PMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the PMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

19.2 PROGRAMME STEERING COMMITTEE (PSC)

The PSC act as the oversight body on behalf of the Sponsor and Funder. The Acne Care Online Programme Steering Committee (PSC) will be the TSC for the RCT. The PSC/TSC will meet in person at least yearly. The Acne Care Online PSC/TCS consists of four independent members, including the Chair. One of the four independent members is a public contributor with experience of acne.

The Acne Care Online PSC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the PSC, including the timing of meetings, frequency and format of meetings.

19.3 DATA MONITORING AND ETHICS

The aim of the DMEC is to safeguard the interests of study participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the study. These duties will be carried out by the Acne Care Online Programme Steering Committee.

20 RECORD RETENTION AND ARCHIVING

Study documents will be retained in a secure location during and after the trial has finished.

The PI or delegate must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure the PI will maintain all source documents and study related documents. All source documents will be retained for a period of 10 years following the end of the study.

21 PUBLICATION POLICY

Data for the RCT from all centres will be analysed together and published as soon as possible. All publications and presentations relating to the trial will be authorised by the Programme Management Group. Participants and participating GP surgeries will be sent a summary of

results once available. The summary will also be made available on the study website in an accessible format.

22 REFERENCES

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