Submission of trial suggestion vignette to the

UK Dermatology Clinical Trials Network

Please complete your contact details:

This is your Network, so feel free to submit ideas that you feel are important to your own clinical practice. It would be helpful if you could use the following headings:

What is the research question?

To compare the efficacy and safety of oral spironolactone (50 mg once a day) vs. co-cyprindiol (2 mg/0.035 mg once a day) vs. oxytetracycline (500 mg twice daily) in adult women with inflammatory acne.

Condition of interest (Include patient group, type of lesion, location etc.)

Persistent or late onset inflammatory or polymorphic acne, in women aged 18 y or over

What treatments do you propose to compare?

1. Spironolactone, 25 mg once a day for 2 weeks, then 50 mg once a day for 22 weeks.
2. Co-cyprindiol (cyproterone acetate 2 mg/ethinylestradiol 0.035 mg) once daily on days 1-21 of menstrual cycle, for 6 cycles.
3. Oxytetracycline 500 mg twice daily for 24 weeks.

For increased efficacy versus comedones, topical adapalene od or its vehicle (placebo) will be included in all treatment arms using a factorial design. This enables us to assess the efficacy of spironolactone alone whilst also testing its efficacy in a more typical clinical scenario.

At the end of week 24, oral treatment will be stopped but topical treatment will be continued for another 12 weeks.

This study would be a clinical trial of an investigational medicinal product (spironolactone is not licensed for acne) and a CTA application would need to be submitted.

What outcome measures will you use?

1. Primary: total lesion count on the face.
2. Secondary: non-inflamed and inflamed lesion counts on the face, FDA 5-point global acne severity scale, subject self-assessment of improvement on a 5 point Likert scale, skin-related quality of life, adverse events, adherence, cost-effectiveness
3. Other: sebum output using Sebutape™ on the forehead and cheek, enumeration of skin propionibacteria on the same sites, estimation of serum hormones

What group of patients do you propose to study? (Include main inclusion/exclusion criteria and estimated patient numbers required. If you are able to provide the rationale for this study sample size please do so.)

Suggested design: Computer randomised, assessor-blind, parallel group, controlled non-inferiority trial of 36 weeks duration. Assessments at baseline, 4, 8, 16, 24 and 36 weeks.

Sample size: a non-inferiority design may be preferable to a superiority trial because the expected difference in efficacy between the three treatments is expected to be small. A study by Gerlinger et al (Drug Information Journal 2008; 42: 607-15) found an empirically validated non-inferiority margin of 10–15 percentage points for total acne lesion counts based on a comparison with patients self assessment. This is consistent with expert opinion (straw poll conducted by Dr Layton amongst colleagues at a recent meeting). With a SD of 30%, 155 patients per arm would be required to be 90% sure that the lower limit of a one sided 95% confidence interval

would be above a non-inferiority limit of 10%. If the SD is 35%, the sample size per arm goes up to 210.

A 10% adjustment will be made to allow for drop-outs; we recognise that the rate might be higher than this if we fail to avoid/manage side effects properly. The drop-out rate due to side effects will be an important study outcome. We will use ANCOVA to compare the groups, which allows adjustment for baseline lesion counts**.**

Analysis will be by intention-to-treat and per protocol. Non-inferiority will be concluded if both analyses show the same result. No subgroup analyses will be conducted.

We recognise that this is a large trial. An alternative design would be to compare spironolactone with co-cyprindiol in a 2-arm study. However, the antibiotic arm reflects current practice. There is pressure from governments and regulatory agencies to reduce the use of antibiotics as part of global efforts to reduce antibiotic resistance rates. This will be easier to achieve in acne if head-to head comparisons show favourable outcomes using non-antibiotic regimens.

Inclusion criterion:

1. Women of any ethnicity, aged 18 or over, with inflammatory or polymorphic acne of the face with or without involvement of non-facial sites. Minimum grade of 3 on the Leeds Revised Scale with at least 15 inflamed and 15 non-inflamed lesions on the face.

Participants with abnormal values for serum hormones at baseline can be included unless associated with a hormone-secreting cancer.

Exclusion criteria:

- Nodular acne
- Any other concomitant dermatosis of the face
- Cushing's syndrome, hormone-secreting tumours, prolactinoma
- Using any form of oral or topical acne medication in the 4 weeks prior to the study
- Allergy to any of the study medications or a closely related drug
- Renal or cardiac disease
- Use of potassium sparing diuretics, ACE inhibitors, angiotensin receptor blockers, salt substitutes or potassium supplements
- Pregnant or intending to become pregnant
- If sexually active, unwilling to use a barrier contraceptive throughout the study
- Family history of breast cancer
- Previous treatment with oral isotretinoin
- Unwilling or unable to comply with treatment regimens

Recruitment will be from research active general practices (PIC sites) using the NIHR regional networks (primarily Yorkshire and Humber) as well as selected secondary care centres (see overleaf). In Harrogate hospital, between 50 and 75 potentially eligible women are referred each year.

What existing evidence is there? (Supporting evidence is crucial to the marking system we use. Please provide references to 2-3 papers.)

There are 2 contrasting reviews on spironolactone for acne in the public domain. One is a Cochrane review, with its primary focus on hirsutism (Brown et al 2009 – see below). This review included evidence from randomised controlled trials (RCTs). The authors located only 2 of 6 RCTs of spironolactone that included acne as an outcome and which were published before 2009. Not surprisingly, it concluded there is no evidence that spironolactone is an effective treatment for acne. In contrast is the detailed review by Kim and Del Rosso (J Clin Aesthet Dermatol 2012;5:37-50) which sets out how and when spironolactone can be used to treat female acne, largely based on the authors' extensive experience. This article does not include a systematic review of clinical data on the efficacy or safety of spironolactone for acne. The authors conclude that " *Overall, spironolactone as a monotherapy or in combination with other agents is well tolerated if properly dosed and adjusted and has been shown to be beneficial for women with AV, especially in those exhibiting the hormonal pattern clinically. Although not first line, some women may benefit, including in cases where an endocrine disorder is suspected and oral isotretinoin therapy is not desired. Use of spironolactone for women with AV is not limited to those who exhibit hyperandrogenism clinically, as spironolactone can be used in women with normal circulating androgen levels*".

We are presently conducting a rigorous systematic review of published data on the clinical efficacy of

spironolactone for acne which will include evidence from case series. Although the review is not yet completed, we have identified 8 RCTs, 8 prospective and 5 retrospective case series. The overall quality of the studies is very low and it is almost certain that no useful conclusions can be drawn from them. We are also aware of at least 25 studies which have measured serum androgen levels pre and post spironolactone treatment for any indication (usually PCOS) in women. Whilst these might be informative regarding the effect of the drug on androgen metabolism, acne severity was studied concomitantly in only four of them.

We could find no head-to-head comparison of spironolactone versus co-cyprindiol or a gold standard like oxytetracycline. However, one open-label RCT compared spironolactone (100 mg/day, n=66) plus a combined oral contraceptive (norgestimate/ethinyl oestradiol) versus co-cyprindiol (n=65) and after 12 months found no difference in anti-acne efficacy between them (Hagag et al. *J Reprod Med* 2014;59:455-63). A smaller RCT compared spironolactone 25mg/day plus desogestrel/ethinyl oestradiol (n=17) versus co-cyprindiol (n=16) and found no difference in anti-acne efficacy after 3 months (Leelaphiwhat et al. *J Obstet Gynaecol Re*s 2015;41:402-10). Neither used lesion counts as an outcome measure.

Has a systematic review been completed (or is ongoing) on your subject? If none, state 'none'. There are 3 related reviews:

1. Arowojolu AO, Gallo MF, Lopez LM, Grimes DA. Combined oral contraceptive pills for treatment of acne. *Cochrane Database of Systematic Reviews* 2012 Jul 11;7:CD004425. Authors conclusion "How COCs compare to alternative acne treatments is unknown since only one trial addressed this issue."

2. Brown J, Farquhar C, Lee O et al. Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. *Cochrane Database of Systematic Reviews* 2009 Apr 15;2:CD000194. Authors' conclusion "From the studies included in this review, there is some evidence to show that spironolactone is an effective treatment to decrease the degree of hirsutism but there was no evidence for effectiveness for the treatment of acne vulgaris. Studies in this area are scarce and small."

3. Koo EB, Petersen TD, Kimball AB. Meta-analysis comparing efficacy of antibiotics versus oral contraceptives in acne vulgaris. *J Am Acad Dermatol* 2014; 71(3):450-9. Authors conclusion "Although antibiotics may be superior at 3 months, OCPs are equivalent to antibiotics at 6 months in reducing acne lesions and, thus, may be a better first-line alternative to systemic antibiotics for long-term acne management in women". Note: data from independent trials of 5 different COCs and 6 different antibiotics, only one small head-to-head RCT with dubious randomisation method [Greenwood R, Brummitt L, Burke B, Cunliffe WJ. Acne: double blind clinical and laboratory trial of tetracycline,estrogen-cyproterone acetate, and combined treatment. Br Med J 1985;291:1231-5].

Do you have a research team in place? Please provide brief details. If 'no', the UKDCTN can help you to find suitable collaborators.

YES – all contacted and agreed to fulfil the roles specified below.

1. Dr Sathya Thozhukat, Senior Lecturer in Diabetes and Endocrinology, Hull York Medical School [Assay of serum hormones]
2. Dr Rob Sheehan-Dare, Department of Dermatology, Leeds Teaching Hospitals NHS Foundation Trust [Patient recruitment]
3. Dr Calum Lyon, Department of Dermatology, York Teaching Hospital NHS Foundation Trust [Patient recruitment]
4. Dr Shernaz Walton, Department of Dermatology, Hull Royal Infirmary [Patient recruitment]
5. Professor Andrew Messenger, Department of Dermatology, Sheffield Teaching Hospitals NHS Foundation Trust [Patient recruitment]
6. Dr Jane Ravenscroft, Department of Dermatology, Queens Medical Centre, Nottingham [Patient recruitment]
7. Professor David Torgeson, York Trials Unit, University of York [Study design and sample size calculations, data management and analyses]
8. Dr Anna Snelling, Senior Lecturer in Microbiology, Life Sciences, University of Bradford [Skin microbiology]

Please tell us what experience you have in developing and/or participating in clinical trials.

Between them the team members have extensive experience of clinical trials. Dr Layton has conducted over 50 clinical trials (phase I-IV) acting as CI/PI. Trials have involved both NIHR and non-portfolio studies examining the efficacy of treatment in a number of common inflammatory dermatoses including acne, psoriasis and eczema.

The clinical team have also worked closely with the regional Clinical Research Network and have close collaborations with a number of active community research practitioners who could act as patient identification centres.

York Trials Unit is a centre of excellence for clinical trials. Professor Torgerson is Director and lead of the York Trials Unit. Dr Thozhukat has extensive experience as chief and principal investigator for multi-centered clinical research studies and is currently the co-lead for the comprehensive local network for Yorkshire and Humber for diabetes, endocrinology and metabolism. Dr Snelling has extensive experience in skin microbiology; Life Sciences at Bradford includes a world renowned centre for lab based dermatology research.

Have you considered patient involvement to develop the study? Please provide brief details. The UKDCTN can help you with this, after the vignette has been accepted.

YES. Charlotte Jones, a very helpful member of the Acne PSP Steering Group, has reviewed this proposal. Specifically she told us "I would not have thought that providing blood, urine & skin samples on each visit would put ladies off". Charlotte is willing to join the study team if the trial goes ahead.

Why is this suggestion particularly suitable for study through the UKDCTN Network?

Like most trials, the success of this one is heavily dependent on identification of suitable women and their willingness to take part. The UK DCTN has considerable experience in recruitment to dermatology trials in both primary and secondary care. They can advise us on the most appropriate recruitment strategies and, if necessary, promote the trial to network members.

We would also welcome members feedback on the following specific aspects of the proposed RCT:

1. Is a lower age limit of 18 y for adult female acne reasonable? 25 y is the generally accepted lower limit for late onset acne but that is relatively uncommon compared to persistent acne. Using 18 and over helps with recruitment and generalizability of the findings.

2. We have proposed a non-inferiority design because it is very likely that any difference between these three treatments will be small (and possibly undetectable by patients). Do you agree with this decision or are there better arguments for a superiority design?

3. Contraception is an issue. What would you recommend?

4. We have chosen a dose of 50 mg/day of spironolactone in order to minimise side effects. In everyday clinical practice dose escalation is feasible but not in the context of a blinded RCT. Have we made the right decision about dose? The literature is not very helpful on this important point except to suggest that side effects are more common on doses above 50 mg/day.

5. The duration of the active treatment phase has been proposed as 24 weeks. In recent years, acne trials have often been shorter than this, typically 3-4 months. We would like to compare maximal responses to all three drug regimens, which may take longer than 4 months to achieve. This is based on Dr Layton's personal clinical experience. Is 24 weeks better than 16? A 16 week assessment in included in the visit schedule.

6. Drug costs for spironolactone will be higher than for co-cyprindiol or oxytetracycline. Might this be a significant concern for the HTA and, if so, how might we address it?

7. The factorial design was suggested by David Torgerson as it allows a comparison of oral monotherapy versus oral and topical combination therapy, which is a better reflection of good prescribing practice but for which there is not much evidence. Are members happy with the factorial design?

Which funding bodies do you suggest should be approached?

This research proposal is based on one submitted to NETSCC in March 2015. Following their appraisal of the findings of the Acne PSP, a request was received from them to submit a study outline to address the question about management of adult female acne - ranked 7th in the top ten treatment uncertainties.

Are you, or someone else from your team, prepared to be Principal Investigator on the potential clinical trial? YES

If 'no', please involve someone else in the development of your vignette who will act as PI, before you submit the vignette.

If you need assistance in finding a suitable PI with adequate clinical trial experience, please contact the UKDCTN, as we may be able to find someone suitable.

Please add here any further information or comments that would help with the discussion of this vignette.

Spironolactone has been used off label as an acne therapy for over 30 years. Despite this, published evidence of anti-acne efficacy is inconsistent and of poor quality. There is no information about endocrine predictors of response. Many questions about its use remain unanswered, amongst which optimum dosing is probably the most important. As an anti-androgen and 17,20-lyase inhibitor, inhibition of sebum synthesis is the most likely primary action of spironolactone. However, its diuretic effect may be beneficial in women with a premenstrual flare associated with fluid retention. It may also have indirect effects on hyperproliferating ductal keratinocytes by blocking androgen binding. As well as its peripheral action on androgen receptors in the skin, some of its beneficial effects in women may be due to effects on ovarian and adrenal androgen metabolism.

Kim and Del Rosso ended their 2012 review of spironolactone for acne by stating that '*Spironolactone should be considered a major agent in the armamentarium for treatment of adult women with acne vulgaris'*. Few are likely to be persuaded to this view without more robust evidence of risk benefit and comparative efficacy.

WHAT THIS STUDY WILL SHOW

- Whether persistent acne in adult women can be managed successfully without an oral antibiotic. This would provide an important alternative for females with acne as many patients remain on long-term antibiotic therapy with the significant risk of increased antimicrobial resistance in targeted and non-targeted bacteria.
- Whether spironolactone has similar anti-acne efficacy to co-cyprindiol and can be used as an alternative for long-term management of women with persistent acne.
- Whether spironolactone and/or co-cyprindiol indirectly reduce number of *P. acnes* via effects on sebum output (similar to oral isotretinoin).
- Whether there are any short-term safety issues associated with the use of spironolactone at the dose tested.
- Whether the effects of spironolactone on serum androgens and other biomarkers are similar to, or different from, co-cyprindiol.

It is important that our Panel reviewer feedback and other UK DCTN support in the development of grant applications is acknowledged. Please tick here that you agree to add an acknowledgement of UK DCTN feedback and support on future funding applications/publications. ✓

Why is this research important to the NHS?

(For advice on this question please refer to the NIHR website https://www.nihr.ac.uk/documents/hta-supporting-information/27265)

If this proposal has been submitted elsewhere, please give details. N/A

Please email or post your completed form to:

Margaret McPhee, UK Dermatology Clinical Trials Network
Email: ukdctn@nottingham.ac.uk