National Institute for Health and Care Excellence

Draft for consultation

Acne vulgaris: management

[F1] Management options for moderate to severe acne – network meta-analyses

NICE guideline tbc

Evidence review underpinning recommendations 1.5.1, 1.5.2 and 1.5.4 to 1.5.12, 1.5.15 to 1.5.21 as well as 1.5.24 and 3 research recommendations in the NICE guideline (see evidence review F2 for the related pairwise analysis)

December 2020

Draft for consultation

These evidence reviews were developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

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Summary of review questions covered in this chapter

A single review protocol and literature search was used to identify randomised trials of treatments for acne vulgaris to address 9 review questions covering topical or oral pharmacological treatments and physical treatments, shown below. Outcomes were prioritised for either pairwise or network meta-analysis (NMA) and the evidence was divided according to the severity of acne into mild to moderate and moderate to severe categories. NMA was employed to assess comparative efficacy, acceptability and tolerability of treatments, which are outcomes commonly reported in the literature for the majority of treatments. Pairwise meta-analysis was used to synthesise outcomes for which evidence was more limited across treatments or was treatment-specific. The evidence was then summarised in four separate reviews covering the treatment of:

- mild to moderate acne (NMA)
- mild to moderate acne (pairwise meta-analysis)
- moderate to severe acne (NMA)
- moderate to severe acne (pairwise meta-analysis)

This evidence report contains information on the NMAs conducted to assess treatments for people with moderate to severe acne vulgaris. Information on the pairwise meta-analyses conducted to assess treatments for people with moderate to severe acne vulgaris is contained in the evidence report F2. Information on the NMAs and pairwise meta-analyses conducted to assess treatments for people with mild to moderate acne vulgaris are contained in the evidence reports E1 and E2, respectively.

1. What is the effectiveness of topical treatments individually or in combination in the treatment of acne vulgaris, for example:

- benzoyl peroxide
- antibiotics
- antiseptics
- retinoids and retinoid-like agents (for example, tretinoin, adapalene)
- azelaic acid
- nicotinamide
- combination of antibiotic and retinoid or retinoid-like agent
- combination of benzoyl peroxide and retinoid or retinoid-like agent
- combination of antibiotic and benzoyl peroxide?

2. What is the effectiveness of oral antibiotic treatments in the treatment of acne vulgaris, for example:

- tetracyclines (for example oxytetracycline, doxycycline, minocycline, tetracycline, lymecycline)
- macrolide antibiotics (for example, erythromycin and azithromycin)
- trimethoprim?

3. What is the effectiveness of an oral antibiotic with a topical agent compared to oral antibiotic alone in the treatment of acne vulgaris?

4. What is the optimal duration of antibiotic treatments (topical and systemic) for acne vulgaris?

5. What is the effectiveness of hormonal contraceptives in the treatment of acne vulgaris?

6. What is the effectiveness of spironolactone in the treatment of acne vulgaris?

7. What is the effectiveness of metformin in the treatment of acne vulgaris?

8. What is the effectiveness of oral isotretinoin in the treatment of acne vulgaris?

9. What is the effectiveness of physical treatments for acne vulgaris, for example
- comedone extraction
- chemical peels (for example, glycolic acid, lactic acid, salicylic acid)
- intralesional steroids
- light devices (for example, intense pulsed light, photopneumatic therapy and photodynamic therapy)?

Management options for people with moderate to severe acne vulgaris - network meta-analyses

Review question

For people with moderate to severe acne vulgaris what are the most effective treatment options?

Introduction

Moderate to severe acne encompasses a spectrum of inflammatory lesions including nodules and cysts, and in the most severe form, acne conglobata and acne fulminans. Individuals within this group may require differing treatments compared to those with mild to moderate acne. There is also potentially a higher risk of scarring within this group. Therefore, this review aims to identifiy the most effective treatment options for this level of acne seveity

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review. The protocol for this topic was written to encompass both the NMA and pairwise analysis. To give the full context of this topic, the summary of the protocol and the full protocol in appendix A contain the details of both (this is also how the protocol is registered on PROSPERO).

Table 1: Summary of the protocol (PICO table)

Population	People with acne vulgaris, of all ages and levels of symptom severity. For all outcomes, separate analyses will be conducted for mild to moderate acne vulgaris and moderate to severe acne vulgaris.
Intervention	Interventions will be categorised into the following classes (and, if relevant, subclasses): ➢ **TOPICAL TREATMENTS** **Abrasive/cleaning agents** • Aluminium oxide [own class] **Anthelmintics** • Cysticide (praziquantel) [own class] • Class of avermectins: ivermectin **Antibacterials** • Class of triclocarban and triclozan **Antibiotics** • Class of sulphones (dapsone) • Fusidic acid (sodium fusidate) [own class] • Class of lincosamides (for example clindamycin) • Class of macrolides (for example clarithromycin, erythromycin with zinc acetate dihydrate) • Class of nitroimidazoles (metronidazole) • Class of carboxylic acids (mupirocin) • Class of penicillins ○ Sub-class of natural (for example almecillin) ○ Sub-class of aminopenicillins (for example ampicillin) ○ Sub-class of β-lactamase-resistant (for example methicillin) ○ Sub-class of carboxypenicillins (for example ticarcillin) ○ Sub-class of ureidopenicillins (for example azlocillin)

	○ Sub-class of other penicillins (mecillinam, pivmecillinam hydrochloride) • Class of pleuromutilins (for example retapamulin) **Antiseptics** • Benzoyl peroxide (trade: Acnecide, Brevoxyl, Panoxyl) [own class] • Chlorhexidine gluconate (trade: Acnemed, Cepton) or digluconate [own class] **Dicarboxylic acids** • Azelaic acid [own class] **Vitamin B3** • Nicotinamide (niacinamide) [own class] **Retinoids or retinoid-like agents** • Class of retinoids or retinoid-like agents (adapalene, isotretinoin, retinol, tazarotene, tretinoin) **Combined interventions** • Benzoyl peroxide & potassium hydroxyguinoline sulfate [own class] • Class of benzoyl peroxide & retinoid (benzoyl peroxide + adapalene) • Class of benzoyl peroxide & lincosamide (benzoyl peroxide + clindamycin) • Class of lincosamides & retinoid (clindamycin + tretinoin) • Class of macrolides & retinoid (erythomycin + retinoid) [topical] • Germolene (phenol 1.2% + chlorhexidine diculconate [own class] ➢ **ORAL ANTIBIOTICS** • Class of carbapenems (for example imipenem, meropenem) • Class of carbapenems with cilastatin (imipenem with cilastatin) • Class of carbapenems with b lactamase inhibitor (meropenem with vaborbactam) • Class of cephamycins/cephalosporins ○ Sub-class of 1st-generation (for example cefadroxil) ○ Sub-class of 2nd-generation (for example cefaclore) ○ Sub-class of 3rd-generation (for example cefdinir) ○ Sub-class of 4th-generation (for example cefozopran) ○ Sub-class of 5th-generation (for example ceftolozane) • Class of cephamycins/cephalosporins with β-lactamase inhibitor (for example ceftraroline or ceftazidime with avibactam, cefoperazone with sulbactam, ceftolozane with tazobactam) • Class of sulphones (dapsone) • Fusidic acid (sodium fusidate) [own class] • Class of lincosamides (for example clindamycin) • Class of macrolides (for example clarithromycin, erythromycin) • Class of monobactams (aztreonam) • Class of monobactams with β-lactamase inhibitor (aztreonam with avibactam) • Class of penicillins ○ Sub-class of natural (for example almecillin) ○ Sub-class of aminopenicillins (for example ampicillin) ○ Sub-class of β-lactamase-resistant (for example methicillin) ○ Sub-class of carboxypenicillins (for example ticarcillin) ○ Sub-class of ureidopenicillins (for example azlocillin) ○ Sub-class of other penicillins (mecillinam, pivmecillinam hydrochloride) • Class of penicillin with β-lactamase inhibitor (for example co-amoxiclav [amoxicillin with clavulanic acid], piperacillin with tazobactam, ticaricillin with clavulanic acid, sultamicillin [ampicillin with sulbactam]) • Class of penicillin with flucloxacilin (co-fluampicil [ampicillin + flucloxacilin]) • Class of pleuromutilins (for example retapamulin) • Class of quinolones ○ Sub-class of 1st-generation (for example rosoxacin) ○ Sub-class of 2nd-generation (for example ofloxacin) ○ Sub-class of 3rd-generation (for example temafloxacin) ○ Sub-class of 4th-generation (for example sitafloxacin) • Class of tetracyclines (for example doxycycline, oxytetracycline) • Trimethoprim [own class] • Co-trimoxazole (trimethoprim-sulfamethoxazole; TMP-SMX) [own class]

➢ **TOPICAL TREATMENTS COMBINED WITH ORAL ANTIBIOTICS**

➢ **ORAL HORMONAL CONTRACEPTIVES AND HORMONE-MODIFYING AGENTS**

- Co-cyprindiol (ethinylestradiol + cyproterone acetate) [own class of combined oral contraceptive]
- Class of combined oral contraceptives
  - Sub-class of 2nd generation (oestrogen, for example ethinylestradiol or estradiol or mestranol combined with levonorgestrel or norethisterone)
  - Sub-class of 3rd generation (oestrogen, for example ethinylestradiol combined with desogestrel or gestodene or norgestimate)
  - Sub-class of 4th generation (oestrogen, for example ethinylestradiol or estradiol combined with dienogest or drospirenone or nomegestrol acetate)

Monophasic and phasic combined oral contraceptives containing the same hormones will be analysed as separate interventions within their sub-class.

- Class of progestogen-only oral contraceptives
  - Sub-class of 1st generation (for example medroxyprogesterone acetate)
  - Sub-class of 2nd generation (for example levonorgestrel, norethisterone/ norethindrone)
  - Sub-class of 3rd generation (for example desogestrel, norgestimate, gestodene)
  - Sub-class of 4th generation (for example dienogest, drospirenone, nomegestrol acetate)
- Class of selective aldosterone receptor antagonists (for example spironolactone alone or combined with furosemide or hydroflumethiazide [co-flumactone], eplerenone, canrenone)
- Class of 5α-reductase inhibitors (dutasteride, finasteride, tamsulosin with dutasteride)
- Class of other non-steroidal anti-androgens (for example abiraterone acetate, apalutamide, bicalutamide, cyproterone acetate, clormadinone acetate, enzalutamide, flutamide)
- Metformin [own class]

➢ **ORAL ISOTRETINOIN**

- Class of oral retinoid and total cumulative dose ≥ 120mg/kg (single course)
  - Sub-class of daily dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day)
  - Sub-class of alternate day dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day)
  - Sub-class of less frequent or other dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day)
- Class of oral retinoid and total cumulative dose < 120mg/kg (single course)
  - Sub-class of daily dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day)
  - Sub-class of alternate day dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day)
  - Sub-class of less frequent or other dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day)

➢ **PHYSICAL TREATMENTS**

- Class of chemical peels
  - Sub-class of superficial peels
  - Sub-class of moderate peels
  - Sub-class of deep peels

  for example amino fruit acid, glycolic acid, Jessner's peel, lactic acid, salicylic acid, trichloroacetic acid [TCA]; these will be categorised into different sub-classes as reported in the included studies, according to the concentration of their active ingredient and treatment duration.
- Comedone extraction [own class]
- Class of photothermal therapy (for example fractional erbium glass laser)
- Class of photochemical therapy (for example blue or red light and their combination)

	• Class of photochemical and photothermal therapy (for example potassium titanyul phosphate laser, Intense Pulsed Light [IPL], Pulsed Dye Laser) • Class of photodynamic therapy (for example 5-aminolevuliniv acid [ALA], liposomal methylene blue gel, methylaminolevulinate [MAL]) • Smoothbeam™ laser [own class] • Photopneumatic therapy (for example intense pulsed light + vacuum) • Radiofrequency (for example fractional microneedling, bipolar)
Comparison	• No treatment • Waiting list • Pill placebo • Other active intervention • Sham physical treatment
Outcomes (for NMA)	**Critical** • Efficacy ○ Clinician-rated improvement at treatment endpoint - % change in acne lesion count from baseline - change or final score on a validated acne severity scale ○ Participant-reported improvement at treatment endpoint - Change in acne severity or symptoms (e.g. assessed using global acne score) ○ Prevention of scarring at any follow-up - Final / change in number of scars from baseline - Incidence of scarring **Important** • Acceptability ○ Treatment discontinuation for any reason • Tolerability ○ Treatment discontinuation due to side-effects

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplement 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Clinical evidence

For brevity we have not listed the references in the included studies section below, but they are summarised in **Error! Reference source not found.**.

Also, the terminology 'observations' rather than 'participants' has been used because the evidence includes split-face RCTs where parts of the face are randomised.

Included studies

64 randomised controlled trials (RCTs) were included in this review.

The included studies are summarised in Table 2.

For the outcome of efficacy, the NMA included 56 RCTs, 28 treatment classes and 16,493 observations relevant to females; of these, 27 treatment classes were relevant also to males, assessed in 55 RCTs and 16,465 observations.

For details of the interventions that have been compared see Figure 1.

For the outcome of discontinuation for any reason, the NMA included 42 RCTs, 23 treatment classes and 14,942 observations relevant to females; of these, 20 treatment classes were relevant also to males, assessed in 38 RCTs and 14,655 observations.

For details of the interventions that have been included in this analysis see Figure 2.

For the outcome of discontinuation due to side effects, the NMA included 32 RCTs, 18 treatment classes and 13,666 observations relevant to females; of these, 15 treatment classes were relevant also to males, assessed in 30 RCTs and 13,484 observations.

For details of the interventions that have been included in this analysis see Figure 3.

For the outcome of participant-reported improvement there were very limited data to allow conducting a meaningful NMA, therefore these have been analysed in pairwise meta-analysis (see evidence report F2).

For the outcome of prevention of scarring there were very limited data to allow conducting a meaningful NMA, therefore these have been analysed in pairwise meta-analysis (see evidence report F2).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies.

Study	Population	Interventions	Outcomes
Bossuyt 2003 **Country**: Europe **Study type**: RCT	N=134 **Sex**: mixed **Number randomised: arm 1**: 66 **Number randomised: arm 2**: 68 **Inclusion details**: Males or females aged between 12 and 30 years. Participants with at least 15 and at most 120 inflammatory facial lesions (papules, pustules, nodules) including at most 2 facial nodules (diameter >1 cm), a maximum of 60 non-inflammatory facial lesions (open and closed comedones) and an acne severity grade between 1 and 5 (Leeds grading scale). Women of childbearing age were required to use contraception during the study and for 1 month after completing the trial. Women on	**Intervention: arm 1**: LYME-oral 300mg **Intervention: arm 2**: MINO-oral 100mg	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
	oral contraceptives were to have been using the same method for 3 months prior to enrolment, or for at least 12 months for contraceptive pills constraining cyproterone acetate. Use of cosmetics was permitted during the course of the study, but contraceptives and cosmetics had to be listed as concomitant medication.		
Braathen 1984 **Country**: Norway **Study type**: RCT	N=na **Sex**: mixed **Number randomised: arm 1**: na **Number randomised: arm 2**: na **Number randomised: arm 3**: na **Inclusion details**: Participants with moderate to severe acne vulgaris.	**Intervention: arm 1**: CLIND-topical 1% + PLC-oral **Intervention: arm 2**: TETRA-oral 500mg bid + Vehicle **Intervention: arm 3**: PLC-oral + Vehicle	• Clinician rated improvement in acne
Chen 2015 **Country**: China **Study type**: RCT	N=50 **Sex**: mixed **Number randomised: arm 1**: 25 **Number randomised: arm 2**: 25 **Inclusion details**: Participants with moderate (acne with inflammatory papules and pustules) to severe (acne with inflammatory papules, nodules, cysts and scars) facial acne vulgaris.	**Intervention: arm 1**: 5ALA 5% photodynamic therapy **Intervention: arm 2**: Sham treatment	• Treatment discontinuation for any reason
Cunliffe 2003 **Country**: Europe **Study type**: RCT	N=242 **Sex**: mixed **Number randomised: arm 1**: 118 **Number randomised: arm 2**: 124 **Inclusion details**: Males and females aged 12 to 30 years with moderate to moderately severe inflammatory acne vulgaris. Global severity grade ranging from 4 to 10 on the Leeds Revised Acne Grading System and at least 15 inflammatory facial lesions (no more than 3 nodules) and at least 20 non-inflammatory facial lesions. Participants taking certain topical and systemic treatments were required to complete specified washout	**Intervention: arm 1**: LYME 300mg + ADAP 0.1% gel **Intervention: arm 2**: LYME 300 mg + Vehicle gel	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
	periods before entering the study.		
Degreef 1982b **Country**: Belgium **Study type**: RCT	N=105 **Sex**: mixed **Number randomised: arm 1**: 52 **Number randomised: arm 2**: 53 **Inclusion details**: Participants with moderate to severe facial acne.	**Intervention: arm 1**: BPO 5%/MICO 2% cream **Intervention: arm 2**: BPO 5% cream	• Treatment discontinuation for any reason
Dhawan 2013 **Country**: United States **Study type**: RCT	N=40 **Sex**: mixed **Number randomised: arm 1**: 20 **Number randomised: arm 2**: 20 **Inclusion details**: Males and females aged 12 to 45 years. Participants with grade 3 or higher according to the investigator static global assessment (ISGA) (3=moderate; 4=severe; 5=very severe). 20 to 50 papules and pustules (inflammatory lesions), 30 to 100 open and closed comedones (non-inflammatory lesions), 1 or fewer small nodular lesions, no facial cystic lesions.	**Intervention: arm 1**: BPO 5%/CLIND 1.2% gel + TAZ 0.1% cream **Intervention: arm 2**: BPO 2.5%/CLIND 1.2% gel + TAZ 0.1% cream	• Clinician rated improvement in acne
Dhir 2008 **Country**: India **Study type**: RCT	N=60 **Sex**: mixed **Number randomised: arm 1**: 30 **Number randomised: arm 2**: 30 **Inclusion details**: Participants with nodulocystic acne.	**Intervention: arm 1**: ISO=120.Daily=0.5 + CLIND 1% during daytime + ADAP 0.1% at bed time **Intervention: arm 2**: ISO=120.Daily=0.5	• Treatment discontinuation for any reason
Dobson 1980 **Country**: United States **Study type**: RCT	N=253 **Sex**: mixed **Number randomised: arm 1**: 127 **Number randomised: arm 2**: 126 **Inclusion details**: Participants with moderate to severe acne vulgaris of the face (at least 10 papules or pustules, one or more comedones, and not more than 5 nodulocystic lesions). No concurrent illness and not receiving any anti-acne treatment (topical or systemic) for at least 2 weeks prior to study entry.	**Intervention: arm 1**: ERYTH 1.5% solution **Intervention: arm 2**: Vehicle	• Treatment discontinuation for any reason • Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
Dogra 2020 **Country**: India **Study type**: RCT	N=750 **Sex**: mixed **Number randomised: arm 1**: 300 **Number randomised: arm 2**: 300 **Number randomised: arm 3**: 150 **Inclusion details**: Participants aged >/=12 years. Facial acne (inflammatory lesion count [papules/pustules] count between >20 to <50; non-inflammatory lesion count [open/closed comedones] between >20 to <100, and nodules [inflammatory lesion 5mm in diameter] 2) and Investigator's Static Global Assessment (ISGA) score of 3 (moderate) or 4 (severe)	**Intervention: arm 1**: Fixed dose tretinoin 0.04% (microsphere) + clindamycin 1.0% gel, o.d. **Intervention: arm 2**: Tretinoin gel 0.025%, o.d. **Intervention: arm 3**: Clindamycin gel 1.0%, o.d.	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Dreno 2011 **Country**: Europe/Mexico/Brazil/Australia **Study type**: RCT	N=378 **Sex**: mixed **Number randomised: arm 1**: 191 **Number randomised: arm 2**: 187 **Inclusion details**: Participants of any race or sex and aged between 12 and 35 years. Moderate to severe acne vulgaris (defined by the Investigator's Global Assessment: IGA score of 3 or 4 on a scale from 0 to 5). Minimum of 20 inflammatory lesions, between 30 and 120 non-inflammatory lesions, and no more than 3 nodulocystic lesions on the face excluding the nose area. Females of childbearing potential had to have a negative urine pregnancy test before and during the study.	**Intervention: arm 1**: ADAP 0·1%/BPO 2·5% gel + LYME 300 mg **Intervention: arm 2**: LYME 300 mg + Vehicle	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Dubertret 2003 **Country**: Europe **Study type**: RCT	N=218 **Sex**: mixed **Number randomised: arm 1**: 111 **Number randomised: arm 2**: 107 **Number randomised: arm 3**: 53 **Inclusion details**: Males and females aged between 16 and 40 years. Acne vulgaris with a minimum of 15 inflammatory facial lesions and a global severity of at least grade 3 on the Leeds	**Intervention: arm 1**: LYME-oral 300mg od + PLC-oral **Intervention: arm 2**: LYME-oral 150mg bid **Intervention: arm 3**: PLC-oral bid	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
	Revised Acne Grading System.		
Eichenfield 2010b **Country**: United States **Study type**: RCT	N=1075 **Sex**: mixed **Number randomised: arm 1**: 533 **Number randomised: arm 2**: 542 **Inclusion details**: Males and females of any race/ethnicity aged 12 years or older. Minimum of 20, but not more than 50, papules and pustules in total on the face and a minimum of 30, but not more than 100, non-inflammatory lesions (open comedones and closed comedones) on the face (excluding the nose). Participants with an Investigator's Global Assessment (IGA) of 3 (moderate; more than half of the face involved. Many comedones, papules and pustules. One small nodule may be present) or 4 (severe; entire face is involved. Covered with comedones, numerous papules and pustules. Few nodules/cysts may or may not be present).	**Intervention: arm 1**: ADAP 0.1% lotion **Intervention: arm 2**: Vehicle	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Feldman 2013; Trial 1 **Country**: North America **Study type**: RCT	N=744 **Sex**: mixed **Number randomised: arm 1**: 372 **Number randomised: arm 2**: 372 **Inclusion details**: Males and females aged between 12 and 45 years, in good general health and agreed to use a medically-acceptable form of contraception throughout the study. Moderate to severe acne vulgaris: Investigator's Static Global Assessment (ISGA) score =3 at baseline; lesion counts of 25 to 50 facial inflammatory lesions (papules plus pustules), including nasal lesions, with no more than one facial nodular lesion (<5 mm) and no cystic lesions, and 30 to 125 facial non-inflammatory lesions (open and closed comedones), excluding nasal lesions. Provide consent.	**Intervention: arm 1**: TAZ 0.1% foam **Intervention: arm 2**: Vehicle	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Feldman 2013;	N=742	**Intervention: arm**	• Treatment

Study	Population	Interventions	Outcomes
Trial 2 **Country**: North America **Study type**: RCT	**Sex**: mixed **Number randomised: arm 1**: 373 **Number randomised: arm 2**: 369 **Inclusion details**: Males and females aged between 12 and 45 years, in good general health and agreed to use a medically-acceptable form of contraception throughout the study. Moderate to severe acne vulgaris: Investigator's Static Global Assessment (ISGA) score =3 at baseline; lesion counts of 25 to 50 facial inflammatory lesions (papules plus pustules), including nasal lesions, with no more than one facial nodular lesion (<5 mm) and no cystic lesions, and 30 to 125 facial non-inflammatory lesions (open and closed comedones), excluding nasal lesions. Provide consent.	**1**: TAZ 0.1% foam **Intervention: arm 2**: Vehicle	discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Fluckiger 1988 **Country**: Switzerland **Study type**: RCT	N=58 **Sex**: mixed **Number randomised: arm 1**: 29 **Number randomised: arm 2**: 29 **Inclusion details**: Participants with moderately severe to severe forms of acne vulgaris. Participants not receiving any treatment 4 weeks prior to study entry.	**Intervention: arm 1**: BPO 5% cream **Intervention: arm 2**: BPO 5%/MICO 2% cream	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Fugere 1990 **Country**: Canada **Study type**: RCT	N=73 **Sex**: female **Number randomised: arm 1**: 40 **Number randomised: arm 2**: 33 **Inclusion details**: Women in good health aged between 18 and 35 years. Moderate to severe androgen-dependent acne vulgaris (defined as presence of comedones, papules and macules on at least half of the face. Previous treatment withdrawn within 6 weeks of starting study treatments.	**Intervention: arm 1**: CPA 2mg + EE 0.035 mg (Diane-35) **Intervention: arm 2**: CPA 2mg + EE 0.05 mg (Diane-50)	• Treatment discontinuation for any reason
Gollnick 2001 **Country**: Germany **Study type**: RCT	N=85 **Sex**: male **Number randomised: arm 1**: 50 **Number randomised: arm 2**: 35 **Inclusion details**: Males over the	**Intervention: arm 1**: AZE-topical 20% cream + MINO-oral 50mg bid **Intervention: arm**	• Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
	age of 16 years. Participants with severe inflammatory facial acne (at least grade 4 using the Cunliffe's classification (Leeds scale)); at least 2 deep inflammatory lesions (nodes, cysts or nodules) and other papules and pustules. No treatment with any systemic treatment for at least 4 weeks prior to the start of the study (or for isotretinoin, 12 months), use of topical treatment had to have been discontinued at least 2 weeks prior to the start of the study. For inclusion in phase II of the study, participants must have achieved a decrease of at least 75% in the number of deep inflammatory lesions in phase I of the study and in whom the efficacy of treatment had been rated as 'very good'.	**2**: ISO<120.Daily=0.5	
Gratton 1982 **Country**: Canada **Study type**: RCT	N=245 **Sex**: mixed **Number randomised: arm 1**: 121 **Number randomised: arm 2**: 124 **Inclusion details**: Participants with moderate to severe acne (defined as presence of a minimum of 12 to 70 inflammatory papules and pustules, and a maximum of 6 nodulocystic lesions on the face above the jawline).	**Intervention: arm 1**: CLIND 1% solution + PLC capsule **Intervention: arm 2**: PLC capsule + PLC solution	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Greenwood 1985 **Country**: United Kingdom **Study type**: RCT	N=92 **Sex**: female **Number randomised: arm 1**: 37 **Number randomised: arm 2**: 30 **Number randomised: arm 3**: 25 **Inclusion details**: Women with moderate or moderately severe acne who had already tried antibiotics for their acne.	**Intervention: arm 1**: CPA 2mg/EE 0.05 mg + TETRA 500 mg bid **Intervention: arm 2**: CPA 2mg/EE 0.05 mg + PLC capsule **Intervention: arm 3**: TETRA 500 mg bid + PLC capsule	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects
Gruber 1998a **Country**: Austria **Study type**: RCT	N=32 **Sex**: female **Number randomised: arm 1**: 14	**Intervention: arm 1**: CPA 2mg/EE 0.035 mg	• Treatment discontinuation for any reason

Study	Population	Interventions	Outcomes
	Number randomised: arm 2: 18 **Inclusion details**: Women with moderate to severe acne who consulted the endocrinology outpatient department for a hormonal evaluation and treatment of their acne. Using barrier contraception during study treatment. Acne treatment had been stopped 6 weeks prior to study commencement.	**Intervention: arm 2**: PLC-lotion	• Clinician rated improvement in acne
Hong 2013 **Country**: Korea, Republic of **Study type**: RCT (split face design)	N=22 **Sex**: mixed **Number randomised: arm 1**: 22 (observations) **Number randomised: arm 2**: 22 (observations) **Inclusion details**: Males and females with active acne lesions and Fitzpatrick skin phototypes IV to V; acne grade at least grade 2 (Cunliffe acne grading system).	**Intervention: arm 1**: MAL 16%-RED PDT **Intervention: arm 2**: MAL 16%-IPL-PDT	• Clinician rated improvement in acne
Horfelt 2006 **Country**: Sweden **Study type**: RCT (split face design)	N=30 **Sex**: mixed **Number randomised: arm 1**: 30 (observations) **Number randomised: arm 2**: 30 (observations) **Inclusion details**: Participants with moderate to severe inflammatory facial acne; moderate defined as at least 10 inflammatory lesions (papules and pustules) and 15 to 100 non-inflammatory lesions (open and closed comedones), excluding the nose. Acne treatments discontinued up to 3 months prior to the study.	**Intervention: arm 1**: MAL 16%-PDT **Intervention: arm 2**: PL	• Clinician rated improvement in acne
Ioannides 2002 **Country**: Greece **Study type**: RCT	N=80 **Sex**: mixed **Number randomised: arm 1**: 40 **Number randomised: arm 2**: 40 **Inclusion details**: Participants with 15 to 80 facial non-inflammatory lesions (open and closed comedones), 10 to 50 inflammatory lesions (papules and pustules) and no more than 3 nodulocystic lesions. No other cutaneous disease on the face. No use of any other topical treatment for 14 days, systemic	**Intervention: arm 1**: ADAP 0.1% gel **Intervention: arm 2**: ISO 0.05% gel	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects

Study	Population	Interventions	Outcomes
	antibiotics for 30 days, or systemic retinoids for at least 6 months prior to start of study treatment. Women who were not pregnant or lactating, and had discontinued oral contraception at least 3 months before study entry.		
Jackson 2010 **Country**: United States **Study type**: RCT	N=54 **Sex**: mixed **Number randomised: arm 1**: 27 **Number randomised: arm 2**: 27 **Inclusion details**: Males and females of any race, aged 12 years or older. Moderate to moderately severe and stable facial acne vulgaris characterised by 15 to 100 facial inflammatory lesions; 15 to 100 facial non-inflammatory lesions, and =2 facial nodules and/or cysts. P. acnes counts of =104 colony-forming units per square centimetre of skin (CFU/cm2) of which no more than 104 CFU/cm2 were erythromycin or clindamycin resistant. Women of childbearing age were required to have a negative urine pregnancy test prior to study enrolment and practice a reliable method of contraceptive during the study. Women taking oestrogens/oral contraceptives =90 days before study baseline could continue with this during the study provided they did not discontinue or alter use during the study. Washout periods and restrictions adhered to for topical and systemic treatments: topical facial treatments, including retinoids, anti-acne products and corticosteroids (2 weeks); topical antibiotics and systemic corticosteroids (4 weeks); systemic antibiotics (6 weeks) and systemic retinoids (6 months).	**Intervention: arm 1**: BPO 5%/CLIND 1% gel **Intervention: arm 2**: CLIND 1%/TRET 0.025% gel	• Treatment discontinuation for any reason
Jones 1981 **Country**: United States **Study type**: RCT	N=175 **Sex**: mixed **Number randomised: arm 1**: 90 **Number randomised: arm 2**: 85 **Inclusion details**: Males and females aged 12 years or older, seeking medical care for acne or recruited volunteers, but otherwise in good general health.	**Intervention: arm 1**: BPO 5%/ERYTH 3% gel **Intervention: arm 2**: Vehicle	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects

Study	Population	Interventions	Outcomes
	Facial acne grades 2 or 3 on the severity scale (grade 2: a moderate number of comedones, papules, and small cysts, occasional pustules, and inflammation; grade 3: a great number of lesions with deeper and larger cysts and minimal scarring). Minimum of 10 papular inflammatory acne lesions in the facial area. Participants could be pregnant or of childbearing age. Unresponsive to treatment with oral tetracycline hydrochloride, topical benzoyl peroxide, and tretinoin.		
Jones 2002 **Country**: United States **Study type**: RCT	N=223 **Sex**: mixed **Number randomised: arm 1**: 112 **Number randomised: arm 2**: 111 **Inclusion details**: Male and females aged =13 years. Moderate to moderately severe acne vulgaris (overall acne severity score =1.5 on the Physician's Global Acne Severity Scale, 15 to 80 inflammatory lesions, 20 to 140 comedones, and =2 nodules or cysts measuring greater than 5mm. The comedone count did not include the nasal and nasolabial fold area). Treatment with systemic antibiotics known to affect acne and systemic corticosteroids should be discontinued 4 weeks prior to study commencement, and 6 months for oral retinoids. A 2-week washout period was required for topical antibiotics and/or anti-acne medication, topical corticosteroids, and topical retinoids.	**Intervention: arm 1**: BPO 5%/ERYTH 3% gel (dual pouch pack) **Intervention: arm 2**: Vehicle	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Khanna 1993 **Country**: India **Study type**: RCT	N=44 **Sex**: mixed **Number randomised: arm 1**: 21 **Number randomised: arm 2**: 23 **Inclusion details**: Males and females with moderately severe acne (defined when acne lesion score (ALS) was 30 to 70) and severe acne (defined as ALS score of more than 70). Participants who had taken oral	**Intervention: arm 1**: TETRA 500 mg po bid **Intervention: arm 2**: MINO 50 mg po bid	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects

Study	Population	Interventions	Outcomes
	antibiotics were included in the study after 1 month discontinuation of the antibiotics.		
Kim 2017 **Country**: Korea **Study type**: RCT	N=32 **Sex**: mixed **Number randomised: arm 1**: 16 **Number randomised: arm 2**: 16 **Inclusion details**: Participants aged between 19 and 45 years. Active acne lesions and Fitzpatrick skin phototypes III to IV; acne severity grade 3 or 4 according to the IGA.	**Intervention: arm 1**: MAL 16%-DL PDT **Intervention: arm 2**: NAFL + MAL 16%-DL PDT	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Kircik 2007 **Country**: United States **Study type**: RCT	N=353 **Sex**: mixed **Number randomised: arm 1**: 118 **Number randomised: arm 2**: 118 **Number randomised: arm 3**: 117 **Inclusion details**: Participants with moderate to severe acne.	**Intervention: arm 1**: BPO 5%/CLIND 1% gel + TRET 0.04% gel **Intervention: arm 2**: BPO 5%/CLIND 1% gel + ADAP 0.1% gel **Intervention: arm 3**: BPO 5%/CLIND 1% gel + TRET 0.1% gel	• Clinician rated improvement in acne
Kircik 2009a **Country**: United States **Study type**: RCT	N=147 **Sex**: mixed **Number randomised: arm 1**: 73 **Number randomised: arm 2**: 74 **Inclusion details**: Males or females of any race, aged 12 years or older. Moderate to severe stable, non-rapidly progressing facial acne vulgaris characterised by 20 to 60 facial inflammatory lesions; 20 to 60 facial non-inflammatory lesions and =2 facial nodules and/or cysts. Women of childbearing potential were required to have a negative urine pregnancy test at baseline and use a reliable method of contraceptive during the study period.	**Intervention: arm 1**: BPO 5%/CLIND 1% gel + TRET 0.04% gel **Intervention: arm 2**: CLIND 1.2%/TRET 0.025% gel + BPO 5% wash	• Treatment discontinuation for any reason
Kuhlman 1986 **Country**: United States **Study type**: RCT	N=na **Sex**: mixed **Number randomised: arm 1**: na **Number randomised: arm 2**: na **Inclusion details**: Men and women aged 12 to 30 years. Moderate to severe acne vulgaris defined as 12 to 70 inflammatory	**Intervention: arm 1**: CLIND 1% lotion **Intervention: arm 2**: Vehicle	• Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
	papules and no more than 6 cystic lesions on the face above the jawline.		
Leyden 2004 **Country**: United States **Study type**: RCT	N=na **Sex**: mixed **Number randomised: arm 1**: na **Number randomised: arm 2**: na **Inclusion details**: Participants with moderately severe acne with a minimum of 20 inflammatory lesions.	**Intervention: arm 1**: MINO 100 mg + PL **Intervention: arm 2**: PL	• Clinician rated improvement in acne
Mei 2013 **Country**: China **Study type**: RCT	N=41 **Sex**: mixed **Number randomised: arm 1**: 21 **Number randomised: arm 2**: 20 **Inclusion details**: Chinese patients aged over 18 years. Participants with II–IV facial acne according to Pillsbury grade and Fitzpatrick skin type II–IV.	**Intervention: arm 1**: 5ALA 10%-IPL-PDT **Intervention: arm 2**: IPL-PT + Vehicle	• Clinician rated improvement in acne
Miller 1986b **Country**: United Kingdom **Study type**: RCT	N=90 **Sex**: female **Number randomised: arm 1**: 28 **Number randomised: arm 2**: 32 **Number randomised: arm 3**: 30 **Inclusion details**: Women aged between 16 and 36 years. Moderate to severe acne (graded according to Burke & Cunliffe, 1984). Any acne medication (other than contraceptive pill) stopped 6 weeks prior to study participation. Oral contraception was continued until the commencement of the trial.	**Intervention: arm 1**: CPA 2mg/EE 0.05 mg (days 5-25) + PL (days 5-14) **Intervention: arm 2**: NOR 1mg/EE 0.05mg (days 5-25) + PL (days 5-14) **Intervention: arm 3**: CPA 50mg (days 5-14), then EE 0.05 mg (days 5-25)	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects
Nicklas 2019 **Country**: Chile **Study type**: RCT	N=46 **Sex**: mixed **Number randomised: arm 1**: 23 **Number randomised: arm 2**: 23 **Inclusion details**: Participants with moderately severe inflammatory acne vulgaris defined by Leeds revised acne grading system with modifications as numerous papules and pustules (40 to 100) usually with many comedones (40 to 100) and occasional (up to 5) larger, deeper nodular inflamed lesions on the face. Males and females aged 18 to 30 years. Phototype	**Intervention: arm 1**: 5ALA 20%-PDT **Intervention: arm 2**: ADAP 0.1% gel + DOXY 100 mg	• Treatment discontinuation due to side effects • Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
	according to Fitzpatrick skin type I to IV with facial acne vulgaris. No other acne treatments permitted during study.		
Paithankar 2015;Trial 1 **Country**: Poland **Study type**: RCT	N=48 **Sex**: mixed **Number randomised: arm 1**: 23 **Number randomised: arm 2**: 25 **Inclusion details**: Males and females aged 16 to 35 years of age. Moderate-to-severe inflammatory facial acne; IGA scores 3 to 4 with at least 25 total papules and pustules present on face Fitzpatrick skin phototype I to III.	**Intervention: arm 1**: GOLDMP + PDL **Intervention: arm 2**: No treatment	• Clinician rated improvement in acne
Pariser 2005 **Country**: United States **Study type**: RCT	N=214 **Sex**: mixed **Number randomised: arm 1**: 70 **Number randomised: arm 2**: 70 **Number randomised: arm 3**: 74 **Inclusion details**: Participants aged 12 to 40 years. Moderate to moderately severe acne vulgaris; minimum of 20 inflammatory facial lesions (not >2 nodules/cysts), 20 non-inflammatory facial lesions; global facial severity grade 4 to 10 according to the Leeds Revised Acne Grading System. Washout periods for certain topical and systemic treatments were required. Negative urine pregnancy test results required at screening and at the final visit for women of childbearing potential.	**Intervention: arm 1**: ADAP 0.3% gel **Intervention: arm 2**: ADAP 0.1% gel **Intervention: arm 3**: Vehicle	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Pariser 2014 **Country**: United States **Study type**: RCT	N=498 **Sex**: mixed **Number randomised: arm 1**: 253 **Number randomised: arm 2**: 245 **Inclusion details**: Males and females of any race and ethnicity, aged 12 to 40 years. Moderate to severe acne vulgaris (a score of 3 or 4 on the Global Severity Score (EGSS), presenting with 20 to 40 inflammatory lesions (papules, pustules, and nodules), 20 to 100 non-inflammatory lesions (open and closed comedones), and =2 nodules. Women of childbearing	**Intervention: arm 1**: BPO 3.75%/CLIND 1.2% gel **Intervention: arm 2**: Vehicle	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
	age were required to have a negative urine pregnancy test and to agree to use an effective form of contraception during the study period. A washout period of up to 1 month was required for participants who used previous prescription and over-the-counter acne treatments (including, topical (face) and systemic treatments: topical astringents and abrasives (1 week); topical anti-acne products, including soaps containing antimicrobials, and known comedogenic products (2 weeks); topical retinoids, retinol, and systemic acne treatments (4 weeks); and systemic retinoids (6 months).		
Pariser 2016 **Country**: United States **Study type**: RCT	N=153 **Sex**: mixed **Number randomised: arm 1**: 100 **Number randomised: arm 2**: 53 **Inclusion details**: Males and females aged 12 to 35 years. Severe facial acne vulgaris (defined by an IGA rating score of 4); 27 to 75 inflammatory lesions (papules, pustules and no more than 3 nodules) and 20 to 100 non-inflammatory lesions (open and closed comedones) on the face; Fitzpatrick skin types I to VI. Confirmed using standardised clinical photographs. Females of childbearing potential were required to use appropriate contraception (same product and dose if using an oral contraceptive) for at least 14 days before the first treatment and during the study.	**Intervention: arm 1**: MAL 8%-RED-PDT **Intervention: arm 2**: Vehicle-RED-PDT	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Peacock 1990 **Country**: United Kingdom **Study type**: RCT	N=na **Sex**: mixed **Number randomised: arm 1**: na **Number randomised: arm 2**: na **Inclusion details**: Males and females aged 16 to 35 years of age attending student health centres at 4 universities. Moderate to severe acne, defined as having a minimum of 12 and a maximum of 100 inflammatory lesions, with no more than 6 nodulocystic lesions above the	**Intervention: arm 1**: CLIND-topical 1% bid **Intervention: arm 2**: MINO-oral 50mg bid	• Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
	jawline.		
Peck 1982a **Country**: United States **Study type**: RCT	N=33 **Sex**: mixed **Number randomised: arm 1**: 16 **Number randomised: arm 2**: 17 **Inclusion details**: Volunteers with at least 10 inflamed deep dermal or subcutaneous acne cysts or nodules of at least 4 mm diameter. History of minimal response to treatment with oral and topical antibiotics, oral vitamin A, topical vitamin A acid, topical benzoyl peroxide, x-irradiation, oral contraceptives, oral dapsone, intralesional injections of corticosteroids, oral prednisone, surgical drainage, applications of liquid nitrogen, photochemotherapy with psoralen and long-wave ultraviolet light, and other acne treatments. Discontinuation of conventional acne treatment for at least 1 month prior to study entry. No other acne treatment (topical or systemic) permitted during 4-month study treatment period.	**Intervention: arm 1**: ISO<120.Daily=0.5 **Intervention: arm 2**: PLC-oral	• Clinician rated improvement in acne
Sami 2008 **Country**: Egypt **Study type**: RCT	N=45 **Sex**: mixed **Number randomised: arm 1**: 15 **Number randomised: arm 2**: 15 **Number randomised: arm 3**: 15 **Inclusion details**: Males and females with moderate to severe facial acne according to Burton classification.	**Intervention: arm 1**: 595 nm PDL PT **Intervention: arm 2**: 550 nm-1200 nm IPL PT **Intervention: arm 3**: BR-LED PT	• Clinician rated improvement in acne
Schmidt 2011 **Country**: United States **Study type**: RCT	N=2010 **Sex**: mixed **Number randomised: arm 1**: 1008 **Number randomised: arm 2**: 1002 **Inclusion details**: Males and females aged over 12 years. Facial acne vulgaris with 20 to 50 inflammatory lesions (papules and pustules), 20 to 100 non-inflammatory lesions (open and closed comedones), and not more than 2 nodules; Evaluators Global Severity Score (EGSS) of moderate or severe. Willing to	**Intervention: arm 1**: CLIND 1.2%/TRET 0.025% gel **Intervention: arm 2**: CLIND 1.2% gel	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
	undergo the specified washout periods for topical antibiotics and other topical antibacterial drugs (2 weeks); facial anti-inflammatory agents and corticosteroids (4 weeks); retinoids, including retinol (4 weeks). Had undergone the specified washout periods of systemic treatments including corticosteroids and intramuscular injections (4 weeks); antibiotics (4 weeks); other systemic acne treatments (4 weeks); systemic retinoids (6 months).		
Shalita 1995 **Country**: United States **Study type**: RCT	N=76 **Sex**: mixed **Number randomised: arm 1**: 38 **Number randomised: arm 2**: 38 **Inclusion details**: Men and women aged 13 to 35 years. Moderate inflammatory acne vulgaris (defined by the presence of at least 15 papules and/or pustules on the face); severity grade according to Allen and Smith's modification of the Cook et al. procedure. Withdrawal of treatments, including topical acne preparations, topical antimicrobial agents, medicated cosmetics, soaps or shampoos, and radiation therapy, topical corticosteroids, and investigational drugs at least 2 weeks before study enrolment; systemic antimicrobials corticosteroids at least 12 weeks before study; and oral isotretinoin at least 2 years prior to study enrolment. Oral contraceptives were permitted as long as they had been used continuously for at least 3 months prior to study and the dosage schedule was not expected to change during the study.	NA	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Sklar 1996 **Country**: United States **Study type**: RCT	N=94 **Sex**: mixed **Number randomised: arm 1**: 30 **Number randomised: arm 2**: 32 **Number randomised: arm 3**: 32 **Inclusion details**: Males and females aged 16 to 30 years. Moderate to moderately severe, papular-pustular, facial acne vulgaris with a minimum number of inflamed lesions. Willingness to	**Intervention: arm 1**: BPO-topical 5%/ ERYTH-topical 3% **Intervention: arm 2**: BPO-topical 10% **Intervention: arm 3**: Vehicle	• Treatment discontinuation for any reason • Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
	co-operate and adhere to study criteria. Absence of interfering medical and dermatological conditions and medications. Absence of pregnancy and avoidance of interference from oral contraceptives.		
Stein Gold 2008 **Country**: United States **Study type**: RCT	N=201 **Sex**: mixed **Number randomised: arm 1**: 101 **Number randomised: arm 2**: 100 **Inclusion details**: Males and females aged between 12 and 35 years.15 to 100 non-inflammatory lesions, at least 20 inflammatory lesions, and no more than 3 nodules.	**Intervention: arm 1**: ADAP 0.1% gel **Intervention: arm 2**: ADAP 0.1% gel for 6 weeks then TAZ 0.1% cream for 6 weeks	• Clinician rated improvement in acne
Stein Gold 2010 **Country**: North America **Study type**: RCT	N=459 **Sex**: mixed **Number randomised: arm 1**: 232 **Number randomised: arm 2**: 227 **Inclusion details**: Males and females of any race, aged 12 to 35 years. Severe facial acne vulgaris (IGA score of 4); minimum of 20 inflammatory lesions, 30 to 120 non-inflammatory lesions, and no more than 3 nodulocystic lesions. Specified washout periods were required for participants using topical and oral acne treatments.	**Intervention: arm 1**: ADAP 0.1%/BPO 2.5% gel + DOXY 100 mg **Intervention: arm 2**: DOXY 100 mg + Vehicle	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Stein Gold 2016 **Country**: United States **Study type**: RCT	N=434 **Sex**: mixed **Number randomised: arm 1**: 217 **Number randomised: arm 2**: 217 **Number randomised: arm 3**: 69 **Inclusion details**: Males and females. Moderate to severe inflammatory facial acne, that is a score of 3 (moderate) or 4 (severe) on the IGA, the presence of 20 to 100 inflammatory lesions, 30 to 150 non-inflammatory lesions (including the nose), and up to 2 nodules on the face. A urine pregnancy test was required	**Intervention: arm 1**: ADAP 0.3%/BPO 2.5% gel **Intervention: arm 2**: ADAP 0.1%/BPO 2.5% gel **Intervention: arm 3**: Vehicle	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
	for females at baseline and throughout the study.		
Stewart 2006 **Country**: United States **Study type**: RCT	N=174 **Sex**: mixed **Number randomised: arm 1**: 59 **Number randomised: arm 2**: 60 **Number randomised: arm 3**: 55 **Inclusion details**: Participants aged 12 to 30 years, weighing between 39.1 kg and 102.3 kg (86 to 225 lb). Diagnosed with moderate to severe facial acne vulgaris; at least 20 and no more than 100 inflammatory facial lesions and <5 facial nodules or cysts. Females of childbearing potential must have had a negative urine pregnancy test result (25 µg/mL sensitivity), be using contraception and will to continue on contraception during the study. Participants or parent/guardian consent provided.	**Intervention: arm 1**: MINO-oral 2mg/kg/day **Intervention: arm 2**: MINO-oral 3mg/kg/day **Intervention: arm 3**: PLC-oral	• Treatment discontinuation due to side effects • Clinician rated improvement in acne
Strauss 1984a **Country**: United States **Study type**: RCT	N=na **Sex**: mixed **Number randomised: arm 1**: na **Number randomised: arm 2**: na **Number randomised: arm 3**: na **Inclusion details**: Participants with treatment-resistant, severe nodulocystic acne; minimum of 10 inflammatory nodulocystic acne lesions at least 4 mm in diameter on the face, back, or chest. Off all treatment for at least 1 month. Female participants were required to have negative pregnancy test within 2 weeks prior to starting treatment.	**Intervention: arm 1**: ISO<120.Daily<0.5 (0.1 mg/kg daily for 140 days) **Intervention: arm 2**: ISO<120.Daily=0.5 (0.5 mg/kg daily for 140 days) **Intervention: arm 3**: ISO=120.Daily=0.5 (1 mg/kg daily for 140 days)	• Clinician rated improvement in acne
Tan 2014 **Country**: Canada **Study type**: RCT	N=266 **Sex**: mixed **Number randomised: arm 1**: 133 **Number randomised: arm 2**: 133 **Inclusion details**: Participants of any race, aged 12 to 35 years.	**Intervention: arm 1**: DOXY 200 mg + ADAP 0.1%/BPO 2.5% gel **Intervention: arm 2**: ISO=120.Daily=0.5 (wk 1-4 0.5 mg), then ISO=120.Daily=0.5 (wk 5-20 1.0 mg)	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Tan 2019;Trial 1 **Country**: US/Canada/Europ	N=1208 **Sex**: mixed **Number randomised: arm 1**:	**Intervention: arm 1**: TRIF 0.05 mg/g **Intervention: arm**	• Treatment discontinuation for any reason

Study	Population	Interventions	Outcomes
e/Russia **Study type**: RCT	612 **Number randomised: arm 2**: 596 **Inclusion details**: Participants aged 9 years and older. Moderate facial acne (defined as IGA score of 3 on the face [=20 inflammatory lesions and =25 non-inflammatory lesions]), and moderate truncal acne (defined as a Physician's Global Assessment [PGA] score of 3 at screening and baseline [=20 inflammatory lesions and 20 to <100 non-inflammatory lesions on the areas of the trunk within reach for self-application]). For participants aged 9 to 11 years, the inclusion criteria relating to truncal acne were optional owing to the relative rarity of this (compared with facial involvement) in this age group.	**2**: Vehicle	• Treatment discontinuation due to side effects • Clinician rated improvement in acne
Tanghetti 2006 **Country**: United States **Study type**: RCT	N=121 **Sex**: mixed **Number randomised: arm 1**: 61 **Number randomised: arm 2**: 60 **Inclusion details**: Participants aged at least 12 years of age. Stable moderate to severe facial inflammatory acne vulgaris (defined as 15 to 60 papules plus pustules, 10 to 100 comedones, and no more than 2 nodulocystic lesions with a maximum diameter of 5 mm). Washout periods required: 2 weeks for topical acne treatments, 30 days for systemic antibiotics and investigational drugs, 12 weeks for oestrogens/birth control pills if previously used for <12 weeks, and 6 months for oral retinoids.	**Intervention: arm 1**: TAZ 0.1% cream + Vehicle gel **Intervention: arm 2**: BPO 5%/CLIND 1% gel + TAZ 0.1% cream	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Tanghetti 2007 **Country**: United States **Study type**: RCT	N=150 **Sex**: mixed **Number randomised: arm 1**: 75 **Number randomised: arm 2**: 75 **Inclusion details**: Participants aged at least 12 years old. Facial acne vulgaris; 15 to 60 papules plus pustules, 10 to 100 comedones, and no more than 2 nodulocystic lesions (with a diameter no more than 5 mm). Washout periods required: 14 days for topical antibiotics and	**Intervention: arm 1**: CLIND 1% gel + TAZ 0.1% cream **Intervention: arm 2**: CLIND 1% gel + TRET 0.025% gel	• Treatment discontinuation due to side effects • Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
	anti-acne treatments, 30 days for systemic antibiotics and investigational drugs, 12 weeks for oestrogens/birth control pills if used for <12 weeks before study entry, and 12 months for oral retinoids.		
Tanghetti 2008 **Country**: United States **Study type**: RCT (split face design)	N=23 **Sex**: mixed **Number randomised: arm 1**: 23 (observations) **Number randomised: arm 2**: 23 (observations) **Inclusion details**: Participants aged between 11 to 45 years of age. Moderate facial acne vulgaris; 25 to 100 non-inflammatory lesions, 25 to 100 inflammatory lesions, up to 2 nodulocystic lesions. Willing to refrain from using non-study acne medications, moisturisers, sunscreens, fragrances, aftershaves, and make-up on the face (oil-free non-comedogenic make-up, mascara, eyeshadow, and lipstick were allowed). Willing to avoid excessive exposure to the sun and the use of tanning booths. Washout periods required: 1 week for medicated facial cleansers; 2 weeks for topical alpha-hydroxy acids, anti-acne medications, topical retinoids, topical and systemic antibiotics, and topical and systemic steroids; 3 months for oestrogens/birth control pills (unless used for at least 3 months); and 6 months for systemic retinoids.	**Intervention: arm 1**: BPO 5% gel **Intervention: arm 2**: BPO 5%/CLIND 1% gel	• Clinician rated improvement in acne
Tanghetti 2019 **Country**: United States **Study type**: RCT	N=210 **Sex**: mixed **Number randomised: arm 1**: 69 **Number randomised: arm 2**: 72 **Number randomised: arm 3**: 69 **Inclusion details**: Participants of any gender, race and ethnicity, aged 12 years or older. Participants with moderate to severe acne; EGSS score of 3 (moderate) or 4 (severe); 20 to 40 inflammatory lesions (papules, pustules, and nodules), 20 to 100 non-inflammatory lesions (open and closed comedones), and 2	**Intervention: arm 1**: TAZ 0.045% lotion **Intervention: arm 2**: TAZ 0.1% cream **Intervention: arm 3**: Lotion vehicle or cream vehicle (arms combined)	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
	nodules or less. Women of childbearing potential were required to have a negative urine pregnancy test at and agree to use a reliable method of contraceptive during the study period. Washout period of 1 month required for participants who previously used prescription and over-the-counter acne treatments, and 6 months for systemic retinoids.		
Thiboutot 2002 **Country**: United States **Study type**: RCT	N=245 **Sex**: mixed **Number randomised: arm 1**: 124 **Number randomised: arm 2**: 121 **Number randomised: arm 3**: 42 **Number randomised: arm 4**: 40 **Inclusion details**: Males and females aged >12 years of age. Moderate to moderately severe acne; 15 to 80 facial inflammatory lesions, 20 to 140 facial comedones (not including the nose or nasolabial area), <2 nodules or cysts >5 mm, and a minimum Physician's Global Acne Severity score of 1.5.	**Intervention: arm 1**: BPO 5%/ERYTH 3% gel **Intervention: arm 2**: BPO 5%/ERYTH 3% jar **Intervention: arm 3**: Vehicle gel **Intervention: arm 4**: Vehicle Jar	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Thiboutot 2005 **Country**: United States **Study type**: RCT	N=467 **Sex**: mixed **Number randomised: arm 1**: 238 **Number randomised: arm 2**: 229 **Inclusion details**: Males and females with severe facial acne (global severity score of at least 4 on a scale ranging from 0 [clear] to 5 [very severe]); minimum of 15 inflammatory lesions and 15 to 100 non-inflammatory facial lesions. Washout periods were required for participants taking certain topical and systemic treatments.	**Intervention: arm 1**: ADAP 0.1% gel + DOXY 100 mg **Intervention: arm 2**: DOXY 100 mg + Vehicle	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Webster 2014 **Country**: North America **Study type**: RCT	N=925 **Sex**: mixed **Number randomised: arm 1**: 464 **Number randomised: arm 2**: 461	**Intervention: arm 1**: Isotretinoin-(lidose formulation) ISO<120.Daily=0.5 **Intervention: arm 2**: ISO<120.Daily=0.5	• Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
	Inclusion details: Participants with severe calcitrant nodular acne, compatible with isotretinoin treatment; 10 or more facial and/or truncal nodular lesions. No prior exposure to systemic isotretinoin or other retinoids. Aged between 12 and 54 years and weighing between 40 and 110 kg.		
Xu 2017 **Country**: China **Study type**: RCT	N=95 **Sex**: mixed **Number randomised: arm 1**: 48 **Number randomised: arm 2**: 47 **Inclusion details**: Males and females aged 15 to 35 years attending a Department of Dermatology, China. Moderate to severe facial acne vulgaris defined by IGA scale of 3 or 4; =10 inflammatory lesions (papules, pustules, or nodules) and =10 non-inflammatory lesions (open and closed comedones) on the face.	**Intervention: arm 1**: MINO 100 mg + 5ALA 5%-RED LED-PDT **Intervention: arm 2**: MINO 100 mg	• Clinician rated improvement in acne
Yin 2010 **Country**: China **Study type**: RCT	N=180 **Sex**: mixed **Number randomised: arm 1**: 45 **Number randomised: arm 2**: 45 **Number randomised: arm 3**: 45 **Number randomised: arm 4**: 45 **Inclusion details**: Chines participants attending a Department of Dermatology in China. Facial inflammatory acne vulgaris (moderate to severe grade according to Pillsbury et al.); Fitzpatrick skin type III and IV. Underwent aminolaevulinic acid-photodynamic therapy treatment and following up from June 2007 to January 2009.	**Intervention: arm 1**: 5ALA 5%-PDT **Intervention: arm 2**: 5ALA 10%-PDT **Intervention: arm 3**: 5ALA 15%-PDT **Intervention: arm 4**: 5ALA 20%-PDT	• Treatment discontinuation due to side effects
Zhang 2017 **Country**: China **Study type**: RCT (split face design)	N=12 **Sex**: mixed **Number randomised: arm 1**: 12 (observations) **Number randomised: arm 2**: 12 (observations) **Inclusion details**: Males and females aged between 18 and 40 years. Acne lesions on the forehead and on both sides of the face and clinically diagnosed with	**Intervention: arm 1**: 5ALA 5%-RED LED-PDT **Intervention: arm 2**: 5ALA 5%-IPL-PDT	• Clinician rated improvement in acne

Study	Population	Interventions	Outcomes
	acne vulgaris and grade 3 to 4 according to the European Guidelines Group.		
Zhang 2019 **Country**: China **Study type**: RCT (split face design)	N=28 **Sex**: mixed **Number randomised: arm 1**: 28 (observations) **Number randomised: arm 2**: 28 (observations) **Inclusion details**: Chinese adult participants attending an outpatient department. Symmetrically distributed severe facial acne (Pillsbury III and IV) and Fitzpatrick skin type III and IV.	**Intervention: arm 1**: 5ALA 5%-PDT **Intervention: arm 2**: 5ALA 10% PDT	• Clinician rated improvement in acne
Zouboulis 2000 **Country**: Europe **Study type**: RCT	N=209 **Sex**: mixed **Number randomised: arm 1**: 104 **Number randomised: arm 2**: 105 **Inclusion details**: Participants aged between 14 and 26 years. Moderate to severe acne vulgaris; scoring =3 on the Cook acne scale.	**Intervention: arm 1**: CLIND 1%/TRET 0.025% gel **Intervention: arm 2**: CLIND 1% lotion	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne

Abbreviations: 1319-LSR: 1319 nm laser phototherapy; 589-LSR: 589 nm laser phototherapy; 5ALA-IPL-PDT: 5-aminolevulinic acid using intense pulsed light; 5ALA-KTP-PDT: 5-aminolevulinic acid using potassium titanyl phosphate laser; 5ALA-RED-PDT: 5-aminolevulinic acid using red light; ADAP + BPO: adapalene + benzoyl peroxide; ADAP: adapalene; AZE: azelaic acid; AZITH: azithromycin ; BiRF: bipolar radiofrequency; BLU-PT: blue light phototherapy; BPO + CLIND: benzoyl peroxide 5%/clindamycin 1%; BPO: benzoyl peroxide; BR-LED: blue + red light light emitting diode; CLIND: clindamycin; CLIND + TRET: clindamycin 1% + tretinoin 0.025%; CLIND: clindamycin; CPA + EE (CO-CYPRINDIOL): ethinylestradiol with cyproterone acetate; CPA: cyproterone acetate; DAPS: dapsone; DEM: demeclocycline; DOXY: doxycycline; EE: ethinyl estradiol; ERYTH + ZINC: erythromycin with zinc acetate dihydrate; ERYTH: erythromycin; GLY: glycolic acid; GOLDMP: gold microparticles; IPL: intense pulsed light; ISO<120.Alt<0.5: isotretinoin ≥0.5mg/kg/every other day total cumulative dose < 120mg/kg; isotretinoin ≥0.5mg/kg/day total cumulative dose < 120mg/kg; ISO<120.Daily≥0.5: isotretinoin <0.5mg/kg/day total cumulative dose < 120mg/kg; ISO<120.Other<0.5: isotretinoin ≥0.5mg/kg/less frequently total cumulative dose < 120mg/kg; ISO<120.Other≥0.5: isotretinoin <0.5mg/kg/less frequently total cumulative dose < 120mg/kg; ISO≥120.Alt<0.5: isotretinoin ≥0.5mg/kg/every other day total cumulative dose ≥ 120mg/kg; ISO≥120.Alt≥0.5: isotretinoin <0.5mg/kg/every other day total cumulative dose ≥ 120mg/kg; ISO≥120.Daily<0.5: isotretinoin ≥0.5mg/kg/day total cumulative dose ≥ 120mg/kg; ISO≥120.Daily≥0.5: isotretinoin <0.5mg/kg/day total cumulative dose ≥ 120mg/kg; ISO≥120.Other<0.5: isotretinoin ≥0.5mg/kg/less frequently total cumulative dose ≥120mg/kg; ISO≥120.Other≥0.5: isotretinoin <0.5mg/kg/less frequently total cumulative dose ≥ 120mg/kg; ISO: isotretinoin ; JES: Jessner's peel; KTP: potassium titanyl phosphate laser; LEVA: levamisole; LYME: lymecycline; MAL-DL-PDT: methyl aminolevulinate using daylight; MAL-IPL-PDT: methyl aminolevulinate using IPL; MAL-RED-PDT: methyl aminolevulinate using red light; MD: microdermabrasion; METF: metformin; MET: metronidazole; MICO: miconazole nitrate; MINO: minocycline; MOT: motretinide; n: number of participants randomised/completed to/in each trial arm; NAFL: fractional erbium glass laser; NBUVB: nearband type B ultraviolet light; NICO: nicotinamide (niacinamid); NOR + EE: northisterone + ethinylestradiol; PDL: pulsed dye laser; PLC: pill placebo; PLC-physical: sham physical treatment; PLC: topical placebo; RED: red light; ROXI: roxithromycin; SAL: salicyclic acid; SARE: sarecycline; SPIRO: spironolactone; TAZ: tazarotene; TETRA: tetracycline; TRET: tretinoin (RETIN A, All-trans retinoic acid); TRIF: trifarotene; ZINCG: zinc gluconate

The network plots of treatment classes for efficacy (% change in total lesion count from baseline), discontinuation for any reason, and discontinuation due to side effects analysed in

NMA are shown in Figure 1, Figure 2, and Figure 3, for each outcome respectively. In each network plot, the width of lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of observations made on each treatment class (which is the sum of the number of participants in parallel trials and number of observations in split-face trials). In addition, the numbers of observations on each treatment class, and on each intervention within class, are shown in

Table 3,

Table 4 and

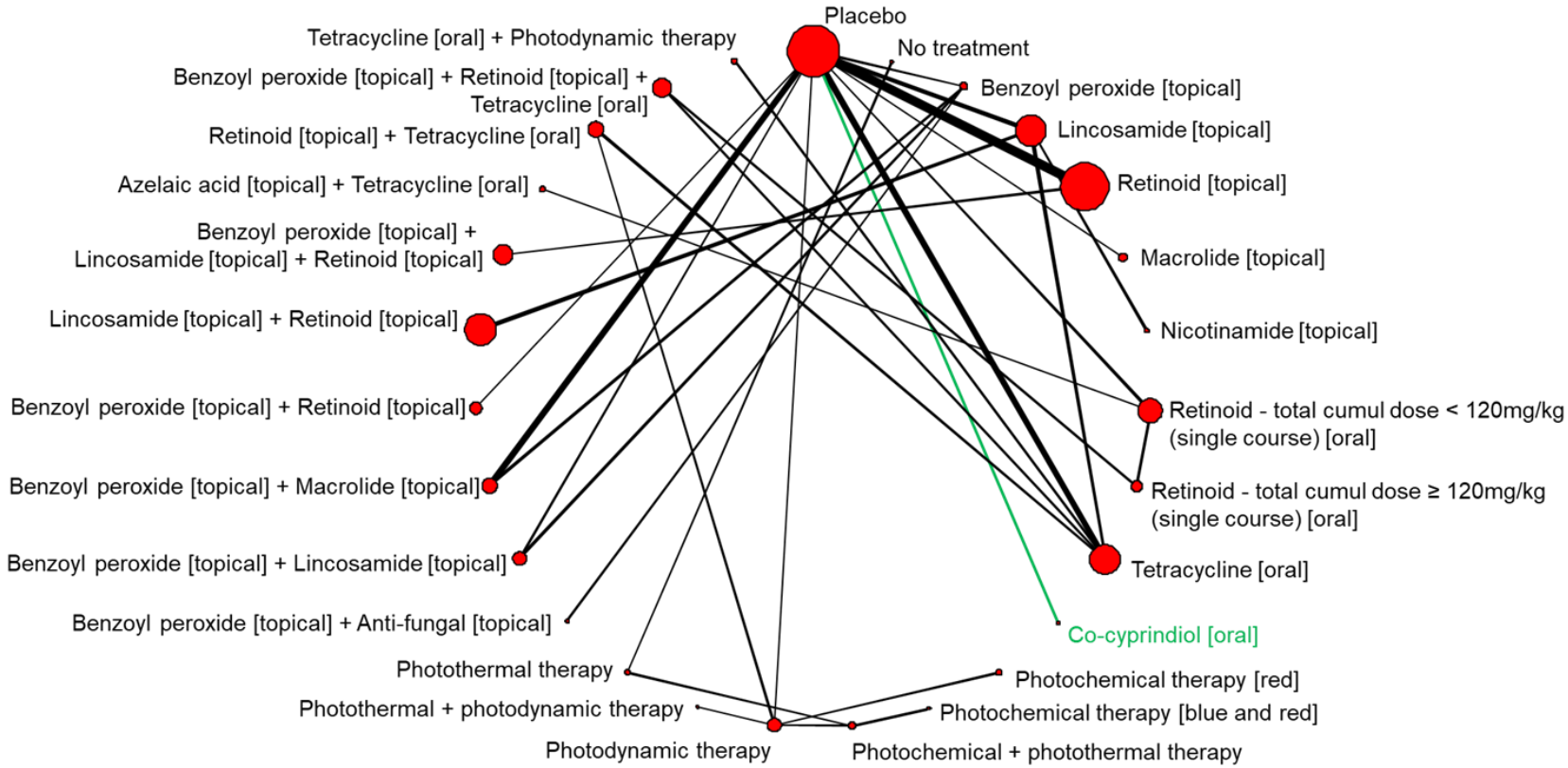
Table 5, for the outcomes of efficacy, discontinuation for any reason, and discontinuation due to side effects, respectively.

See the full evidence tables in appendix D and the NMA results including forest plots, effects versus placebo and ranking tables in appendix E. Where bias models suggested evidence of bias, bias-adjusted effects versus placebo and corresponding ranking tables are also shown in the same appendix. Full NMA methods including NMA models, inconsistency checks, bias-adjusted models, as well as NMA results are provided in appendix M.

1

2 **Efficacy (% change in total lesion from baseline)**

3 **Figure 1. Efficacy network of treatment classes for people with moderate to severe acne.**



4
5 *Treatment classes and lines in green indicate treatments and comparisons relevant to females only.*

6

Table 3. Treatment classes, interventions and numbers of observations made on each, in the efficacy network of treatments for people with moderate to severe acne.

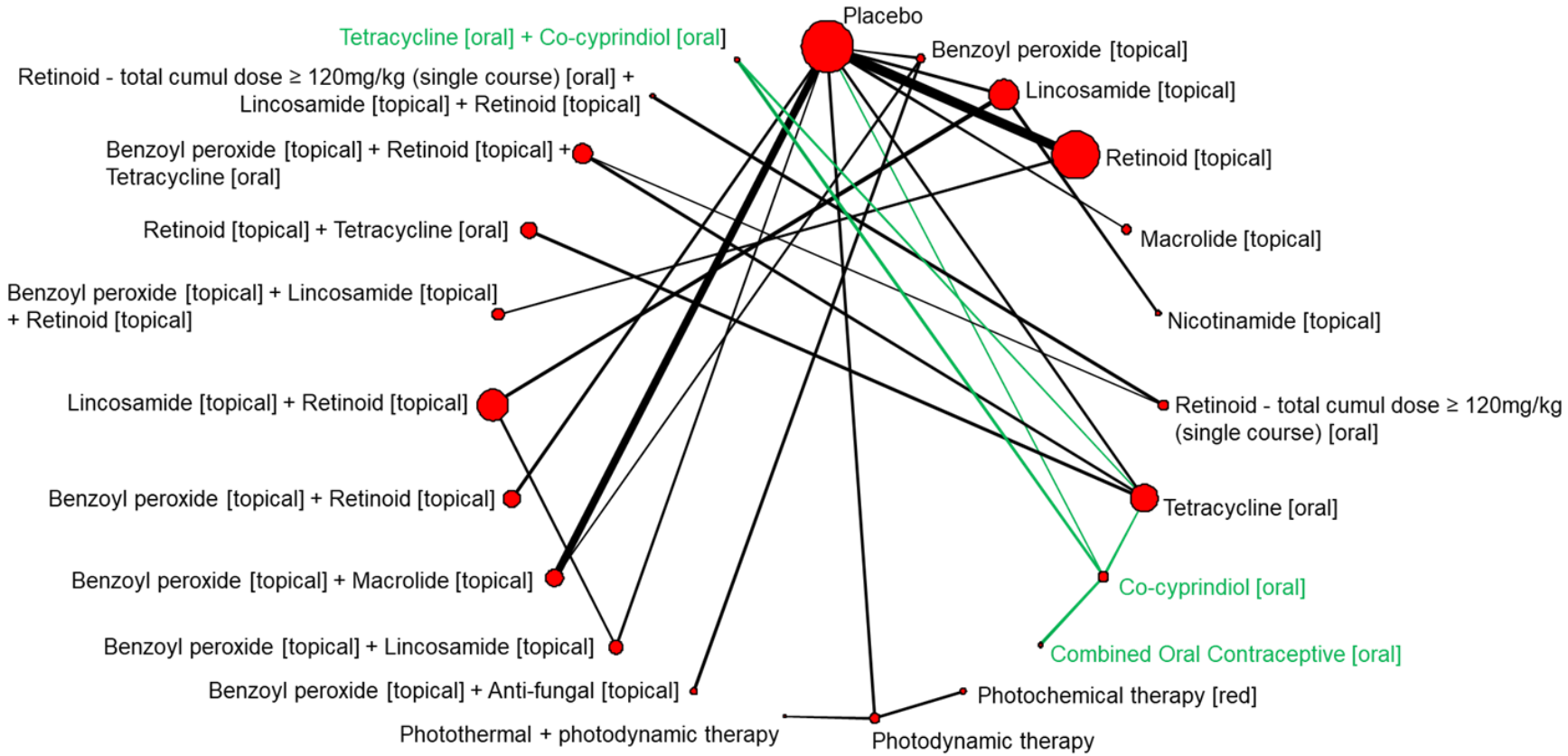
Class	n	Treatment	n	Duration	n
Placebo	4122F 4106M	Placebo [oral]	162	0 to <6 weeks	17
				12 to <24 weeks	145
		Placebo [physical]	30	NA	
		Placebo [topical]	3901F 3885M	6 to <12 weeks	276
				12 to <24 weeks	3625F 3609M
		Placebo [oral + physical]	29	12 to <24 weeks	29
No treatment	25	No treatment	25	NA	
Benzoyl peroxide [topical]	80	Benzoyl peroxide [topical]	80	0 to <6 weeks	23
				12 to <24 weeks	57
Lincosamide [topical]	1479	Clindamycin [topical]	1479	6 to <12 weeks	164
				12 to <24 weeks	1315
Retinoid [topical]	3570	Adapalene [topical]	1309	12 to <24 weeks	1309
		Tazarotene [topical]	947	12 to <24 weeks	947
		Trifarotene [topical]	1214	12 to <24 weeks	1214
		Adapalene [topical] followed by Tazarotene [topical]	100	12 to <24 weeks	100
Macrolide [topical]	109	Erythromycin [topical]	109	12 to <24 weeks	109
Nicotinamide [topical]	29	Nicotinamide (Niacinamid) [topical]	29	6 to <12 weeks	29
Retinoid - total cumulative dose < 120mg/kg (single course) [oral]	938	Isotretinoin < 120. Daily < 0.5 [oral]	46	12 to <24 weeks	46
		Isotretinoin < 120.Daily ≥ 0.5 [oral]	892	0 to <6 weeks	16
				12 to <24 weeks	841
				24+ weeks	35
Retinoid - total cumulative dose ≥ 120mg/kg (single course) [oral]	182	Isotretoinoin ≥ 120. Daily ≥ 0.5 [oral]	182	12 to <24 weeks	182
Tetracycline [oral]	1386	Doxycycline [oral]	456	12 to <24 weeks	456
		Lymecycline [oral]	595	12 to <24 weeks	595
		Minocycline [oral]	306	0 to <6 weeks	47
				12 to <24 weeks	259
		Tetracycline [oral]	29	6 to <12 weeks	29
Co-cyprindiol [oral]	12F	Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	12F	12 to <24 weeks	12F
Photochemical therapy [red]	53	Red light	53	NA	
Photochemical therapy [blue and red]	15	Blue + Red light	15	NA	
Photochemical + photothermal therapy	71	Intense Pulsed Light (IPL)	35	NA	
		Pulsed Dye Laser	36		

Class	n	Treatment	n	Duration	n
Photodynamic therapy	298	5-Aminolevulinic Acid (ALA) using IPL	33	NA	
		5-Aminolevulinic Acid (ALA) using red light	81		
		Methyl Aminolevulinate (MAL) using daylight	14		
		Methyl Aminolevulinate (MAL) using IPL	20		
		Methyl Aminolevulinate (MAL) using red light	150		
Photothermal + photodynamic therapy	14	Fractional Erbium Glass Laser + Methyl Aminolevulinate (MAL) using daylight	14	NA	
Photothermal therapy	46	Gold Microparticles	46	NA	
Benzoyl peroxide [topical] + Anti-fungal [topical]	25	Benzoyl peroxide [topical] + Miconazole Nitrate [topical]	25	12 to <24 weeks	25
Benzoyl peroxide [topical] + Lincosamide [topical]	276	Benzoyl peroxide [topical] + Clindamycin [topical]	276	0 to <6 weeks	23
				12 to <24 weeks	253
Benzoyl peroxide [topical] + Macrolide [topical]	365	Benzoyl peroxide [topical] + Erythromycin [topical]	365	6 to <12 weeks	337
				12 to <24 weeks	28
Benzoyl peroxide [topical] + Retinoid [topical]	217	Benzoyl peroxide [topical] + Adapalene [topical]	217	12 to <24 weeks	217
Lincosamide [topical] + Retinoid [topical]	1548	Clindamycin [topical] + Tazarotene [topical]	75	12 to <24 weeks	75
		Clindamycin [topical] + Tretinoin [topical]	1473	12 to <24 weeks	1173
Benzoyl peroxide [topical] + Lincosamide [topical] + Retinoid [topical]	600	Benzoyl peroxide [topical] + Clindamycin [topical] + Adapalene [topical]	118	12 to <24 weeks	118
		Benzoyl peroxide [topical] + Clindamycin [topical] + Tazarotene	100	12 to <24 weeks	100
		Benzoyl peroxide [topical] + Clindamycin [topical] + Tretinoin [topical]	382	12 to <24 weeks	382
Azelaic acid [topical] + Tetracycline [oral]	50	Azelaic Acid [topical] + Minocycline [oral]	50	24+ weeks	50
Retinoid [topical] + Tetracycline [oral]	379	Adapalene [topical] + Doxycycline [oral]	261	6 to <12 weeks	23
				12 to <24 weeks	238
		Adapalene [topical] + Lymecycline [oral]	118	12 to <24 weeks	118
Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral]	556	Benzoyl peroxide [topical] + Adapalene [topical] + Doxycycline [oral]	365	12 to <24 weeks	365
		Benzoyl peroxide [topical] + Adapalene [topical] + Lymecycline [oral]	191	12 to <24 weeks	191
Tetracycline [oral] + Photodynamic therapy	48	Minocycline [oral] + 5-Aminolevulinic Acid (ALA) using red light	48	0 to <6 weeks	48

In green, classes and numbers of observations from RCTs assessing treatments relevant to females; in blue, numbers of observations from RCTs assessing treatments also relevant to males.

Discontinuation for any reason

Figure 2. Discontinuation for any reason network of treatment classes for people with moderate to severe acne.



Treatment classes and lines in green indicate treatments and comparisons relevant to females only.

Table 4. Treatment classes, interventions and numbers of observations made on each, in the discontinuation for any reason network of treatments for people with moderate to severe acne.

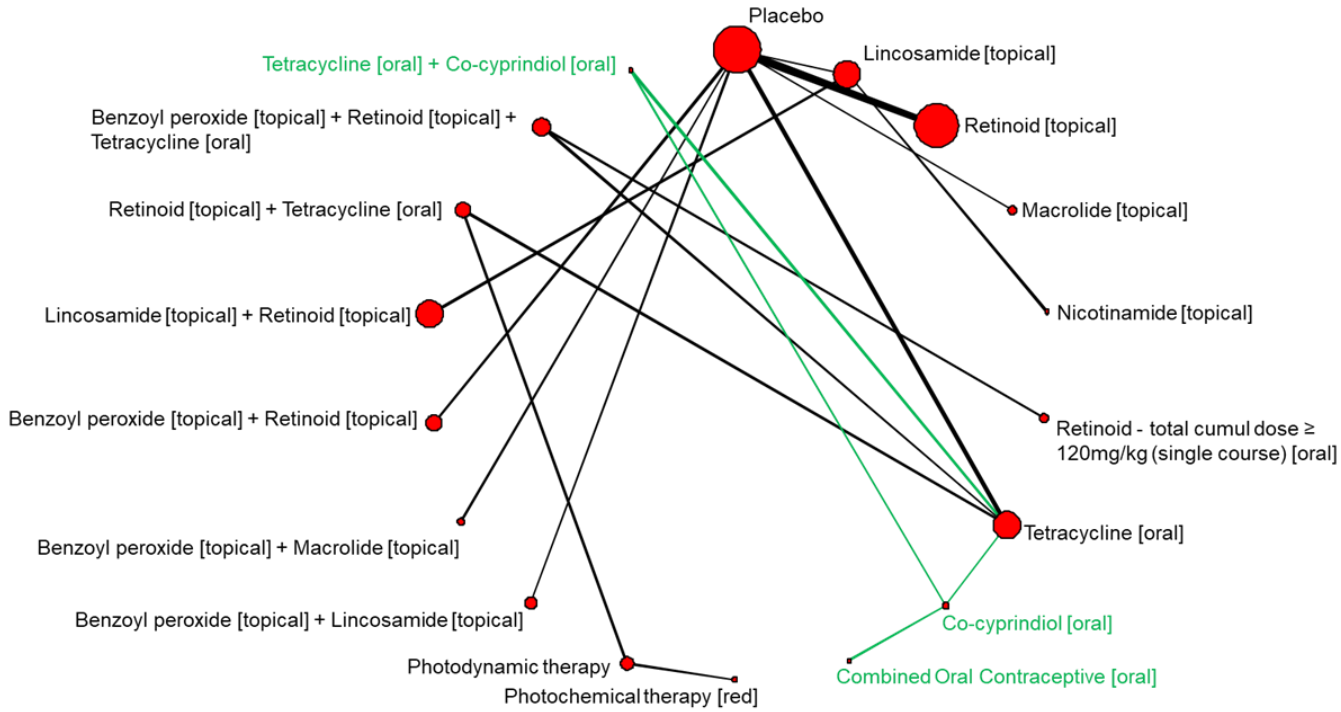
Class	n	Treatment	n	Duration	n
Placebo	4133F 4115M	Placebo [oral]	53F 35M	12 to <24 weeks	53F 35M
		Placebo [topical]	4055	6 to <12 weeks	317
				12 to <24 weeks	3738
		Placebo [physical]	25	0 to <6 weeks	25
Benzoyl peroxide [topical]	114	Benzoyl peroxide [topical]	114	12 to <24 weeks	114
Lincosamide [topical]	1416	Clindamycin [topical]	1416	6 to <12 weeks	159
				12 to <24 weeks	1257
Retinoid [topical]	3449	Adapalene [topical]	1248	12 to <24 weeks	1248
		Isotretinoin [topical]	40	12 to <24 weeks	40
		Tazarotene [topical]	947	12 to <24 weeks	947
		Trifotene [topical]	1214	12 to <24 weeks	1214
Macrolide [topical]	127	Erythromycin [topical]	127	12 to <24 weeks	127
Nicotinamide [topical]	38	Nicotinamide (Niacinamid) [topical]	38	6 to <12 weeks	38
Retinoid - total cumulative dose ≥ 120mg/kg (single course) [oral]	163	Isotretinoin ≥ 120. Daily ≥ 0.5 [oral]	163	12 to <24 weeks	133
				24+ weeks	30
Tetracycline [oral]	1188F 1167M	Doxycycline [oral]	456	12 to <24 weeks	456
		Lymecycline [oral]	595	12 to <24 weeks	595
		Minocycline [oral]	91	12 to <24 weeks	91
		Tetracycline [oral]	46F 21M	12 to <24 weeks	21
				24+ weeks	25F
Co-cyprindiol [oral]	175F	Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	175F	12 to <24 weeks	14F
				24+ weeks	161F
Combined Oral Contraceptive [oral]	32F	Ethinylestradiol [oral] + Norethisterone [oral]	32F	24+ weeks	32F
Photochemical therapy [red]	53	Red light	53	NA	
Photodynamic therapy	141	5-Aminolevulinic Acid (ALA) using red light	25	NA	
		Methyl Aminolevulinate (MAL) using daylight	16		
		Methyl Aminolevulinate (MAL) using red light	100		
Photothermal + photodynamic therapy	16	Fractional Erbium Glass Laser + Methyl Aminolevulinate (MAL) using daylight	16		
Benzoyl peroxide [topical] + Anti-fungal [topical]	81	Benzoyl peroxide [topical] + Miconazole Nitrate [topical]	81	12 to <24 weeks	81
Benzoyl peroxide [topical] + Lincosamide [topical]	280	Benzoyl peroxide [topical] + Clindamycin [topical]	280	12 to <24 weeks	280
Benzoyl peroxide [topical] + Macrolide [topical]	477	Benzoyl peroxide [topical] + Erythromycin [topical]	477	6 to <12 weeks	357
				12 to <24 weeks	120

Benzoyl peroxide [topical] + Retinoid [topical]	434	Benzoyl peroxide [topical] + Adapalene [topical]	434	12 to <24 weeks	434
Lincosamide [topical] + Retinoid [topical]	1439	Clindamycin [topical] + Tretinoin (RETIN A, All-trans retinoic acid) [topical]	1139	12 to <24 weeks	1139
Benzoyl peroxide [topical] + Lincosamide [topical] + Retinoid [topical]	207	Benzoyl peroxide [topical] + Clindamycin [topical] + Tazarotene [topical]	60	12 to <24 weeks	60
		Benzoyl peroxide [topical] + Clindamycin [topical] + Tretinoin (RETIN A, All-trans retinoic acid) [topical]	147	12 to <24 weeks	147
Retinoid [topical] + Tetracycline [oral]	356	Adapalene [topical] + Doxycycline [oral]	238	12 to <24 weeks	238
		Adapalene [topical] + Lymecycline [oral]	118	12 to <24 weeks	118
Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral]	556	Benzoyl peroxide [topical] + Adapalene [topical] + Doxycycline [oral]	365	12 to <24 weeks	365
		Benzoyl peroxide [topical] + Adapalene [topical] + Lymecycline [oral]	191	12 to <24 weeks	191
Retinoid - total cumulative dose ≥ 120mg/kg (single course) [oral] + Lincosamide [topical] + Retinoid [topical]	30	Isotretinoin ≥ 120. Daily ≥ 0.5 [oral] + Clindamycin [topical] + Adapalene [topical]	30	24+ weeks	30
Tetracycline [oral] + Co-cyprindiol [oral]	37F	Tetracycline [oral] + Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	37F	24+ weeks	37F

In green, classes and numbers of observations from RCTs assessing treatments relevant to females; in blue, numbers of observations from RCTs assessing treatments also relevant to males.

Discontinuation due to side effects

Figure 3. Discontinuation due to side effects network of treatment classes for people with moderate to severe acne.



Treatment classes and lines in green indicate treatments and comparisons relevant to females only.

Table 5. Treatment classes, interventions and numbers of observations made on each, in the discontinuation due to side effects network of treatments for people with moderate to severe acne.

Class	n	Treatment	N	Duration	n
Placebo	3920	Placebo [oral]	108	12 to <24 weeks	108
		Placebo [topical]	3812	6 to <12 weeks	124
				12 to <24 weeks	3688
Lincosamide [topical]	1266	Clindamycin [topical]	1266	6 to <12 weeks	159
				12 to <24 weeks	1107
Retinoid [topical]	3388	Adapalene [topical]	1248	12 to <24 weeks	1248
		Isotretinoin [topical]	40	12 to <24 weeks	40
		Tazarotene [topical]	886	12 to <24 weeks	886
		Trifotene [topical]	1214	12 to <24 weeks	1214
Macrolide [topical]	127	Erythromycin [topical]	127	12 to <24 weeks	127
Nicotinamide [topical]	38	Nicotinamide (Niacinamid) [topical]	38	6 to <12 weeks	38
Retinoid - total cumulative dose ≥ 120mg/kg (single course) [oral]	133	Isotretinoin ≥ 120.Daily ≥ 0.5 [oral]	133	12 to <24 weeks	133
Tetracycline [oral]	1307F 1282M	Doxycycline [oral]	456	12 to <24 weeks	456
		Lymecycline [oral]	595	12 to <24 weeks	595
		Minocycline [oral]	210	12 to <24 weeks	210
		Tetracycline [oral]	46F 21M	12 to <24 weeks	21
				24+ weeks	25F
Co-cyprindiol [oral]	88F	Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	88F	24+ weeks	91F
Combined Oral Contraceptive [oral]	32F	Ethinylestradiol [oral] + Norethisterone [oral]	32F	24+ weeks	33F
Photochemical therapy [red]	53	Red light	53	NA	
Photodynamic therapy	303	5-Aminolevulinic Acid (ALA) using red light	203	NA	
		Methyl Aminolevulinate (MAL) using red light	100		
Benzoyl peroxide [topical] + Lincosamide [topical]	253	Benzoyl peroxide [topical] + Clindamycin [topical]	253	12 to <24 weeks	253
Benzoyl peroxide [topical] + Macrolide [topical]	90	Benzoyl peroxide [topical] + Erythromycin [topical]	90	12 to <24 weeks	90
Benzoyl peroxide [topical] + Retinoid [topical]	434	Benzoyl peroxide [topical] + Adapalene [topical]	434	12 to <24 weeks	434
Lincosamide [topical] + Retinoid [topical]	1262	Clindamycin [topical] + Tazarotene [topical]	75	12 to <24 weeks	75
		Clindamycin [topical] + Tretinoin [topical]	1187	12 to <24 weeks	1187
Retinoid [topical] + Tetracycline [oral]	379	Adapalene [topical] + Doxycycline [oral]	261	6 to <12 weeks	23
				12 to <24 weeks	238
		Adapalene [topical] + Lymecycline [oral]	118	12 to <24 weeks	118
Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral]	556	Benzoyl peroxide [topical] + Adapalene [topical] + Doxycycline [oral]	365	12 to <24 weeks	365
		Benzoyl peroxide [topical] + Adapalene [topical] + Lymecycline [oral]	191	12 to <24 weeks	191
Tetracycline [oral] + Co-cyprindiol [oral]	37F	Tetracycline [oral] + Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	37F	24+ weeks	37F

In green, classes and numbers of observations from RCTs assessing treatments relevant to females; in blue, numbers of observations from RCTs assessing treatments also relevant to males.

Quality assessment of studies included in the evidence review

The Cochrane Risk of Bias tool version 2.0 (RoB 2, 2019) for RCTs was used to assess potential bias in each study. For each domain on the Cochrane Risk of Bias tool that had sufficient variability in the ratings, bias adjustment NMA models were fitted to downweight trials at high or unclear risk of bias. NMA models that adjusted for small study bias were also fitted. Bias-adjusted NMA models and results are shown in appendix M.

Threshold analysis was undertaken to test the robustness of treatment recommendations based on the NMA, to potential biases or sampling variation in the included evidence. Threshold analysis has been developed as an alternative to GRADE for assessing confidence in guideline recommendations based on network meta-analysis (Phillippo 2018). Full methods and results of threshold analysis are presented in appendix N.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline but no economic studies were identified which were applicable to this review question. See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Economic model

A decision-analytic model was developed to assess the relative cost effectiveness of treatments for people with moderate to severe acne. The objective of economic modelling, the methodology adopted, the results and the conclusions from this economic analysis are described in detail in appendix J. The respective economic evidence profile is shown in Appendix I. This section provides a summary of the methods employed and the results of the economic analysis.

Overview of economic modelling methods

A decision-analytic model comprising a decision-tree was constructed to evaluate the relative cost effectiveness of a range of topical, oral and physical treatments for people with moderate to severe acne who present to primary care services, although they may be subsequently referred to a specialist dermatology setting. The measure of outcome of the economic analysis was the number of QALYs gained. The perspective of the analysis was that of the NHS and personal social services. The time horizon of the analysis was 1 year. The range of interventions assessed in the economic analysis was determined by the availability of relevant clinical data included in the guideline NMA on the efficacy outcome.

Based on the advice of the committee, only treatment classes with evidence of effect versus placebo with at least 40 observations each across the RCTs included in the NMA of efficacy were considered in the economic analysis, as this was deemed as the minimum amount of evidence that could suggest that a treatment may be effective and potentially cost-effective. A treatment class demonstrated evidence of effect if the 95% credible intervals [CrI] of its effect versus placebo did not cross the line of no effect.

One intervention was selected as a representative from each treatment class; this was necessary only for costing purposes, as there was no adequate evidence to estimate individual treatment effects within each treatment class. The criteria for selecting interventions to represent each treatment class were the intervention availability and usage in the UK and other practicalities of use (e.g. a combination of topical treatments available in a single formulation was preferred to combinations that are only available as separate formulations); the evidence base for each intervention within class; the risk of side effects of individual interventions within a class; and, for pharmacological treatments, the drug acquisition cost (drugs with lower acquisition costs were preferred).

Based on the above criteria, the economic analysis included the following treatment classes and interventions:

- Topical retinoids: adapalene
- Benzoyl peroxide (topical treatment, own class)
- Topical lincosamides: topical clindamycin
- Benzoyl peroxide + topical retinoid (adapalene)
- Benzoyl peroxide + topical lincosamide (clindamycin)
- Benzoyl peroxide + topical macrolide (erythromycin)
- Topical retinoid + topical lincosamide: tretinoin + clindamycin
- Benzoyl peroxide + topical retinoid (tretinoin) + topical lincosamide (clindamycin)
- Oral tetracycline: lymecycline
- Topical retinoid (adapalene) + oral tetracycline (lymecycline)
- Azelaic acid (topical treatment, own class) + oral tetracycline (lymecycline)
- Benzoyl peroxide + topical retinoid (adapalene) + oral tetracycline (lymecycline)
- Oral isotretinoin - total cumulative dose ≥ 120mg/kg (single course)
- Oral isotretinoin - total cumulative dose < 120mg/kg (single course)
- Photodynamic therapy
- Photochemical therapy (red light)
- Photothermal therapy
- Photodynamic therapy + oral tetracycline (lymecycline)
- GP care, comprising GP consultations without provision of any pharmacological or physical treatment, reflecting the placebo arm of the network.

According to the model structure, hypothetical cohorts of people with moderate to severe acne were initiated on each of the treatment options assessed, including GP care, and followed for one year (52 weeks). People within each cohort might receive a full course of treatment, or they might discontinue treatment due to intolerable side effects or any other reason. Following treatment, people might experience ‘excellent’, ‘good’, ‘moderate’ or no improvement. People with excellent and good improvement and some people with moderate improvement received maintenance therapy, as appropriate. People who discontinued treatment, people with no improvement and some of those with moderate improvement received ‘average acne care’, comprising a mixture of care that is anticipated to be currently received by people with acne in the NHS. By the end of one year, those who experienced excellent, good or moderate improvement might relapse and return to their initial state of moderate to severe acne, otherwise they remained at the same level of improvement. Those who experienced no improvement remained in the state of no improvement until the model endpoint.

Efficacy and discontinuation data were derived from the respective guideline NMAs. Other clinical input parameters (baseline efficacy and risk of discontinuation, relationship between efficacy and perceived improvement, risk of relapse,) were derived from RCTs, other

published literature and the committee's expert opinion where evidence was lacking. Utility data were estimated based on limited available evidence, identified from a systematic literature review, and the committee's expert opinion. Resource use was based on RCT relevant information and other published literature supplemented with the committee's expert opinion. National UK unit costs were used. The cost year was 2019. Model input parameters were synthesised in a probabilistic analysis. This approach allowed more comprehensive consideration of the uncertainty characterising the input parameters and captured the non-linearity characterising the economic model structure. A number of one-way deterministic sensitivity analyses were also carried out.

Results were expressed in the form of Net Monetary Benefits (NMBs). Incremental mean costs and effects (QALYs) of each treatment option versus GP care were presented in the form of cost effectiveness planes. The cost effectiveness acceptability frontier (CEAF) was also plotted, showing the treatment option with the highest mean NMB over different cost effectiveness thresholds, and the probability that the option with the highest NMB is the most cost-effective among those assessed.

Overview of economic modelling results and conclusions

The results of the economic analysis suggest that all assessed topical, oral and physical treatments are more cost-effective for people with moderate to severe acne compared with GP care. Photothermal therapy, topical combinations such as tretinoin with lincosamide or adapalene with benzoyl peroxide, topical treatments combined with oral antibiotics such as adapalene with or without benzoyl peroxide combined with oral lymecycline, and azelaic acid combined with oral lymecycline, oral isotretinoin of total cumulative dose ≥ 120mg/kg, and topical clindamycin are likely to comprise the most cost-effective treatment options for this population. Topical combinations of benzoyl peroxide with clindamycin, benzoyl peroxide with tretinoin with clindamycin, and benzoyl peroxide with erythromycin, as well as topical adapalene, appear to be less cost-effective, although more cost-effective than GP care alone. In-between, there is another group of treatments (photodynamic therapy alone or combined with oral lymecycline, benzoyl peroxide, oral isotretinoin of total cumulative dose < 120mg/kg, oral tetracyclines and photochemical therapy [red]) that occupied middle cost effectiveness rankings in the guideline economic analysis.

Results of the economic analysis were overall robust to changes in input parameters tested in deterministic sensitivity analysis.

The guideline economic analysis was based on the best quality data derived from the guideline NMA. However, the NMAs were overall characterised by inconsistency between direct and indirect evidence, high between-study heterogeneity, as well as large effects and considerably wide 95% credible intervals for some treatments, and this was taken into account when interpreting the results of the analysis.

The committee's discussion of the evidence

This section includes the committee's discussion of evidence from both the NMA (covered in this evidence report) and the pairwise meta-analysis (covered in evidence report F2).

Interpreting the evidence

The outcomes that matter most

NMA

Clinician-rated improvement at treatment endpoint (measured by percentage change in total acne lesion count and/or change in score or final score on a validated acne severity scale) as well as prevention of scarring at any follow-up (measured by final number or change in the

number of scars from baseline and/or by incidence of scarring at follow up) were considered critical outcomes by the committee as they both reflected primary aims of treatment.

Prevention of scarring data were particularly limited and were eventually analysed in pairwise meta-analysis, as they failed to form a network of at least 3 treatments.

Treatment discontinuation for any reason and due to side effects were considered as important outcomes that reflected acceptability and tolerability of treatments, respectively.

Generally, changes in numbers of acne lesion counts, number of scars and symptom scores from baseline were favoured over final (post-treatment or follow up) outcomes, because although in theory randomisation should balance out any differences at baseline, this assumption can be violated by small sample sizes. The committee also expressed a general preference for clinician-rated improvement over participant-reported improvement as the former, but not the latter, can be blinded. Furthermore, percentage change in acne lesion counts was preferred over either clinician-rated or patient-reported scale scores as it can be more objectively measured.

Pairwise meta-analysis

The committee selected side effects and participant reported improvement of acne as important outcomes. These outcomes were chosen as they indicate the safety of the intervention and perceived improvement in acne symptoms, respectively.

The quality of the evidence

NMA

The quality of the individual studies ranged from very low to moderate. This was predominately due to serious risk of bias of individual studies included in the NMA. This impacted on the quality of the NMAs.

The NMAs allowed estimation of relative effects between all pairs of treatments for people with moderate to severe acne for which RCT evidence was available, via direct and indirect comparisons, without breaking the rules of randomisation.

All networks were disconnected at the intervention level, which was resolved by fitting class effects models. In principle, these models still allow estimation of individual intervention effects within the class, but the available evidence was inadequate to suggest different intervention effects within classes.

Ideally, the committee wanted to look at the effects of different treatment durations of the same intervention, but looking at these would result in sparse, disconnected networks for each duration category, since included RCTs did not compare directly different durations of the same intervention. This was also resolved by fitting class effects models, where duration was only considered at intervention level. Nevertheless, also in this case there was inadequate evidence to suggest that the treatment relative effects differed by treatment duration.

All 3 NMAs (clinician improvement as reflected in % change in total acne lesion count, discontinuation for any reason, discontinuation due to side effects) showed some evidence of inconsistency between direct and indirect evidence. Heterogeneity across all NMAs was found to be rather high. Some relative effects versus placebo were characterised by considerably wide 95% credible intervals. The committee attributed the inconsistency and high heterogeneity identified across the NMAs to the heterogeneity in the populations included in the trials, as there was a range of definitions of moderate to severe acne across the RCTs included in the NMAs. Following consideration of the inconsistency and heterogeneity in the evidence, the committee did not make recommendations by strictly following a hierarchy of treatments according to their ranking in the NMA and the guideline

economic analysis that was informed by the NMA, but instead considered treatments with small differences in clinical and cost-effectiveness as broadly similar. For this reason, recommendations for first line treatment included a range of interventions that were considered to have broadly similar clinical and cost-effectiveness, with the final choice being determined by the values and preferences of the person with acne on the benefits, risks and other related characteristics of recommended treatment options.

Effects for several treatments in the NMA were informed by limited evidence: nicotinamide, co-cyprindiol, combined benzoyl peroxide with topical anti-fungal, photothermal therapy, photothermal + photodynamic therapy, photochemical therapy [blue and red], and photodynamic therapy combined with an oral tetracycline had fewer than 50 observations available each on the efficacy outcome. The committee noted that topical treatments alone or combined with other topical or oral treatments, as well as oral isotretinoin, had overall larger evidence base compared with physical treatments.

Bias adjustment analyses suggested no evidence of bias in the NMAs of clinician-rated improvement and discontinuation for any reason; on the other hand, the NMA of discontinuation due to side effects was characterised by potential bias due to domain 4 in the Cochrane risk assessment tool (outcome measurement - efficacy). A bias-adjusted NMA on this outcome was thus run and considered by the committee when making recommendations.

The committee also noted that comparisons with placebo were very limited for physical interventions and oral isotretinoin. The estimated effects of physical treatments versus placebo were by and large determined by indirect evidence, via photodynamic therapy. Most evidence on oral isotretinoin involved comparisons between different oral isotretinoin regimes; only one trial compared oral isotretinoin with placebo. On the other hand, there were several direct comparisons between different topical treatments alone or combined with other topical or oral treatments.

Threshold analysis suggested that the conclusions of the NMA on efficacy were sensitive to plausible changes in the evidence. This issue, which affected recommendations, has been discussed in detail in the next section, under ‘benefits and harms’.

The committee noted the strengths and limitations of the NMA when interpreting the results. However, the committee agreed to make strong recommendations despite the uncertainty and limitations in the evidence, as the clinical evidence was strong for some treatments and supported by economic evidence and the committee’s clinical experience. The committee decided to make weaker (‘consider’) recommendations on interventions that were supported by a more limited evidence base.

Pairwise meta-analysis

The quality of the evidence ranged from very low to moderate, with most of the evidence being of a very low quality. This was predominately due to serious risk of bias of individual studies and imprecision around the effect estimate.

Benefits and harms

The committee discussed the results of the NMA and noted the total size of the evidence base and the relative size of the evidence base of each treatment versus the other treatment classes in the network. Although they had decided to include in economic analysis treatments with evidence of effect versus placebo and with at least 40 observations each across the RCTs included in the NMA of efficacy, after looking at the relative size of the evidence base of each treatment in the network they decided to consider as candidates for practice recommendations only treatments that had at least 50 observations (rather than participants, as some data were derived from split-face trials) each, across trials included in the NMA of efficacy, as this was considered the minimum adequate evidence base that

would allow drawing more robust conclusions on a treatment's effectiveness; for treatments with a small (as deemed by the committee) number of observations across trials (roughly 50-200) the committee used also their clinical experience in drawing conclusions on treatments' effectiveness.

According to the results of the NMA of efficacy, among treatments with at least 50 observations across RCTs, the treatments that showed evidence of effect versus placebo, ranked by effectiveness (from highest to lowest), were: oral isotretinoin in a total cumulative dose of ≥120mg/kg (single course), oral isotretinoin in a total cumulative dose of <120mg/kg (single course), combined topical retinoid with a topical lincosamide, combined topical retinoid with benzoyl peroxide and an oral tetracycline, photodynamic therapy, combined azelaic acid with an oral tetracycline, combined topical retinoid with an oral tetracycline, combined topical retinoid with benzoyl peroxide, topical lincosamide, photochemical therapy (red), benzoyl peroxide, oral tetracyclines, combined topical benzoyl peroxide with a topical retinoid and a topical lincosamide, combined benzoyl peroxide with a topical lincosamide, combined benzoyl peroxide with a topical macrolide, and topical retinoids.

The following treatments with at least 50 observations across RCTs showed no evidence of effect versus placebo, as their 95% CrI crossed the line of no effect: photochemical and photothermal therapy, topical macrolides.

First-line treatment

The committee noted that, among pharmacological treatments that could be used as first-line treatment options for people with moderate to severe acne, combined topical lincosamide (class of antibiotics with only clindamycin being available in the UK) with topical retinoid, combined benzoyl peroxide with a topical retinoid and an oral tetracycline, combined azelaic acid with an oral tetracycline, and combined benzoyl peroxide with topical retinoid were among the most effective treatment options. The committee agreed that the findings of the network meta-analysis were consistent with their clinical experience. Based on their clinical judgment and after taking into account the inconsistency and uncertainty characterising the NMA, the committee expressed the opinion that there were no considerable differences in clinical effectiveness among these treatments. When making recommendations for specific interventions from each treatment class, the committee expressed a clear preference for single, fixed formulations of combined topical treatments for practicality and cost issues, as discussed under section 'Other factors the committee took into account'. Therefore, the committee recommended 4 alternative first-line treatment options for people with moderate to severe acne: a fixed combination of topical adapalene with benzoyl peroxide combined with either oral lymecycline or oral doxycycline; a combination of topical azelaic acid and oral lymecycline or oral doxycycline; a fixed combination of topical tretinoin with clindamycin; and a fixed combination of topical adapalene with benzoyl peroxide. The choice should be determined following shared decision-making with the person with acne, after taking into account their values and preferences on the benefits, risks and other related characteristics of each of the 4 treatment options (some of these considerations were summarised in a table in the guideline to help shared decision making).

The committee selected tretinoin as the topical retinoid recommended for combination with clindamycin, and adapalene as the topical retinoid recommended for combination with benzoyl peroxide, because tretinoin with clindamycin, and adapalene with benzoyl peroxide are available in single, fixed formulations.

The committee recommended either lymecycline or doxycycline among oral tetracyclines because both are usually taken once a day, which may improve adherence to the oral antibiotic treatment component. There was some evidence from pairwise meta-analysis indicating increased participant reported improvement when using oral tetracyclines, and moreover, lymecycline and doxycycline have a lower risk for side effects compared with other tetracyclines (for example, minocycline, which may result in pigmentation).

The option of azelaic acid combined with an oral tetracycline was offered despite its more limited evidence base (50 observations), because the finding on its clinical effectiveness was consistent with the committee's clinical experience and it was considered as a good alternative for people who have irritation to topical retinoids (as all other recommended options included a topical retinoid).

The committee noted that the combination of a topical retinoid with an oral tetracycline was also amongst the most effective options, but they decided not to recommend it, as they had already decided to recommend the fixed combination of topical adapalene with benzoyl peroxide and an oral tetracycline, which was more effective than topical retinoid alone combined with an oral tetracycline, at no additional cost.

The committee noted that the evidence showed that combinations of topical treatments that included benzoyl peroxide, lincosamide and/or a retinoid were overall more effective than these interventions being used as topical monotherapies. The committee agreed that this was consistent with their clinical experience. The evidence also showed that a combination of these 3 topical agents was less or similarly effective compared with a combination of any 2 agents, so triple therapy and monotherapies were not recommended as first-line treatment options.

The committee noted that the combination of benzoyl peroxide with either a topical lincosamide (clindamycin) or a topical macrolide was less effective compared with other treatments; therefore, no recommendation was considered for either of these combinations.

The committee noted that topical retinoids and oral antibiotics are contra-indicated for some populations, for example, during pregnancy. Therefore, they decided to make a weaker ('consider') recommendation for benzoyl peroxide, for people with acne who do not want topical retinoids or topical or oral antibiotics or for whom these are contra-indicated, because benzoyl peroxide was shown to be effective, albeit somewhat less effective compared with other recommended pharmacological options, and threshold analysis showed that results of the NMA on the efficacy outcome were sensitive to plausible changes in the evidence, resulting in benzoyl peroxide becoming one of the most effective treatment classes.

Factors to take into account during consultation

There was a lack of evidence on the comparative effectiveness of different durations of treatments (including antibiotics). The committee discussed that usually, the positive effects of topical treatments often only become visible after 6 to 8 weeks, so agreed it was important to encourage adherence and discuss the need for continued treatment with the person.

Factors to take into account when choosing a treatment option

The committee reviewed the results of the bias-adjusted NMA on discontinuation due to side effects, which suggested that topical retinoids are associated with an increased risk of discontinuation due to side effects; moreover, evidence from pairwise meta-analysis indicated that topical agents such as benzoyl peroxide and retinoids can cause skin irritation when compared to other active agents or vehicle. The committee confirmed that these findings were consistent with their clinical experience and, therefore, recommended that topical treatments associated with skin irritation, such as benzoyl peroxide or retinoids, be initiated with alternate-day or short-contact application.

Since some of the recommended options include a topical retinoid oral an oral tetracycline, the committee highlighted, based on expertise, that these are contraindicated during pregnancy or planning a pregnancy. Therefore, effective contraceptive methods should be discussed.

Even though there was no evidence for the combined oral contraceptive pill in this population, based on consensus and clinical experience the committee decided that women who need contraceptives could be given the combined oral contraceptive pill in addition to a

first-line treatment option. This would be preferable to the progesterone-only pill, which is known to potentially cause acne (the committee noted that general information about combined hormonal contraception is outside the scope of this guideline but can be accessed from guidance by the Faculty of Sexual and Reproductive Healthcare of the Royal College of Obstetricians and Gynaecologists). The committee also recognised that making recommendations about contraceptive methods is outside the scope of this guideline, and that the most reliable contraceptive is the one which the women would prefer to use after shared decision making looking at all options. The committee also noted that co-cyprindiol showed no effectiveness versus placebo, and this finding was based on very limited evidence (12 observations); hence, no recommendation for co-cyprindiol was made.

The committee were aware that combined treatments that contain an oral antibiotic need to have been tried and failed before oral isotretinoin can be offered according to MHRA guidance, and therefore made a relevant recommendation to increase awareness.

The committee agreed that a topical or an oral antibiotic as a monotherapy or in combination should not be used due to an increased risk for the development of antibiotic resistance; they also noted the lack of effectiveness of topical macrolides (erythromycin) as monotherapy compared with placebo and the lower effectiveness of oral tetracyclines (doxycycline, lymecycline, minocycline, tetracycline) and topical lincosamides (clindamycin) as monotherapies compared with other treatments in people with moderate to severe acne and decided to make a negative ('do not use') recommendation for topical or oral antibiotics as monotherapies or in combination.

Factors to take into account at review

The committee agreed that all treatment options should be given as a 12-week course, as this allows treatment to reach its maximum effect, it is consistent with current practice and also the most common course length in the evidence; treatment should be reviewed at 12 weeks to determine if it is effective and tolerable.

The committee were aware of the increased risk of developing antibiotic resistance following long-term use of antibiotics and made a weak ('consider') recommendation to stop the oral antibiotic component of combined topical and oral treatments after the 12-week review, if the acne is completely clear at this point, but to continue the oral antibiotic (alongside topical treatment) for up to 12 more weeks if acne has not completely cleared. For the same reason, the committee recommended that treatments including topical or oral antibiotics last no longer than 6 months. The committee did not make a recommendation on length of treatment for other topical treatments, as they expressed the view that it was safe for these to be continued for longer, when appropriate.

The committee took into account the principles of antimicrobial guidance and policy, as outlined in the NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use, as well as the Global action plan on antibiotic resistance from the World Health Organization. All of these antibiotic treatments increase the risk of antimicrobial resistance and noted that people should be aware of the principles of antimicrobial stewardship when considering treatments for acne.

Oral isotretinoin

The committee noted the high clinical effectiveness of oral isotetinoin, as demonstrated in the NMA, and confirmed that this finding was consistent with their clinical experience. However, after taking into account the MHRA safety advice on isotretinoin, and specifically the possibility of psychiatric side effects, the committee agreed to define the situations where the benefits outweighed the risks.

The committee re-iterated the MHRA safety advice that it should be prescribed through a consultant dermatologist-led team to ensure that those who are taking it are advised about

the important safety issues associated with this medicine, and monitored as needed, including the person's psychological wellbeing and the need for contraceptive use.

The committee noted from the evidence that results were almost exclusively derived from trials testing oral isotretinoin in dosages of at least 0.5 mg/kg/day, and that total cumulative doses of at least 120 mg/kg in a single course were more effective compared with total cumulative doses lower than 120 mg/kg in a single course. There was some evidence from pairwise meta-analysis showing fewer side effects of mucosal or cutaneous changes with lower dose isotretinoin (<0.5 mg/kg/less frequently, total cumulative dose <120mg/kg) compared to a higher dose (≥0.5/mg/kg/day, total cumulative dose ≥120mg/kg). After reviewing the evidence, and based on their clinical experience, the committee decided to recommend a daily dose of 0.5 to 1 mg/kg. The committee agreed based on expertise and clinical experience that people who have an intolerance or are at risk of significant adverse effects are likely to require dosage adjustment as some adverse events are dose dependent. They decided to recommend a reduced dose for people with severe nodulo-cystic acne to avoid an acute flare. The committee also discussed that particular care needs to be taken when prescribing isotretinoin for people with a past or current history of a mental health disorder, for example depression by giving a lower dose to see whether it is tolerated. People with abnormal laboratory test results would require a dose reduction (for example renal impairment, elevated lipid profile and abnormal haematological profile).

The evidence suggested that a cumulative dose of 120 to 150 mg/kg is effective, but it was known from the committee's experience that sometimes clearance of acne lesions may occur before this has been reached. Therefore, they recommended that, as long as clearance is sustained for 4 to 8 weeks, treatment could be discontinued before the total cumulative dose of 120 to 150 mg/kg has been reached.

The committee noted that a recent drug safety update specifically reminded healthcare professionals of adverse events related to mental health. They therefore emphasised that people taking oral isotretinoin should have their psychological wellbeing reviewed so that changes can promptly be recognised and addressed. They also recommended that advice should be given on how to get help when a person feels that their mental health is affected or worsening so that they can be seen promptly when needed.

The committee noted that the evidence for lower dose oral isotretinoin was limited, and therefore made a research recommendation to investigate its effects further.

Physical treatments

The committee noticed that a number of physical treatments (light therapies) ranked in a high position in the NMA of efficacy. The largest size of evidence was for photodynamic therapy, based on 298 observations. However, the committee inspected the network plot and noted that the evidence of photodynamic therapy versus placebo was very thin; no other light therapy had been directly compared with placebo, and the only (indirect) comparisons were via photodynamic therapy. There was limited evidence from pairwise meta-analysis showing greater participant reported improvement in those using pulsed dye laser compared to those using blue and red light photochemical therapy. Overall, the committee decided not to make a strong recommendation because these treatments had a more limited evidence base compared with pharmacological treatments and the clinical experience with light therapies for the treatment of acne is very limited within the NHS context. Instead, they made a weaker ('consider) recommendation for photodynamic therapy, which had the largest evidence base among physical therapies, as an alternative option for people with moderate to severe acne aged 18 and over, if other treatments are ineffective, not tolerated or contraindicated. The committee acknowledged that existing evidence on light therapies is limited but promising and therefore also made a research recommendation. In addition, the committee noted the lack of any evidence on chemical peels in the treatment of people with moderate to severe acne and their promising results in people with mild to moderate acne, and made a research recommendation for chemical peels for all levels of severity of acne.

Pairwise meta-analysis

Evidence showed that topical treatments, such as retinoids, were associated with skin irritation. For this reason, the committee recommended when beginning topical treatments to start with alternate-day or short contact application.

Pairwise evidence indicated higher cumulative and daily doses of oral isotretinoin were associated with fewer relapses than lower doses, but more mucosal and cutaneous side effects. However, even with lower doses most people did not relapse. The committee discussed the issue around relapse and concerns about not stopping too early. However, they decided after balancing the potential adverse events and effectiveness, that for some people based on clinical judgement, treatment can be complete before a total cumulative dose of 120 to 150mg/kg is reached if there is sustained clear skin for 4 to 8 weeks.

Cost effectiveness and resource use

No published economic evidence was identified. The committee considered the results of the guideline economic analysis when making recommendations, which was informed by the NMAs conducted for the guideline. Therefore, the strengths and limitations of the NMA characterise the guideline economic analysis as well. Results of the guideline economic analysis were partially applicable to the NICE decision-making context, as the QALY estimates were based on the committee's expert opinion due to lack of relevant data of adequate quality. On the other hand, resource use and costs were directly relevant to the NHS context as they reflected clinical practice in England. The guideline base-case economic analysis was overall characterised by minor methodological limitations, so the committee were confident to use its findings to support recommendations. The committee was aware that discontinuation data were not available for a number of treatments, so other treatments served as proxies (based on committee's expert opinion) to inform discontinuation where relevant data were not available. Nevertheless, they noted that the impact of discontinuation data on the results of the economic model was relatively small as it affected only costs associated with discontinuation and not outcomes; this is because efficacy data used in the economic analysis were taken from intention-to-treat rather than completer analysis, where possible, and therefore they reflected effects on both those completing treatment and those discontinuing treatment early.

For costing purposes, the economic analysis selected one intervention as a representative from each treatment class modelled. The criteria for selecting interventions to represent each treatment class were the intervention availability and usage in the UK and other practicalities of use (e.g. a combination of topical treatments available in a single formulation was preferred to combinations that are only available as separate formulations); the evidence base for each intervention within class; the risk of side effects of individual interventions within a class; and, for pharmacological treatments, the drug acquisition cost (drugs with lower acquisition costs were preferred). The committee agreed that these were important factors to take into account and recommended specific interventions that were considered in economic modelling.

The results of the economic analysis suggested that all assessed topical, oral and physical treatments are more cost-effective for people with moderate to severe acne compared with GP care. Among pharmacological treatments that could be used as first-line treatment options for people with moderate to severe acne, combined topical tretinoin with clindamycin, combined topical adapalene with benzoyl peroxide and oral lymecycline, combined azelaic acid with oral lymecycline, and combined topical adapalene with benzoyl peroxide were among the most cost-effective treatment options, without considerable differences in their relative cost-effectiveness. This finding supported a recommendation for these four alternative options as first-line treatments for this population (with oral doxycycline and oral lymecycline being considered as equal alternatives based on clinical criteria and acquisition costs), with the final choice being determined following shared decision-making with the

person with acne, after taking into account their values and preferences on the benefits, risks and other related characteristics of each of the four treatment options.

The committee noted that topical clindamycin was found to be more cost-effective than the fixed combination of topical adapalene with benzoyl peroxide which was recommended as a treatment option, but on the other hand it was less clinically effective and the committee decided not to recommend it as a monotherapy due to the risk of development of antimicrobial resistance.

The committee noted the high relative cost-effectiveness of oral isotetinoin, despite its high intervention cost (which involves prescribing and monitoring by a consultant dermatologist-led team), which supported relevant recommendations.

The committee noted that benzoyl peroxide was a cost-effective treatment option, albeit less cost-effective compared with other recommended first-line treatments; this finding supported a recommendation for use of benzoyl peroxide for people with acne who do not want topical retinoids or topical or oral antibiotics or for whom these are contra-indicated.

The committee noticed the middle cost-effectiveness ranking of photodynamic therapy compared with other assessed treatments and agreed that this justified the weak ('consider') recommendation for photodynamic therapy as an option for people with moderate to severe acne aged 18 and over, if other treatments are ineffective, not tolerated or contraindicated.

The committee advised that the recommendations for first-line treatments largely reflect current practice, but discussions on the advantages and disadvantages of each option with the person may mean additional resource use (for example, if longer or more consultations are needed). This will, however, likely to lead to later benefits and reductions in resource use from better understanding and compliance with medication. The recommendation against oral or topical antibiotics used as monotherapy or in combination may lead to a significant change in current clinical practice, as topical and oral antibiotics are often used as a monotherapy or in combination for the treatment of acne vulgaris, in particular moderate to severe forms. Currently, some antibiotic treatment is not reviewed and given indefinitely, so the recommended 6-month time limit will be a change in practice. This could have related cost savings and benefits of reduced antibiotic resistance. The recommendation not to use antibiotic monotherapy or combined topical antibiotic and oral antibiotic treatment should lead to substantially lower prescribing of antibiotic treatments for acne vulgaris, and associated savings.

The recommendations for oral isotretinoin are expected to reinforce current practice, but may potentially lead to additional resource use, for example, if referral to mental health services is made or if longer or more consultations are needed. However, this is expected to lead to future benefits and cost savings, with reduction in potential adverse outcomes and shorter overall duration of treatment. Finally, photodynamic therapy is not part of current practice in the NHS for the management of acne, therefore, the recommendation is expected to result in a change in current practice and have some impact on resources and training. However, this impact is not expected to be substantial, because this is only a weak ('consider') recommendation, the majority of dermatology centres across the country already have photodynamic therapy facilities, and the proportion of people with acne fulfilling the criteria for photodynamic therapy is expected to be rather low.

Other factors the committee took into account

The committee recommended single formulations of combined topical treatments for practicality and cost issues. They advised that combined topical treatments that are not available as fixed combinations need to be applied separately and thus are impractical to use, but also impractical and potentially costly for pharmacists to prepare on an individual basis.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1, 1.5.2 and 1.5.4 to 1.5.12, 1.5.15 to 1.5.21 as well as 1.5.24 and 3 research recommendations on the effectiveness of a reduced dose of oral isotretinoin, physical modalities and the effectiveness of chemical peels in the NICE guideline. Other evidence supporting these recommendations can be found in the evidence reviews on management options for moderate to severe acne (pairwise analysis – evidence report F2).

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Appendices

Appendix A – Review protocol

Review protocol for review question: For people with moderate to severe acne vulgaris what are the most effective treatment options?

A single review protocol and literature search was used to identify randomised trials of treatments for acne. Outcomes were prioritised for either pairwise or network meta-analysis (NMA) and the evidence was divided according to the severity of acne into mild to moderate and moderate to severe categories. The evidence was then summarised in four separate reviews covering the treatment of:

- mild to moderate acne (NMA)
- mild to moderate acne (pairwise meta-analysis)
- moderate to severe acne (NMA)
- moderate to severe acne (pairwise meta-analysis)

Table 6: Review protocol

Field	Content
PROSPERO registration number	CRD42020154100
Review title	Comparative effectiveness, acceptability and tolerability of topical or oral pharmacological and physical interventions in the treatment of acne vulgaris: a systematic review using network and pairwise meta-analysis
Review question	2.1 What is the effectiveness of topical treatments individually or in combination in the treatment of acne vulgaris? 3.1 What is the effectiveness of oral antibiotic treatments in the treatment of acne vulgaris? 4.1 What is the effectiveness of combining an oral antibiotic with a topical agent compared to an oral antibiotic alone in the treatment of acne vulgaris? 5.1 What is the optimal duration of antibiotic treatments (topical and systemic) for acne vulgaris? 6.1 What is the effectiveness of oral hormonal contraceptives in the treatment of acne vulgaris? 6.2 What is the effectiveness of non- hormonal contraceptive anti-androgens (including spironolactone) in the treatment of acne vulgaris? 6.3 What is the effectiveness of metformin in the treatment of acne vulgaris?

Field	Content
	8.1 What is the effectiveness of oral isotretinoin in the treatment of acne vulgaris? 9.1 What is the effectiveness of physical treatments for acne vulgaris?
Objective	The objective of this review is to establish which topical or oral pharmacological and physical interventions are effective, acceptable and tolerable in the treatment of acne vulgaris.
Searches	• The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • Date: No restriction • Language of publication: English language only • Publication status: Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias. Unpublished data will also be excluded. • Standard exclusions filter (animal studies/low level publication types) will be applied • For each search, the principal database search strategy is quality assured by a second information specialist using an adaption of the PRESS 2015 Guideline Evidence-Based Checklist Other search methods will involve scanning the reference lists of all eligible systematic reviews for published studies meeting inclusion criteria.
Condition or domain being studied	Acne vulgaris
Population	Inclusion: People with acne vulgaris, of all ages and levels of symptom severity. Studies need to provide data specific to people with mild to moderate acne, and/or people with moderate to severe acne. See under 'Analysis of sub-groups' for the approach followed in order to categorise population in the studies into mild to moderate acne or moderate to severe acne. All settings (community, primary, secondary, and tertiary health care) will be considered. Exclusions: • Neonatal acne • People with post-inflammatory dyspigmentation • Trials recruiting specifically people with acne vulgaris and polycystic ovary syndrome (PCOS) • Trials of maintenance treatment ('relapse prevention' trials), which recruit people currently in remission or people who have responded to treatment or who have had successful treatment or who are reported to have received primary or 'acute' treatment immediately prior to randomisation to maintenance treatment. • Trials that have specifically recruited people who have not responded to previous treatment (refractory or resistant acne) for

Field	Content
	the same episode of acne; however, trials of people with recurrent or persistent acne, who are treated for a new episode of acne, will be included • Trials that include all ranges of severity • Trials with indirect population: Where studies with a mixed population (i.e. include people with acne vulgaris and another condition, e.g. hirsutism) are identified, those with <66% of the relevant population will be excluded, unless subgroup analysis for acne vulgaris is reported.
Intervention	Interventions will be categorised into the following classes, and, if relevant, subclasses (the list is non-exhaustive): ➢ **TOPICAL TREATMENTS** **Abrasive/cleaning agents** • Aluminium oxide [own class] **Anthelmintics** • Cysticide (praziquantel) [own class] • Class of avermectins: ivermectin **Antibacterials** • Class of triclocarban and triclozan **Antibiotics** • Class of sulphones (dapsone) • Fusidic acid (sodium fusidate) [own class] • Class of lincosamides (for example clindamycin) • Class of macrolides (for example clarithromycin, erythromycin with zinc acetate dihydrate) • Class of nitroimidazoles (metronidazole) • Class of carboxylic acids (mupirocin) • Class of penicillins ○ Sub-class of natural (for example almecillin) ○ Sub-class of aminopenicillins (for example ampicillin) ○ Sub-class of β-lactamase-resistant (for example methicillin) ○ Sub-class of carboxypenicillins (for example ticarcillin) ○ Sub-class of ureidopenicillins (for example azlocillin) ○ Sub-class of other penicillins (mecillinam, pivmecillinam hydrochloride) • Class of pleuromutilins (for example retapamulin) **Antiseptics**

Field	Content
	• Benzoyl peroxide (trade: Acnecide, Brevoxyl, Panoxyl) [own class] • Chlorhexidine gluconate (trade: Acnemed, Cepton) or digluconate [own class] **Dicarboxylic acids** • Azelaic acid [own class] **Vitamin B3** • Nicotinamide (niacinamide) [own class] **Retinoids or retinoid-like agents** • Class of retinoids or retinoid-like agents (adapalene, isotretinoin, retinol, tazarotene, tretinoin) **Combined interventions** • Benzoyl peroxide & potassium hydroxyguinoline sulfate [own class] • Class of benzoyl peroxide & retinoid (benzoyl peroxide + adapalene) • Class of benzoyl peroxide & lincosamide (benzoyl peroxide + clindamycin) • Class of lincosamides & retinoid (clindamycin + tretinoin) • Class of macrolides & retinoid (erythomycin + retinoid) [topical] • Germolene (phenol 1.2% + chlorhexidine diculconate [own class] ➢ **ORAL ANTIBIOTICS** • Class of carbapenems (for example imipenem, meropenem) • Class of carbapenems with cilastatin (imipenem with cilastatin) • Class of carbapenems with b lactamase inhibitor (meropenem with vaborbactam) • Class of cephamycins/cephalosporins ○ Sub-class of 1st-generation (for example cefadroxil) ○ Sub-class of 2nd-generation (for example cefaclore) ○ Sub-class of 3rd-generation (for example cefdinir) ○ Sub-class of 4th-generation (for example cefozopran) ○ Sub-class of 5th-generation (for example ceftolozane) • Class of cephamycins/cephalosporins with β-lactamase inhibitor (for example ceftraroline or ceftazidime with avibactam, cefoperazone with sulbactam, ceftolozane with tazobactam) • Class of sulphones (dapsone) • Fusidic acid (sodium fusidate) [own class] • Class of lincosamides (for example clindamycin) • Class of macrolides (for example clarithromycin, erythromycin) • Class of monobactams (aztreonam)

Field	Content

	• Class of monobactams with β-lactamase inhibitor (aztreonam with avibactam)
	• Class of penicillins
	  ○ Sub-class of natural (for example almecillin)
	  ○ Sub-class of aminopenicillins (for example ampicillin)
	  ○ Sub-class of β-lactamase-resistant (for example methicillin)
	  ○ Sub-class of carboxypenicillins (for example ticarcillin)
	  ○ Sub-class of ureidopenicillins (for example azlocillin)
	  ○ Sub-class of other penicillins (mecillinam, pivmecillinam hydrochloride)
	• Class of penicillin with β-lactamase inhibitor (for example co-amoxiclav [amoxicillin with clavulanic acid], piperacillin with tazobactam, ticaricillin with clavulanic acid, sultamicillin [ampicillin with sulbactam])
	• Class of penicillin with flucloxacilin (co-fluampicil [ampicillin + flucloxacilin])
	• Class of pleuromutilins (for example retapamulin)
	• Class of quinolones
	  ○ Sub-class of 1st-generation (for example rosoxacin)
	  ○ Sub-class of 2nd-generation (for example ofloxacin)
	  ○ Sub-class of 3rd-generation (for example temafloxacin)
	  ○ Sub-class of 4th-generation (for example sitafloxacin)
	• Class of tetracyclines (for example doxycycline, oxytetracycline)
	• Trimethoprim [own class]
	• Co-trimoxazole (trimethoprim-sulfamethoxazole; TMP-SMX) [own class]
	
	➢ **TOPICAL TREATMENTS COMBINED WITH ORAL ANTIBIOTICS**
	
	➢ **ORAL HORMONAL CONTRACEPTIVES AND HORMONE-MODIFYING AGENTS**
	• Co-cyprindiol (ethinylestradiol + cyproterone acetate) [own class of combined oral contraceptive]
	• Class of combined oral contraceptives
	  ○ Sub-class of 2nd generation (oestrogen, for example ethinylestradiol or estradiol or mestranol combined with levonorgestrel or norethisterone)
	  ○ Sub-class of 3rd generation (oestrogen, for example ethinylestradiol combined with desogestrel or gestodene or norgestimate)
	  ○ Sub-class of 4th generation (oestrogen, for example ethinylestradiol or estradiol combined with dienogest or drospirenone or nomegestrol acetate)
	
	Monophasic and phasic combined oral contraceptives containing the same hormones will be analysed as separate interventions within their sub-class.
	
	• Class of progestogen-only oral contraceptives
	  ○ Sub-class of 1st generation (for example medroxyprogesterone acetate)
	  ○ Sub-class of 2nd generation (for example levonorgestrel, norethisterone/ norethindrone)
	  ○ Sub-class of 3rd generation (for example desogestrel, norgestimate, gestodene)

Field	Content
	○ Sub-class of 4th generation (for example dienogest, drospirenone, nomegestrol acetate) • Class of selective aldosterone receptor antagonists (for example spironolactone alone or combined with furosemide or hydroflumethiazide [co-flumactone], eplerenone, canrenone) • Class of 5α-reductase inhibitors (dutasteride, finasteride, tamsulosin with dutasteride) • Class of other non-steroidal anti-androgens (for example abiraterone acetate, apalutamide, bicalutamide, cyproterone acetate, clormadinone acetate, enzalutamide, flutamide) • Metformin [own class] ➢ **ORAL ISOTRETINOIN** • Class of oral retinoid and total cumulative dose ≥ 120mg/kg (single course) ○ Sub-class of daily dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day) ○ Sub-class of alternate day dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day) ○ Sub-class of less frequent or other dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day) • Class of oral retinoid and total cumulative dose < 120mg/kg (single course) ○ Sub-class of daily dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day) ○ Sub-class of alternate day dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day) ○ Sub-class of less frequent or other dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day) ➢ **PHYSICAL TREATMENTS** • Class of chemical peels ○ Sub-class of superficial peels ○ Sub-class of moderate peels ○ Sub-class of deep peels for example amino fruit acid, glycolic acid, Jessner's peel, lactic acid, salicylic acid, trichloroacetic acid [TCA]; these will be categorised into different sub-classes as reported in the included studies, according to the concentration of their active ingredient and treatment duration. • Comedone extraction [own class] • Class of photothermal therapy (for example fractional erbium glass laser) • Class of photochemical therapy (for example blue or red light and their combination) • Class of photochemical and photothermal therapy (for example potassium titanyul phosphate laser, Intense Pulsed Light [IPL], Pulsed Dye Laser) • Class of photodynamic therapy (for example 5-aminolevuliniv acid [ALA], liposomal methylene blue gel, methylaminolevulinate [MAL]) • Smoothbeam™ laser [own class] • Photopneumatic therapy (for example intense pulsed light + vacuum) • Radiofrequency (for example fractional microneedling, bipolar)

Field	Content
	Combined interventions within and across classes will be considered. Only drug classes available in the UK will be considered. To estimate class effects, we will consider any intervention belonging to a class, irrespective of its availability in the UK. However, we will only report individual drug effects for interventions that are currently (or soon expected to be) available in the UK. These may include pharmacological interventions that are (or soon expected to be) licensed in the UK for the treatment of acne or another condition. If existing evidence is not adequate to allow estimation of individual drug effects within each class, we will exclude drugs that are not available in the UK. We will include pharmacological interventions listed above, alone or in combinations, administered in fixed or flexible doses within the therapeutic range recommended by the British National Formulary (BNF), or, if not available in the UK, recommended by the US Food and Drug Administration (FDA). The only exception will be oral isotretinoin, for which we will allow lower doses to be considered, as there is indication that these are efficacious while the rate of isotretinoin-related side effects is lower. Trial arms evaluating a class or sub-class of pharmacological interventions that is of interest, as determined above (for example a mixture of oral macrolides, a mixture of COC), rather than an individual drug, will be included as separate nodes within the class. However, trial arms evaluating broad types of interventions that are wider than classes as defined above (for example oral antibiotics) will be excluded from consideration. We will consider substantially different durations of treatment within the same class/drug as different interventions, that is as different network nodes, as duration of treatment may impact on its effects. We will consider the following durations of treatment: 0 to <6 weeks; ≥6 to <12 weeks, ≥12 to <24 weeks, ≥24 weeks. We will not consider in the NMA interventions that do not meet inclusion criteria, unless they act as the sole connectors of the interventions of interest in the network. In this case, interventions not meeting inclusion criteria will be included in the NMA but will not form part of the decision problem. A network diagram for all outcomes of interest will be constructed to explore whether all interventions are connected to the network. If more than one networks are formed, then separate NMAs will be conducted for each network, as long as the network contains at least 3 interventions that are part of the decision problem. If pairs of interventions are not connected to a network, they will be analysed in pairwise meta-analysis. We assume that any individual that meets all inclusion criteria is, in principle, equally likely to be randomized to any of the interventions in the synthesis comparator set.
Comparator	• No treatment • Waiting list • Pill placebo • Other active intervention • Sham physical treatment
Types of study to be	Included study designs:

Field	Content
included	• Systematic reviews/meta-analyses of randomised controlled trials (RCTs) • RCTs (individual or cluster); this includes RCTs of topical or physical treatments that randomise different parts of body (for example left-right side of face/body) in each participant Excluded study designs: • Quasi-randomised or non-randomised controlled trials • Case-control studies • Cohort studies • Cross-sectional studies • Epidemiological reviews or reviews on associations • Non-comparative studies Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
Other exclusion criteria	• Trials with <50% completion data (drop-out of ≥ 50%)
Context	Recommendations will apply to those receiving care in any healthcare setting (for example community, primary care, secondary care, tertiary care). For antibiotics, the committee will consider the evidence in conjunction with considerations regarding antimicrobial resistance patterns (for example ESPAUR report), the safety of the specific antibiotic as determined by any relevant MHRA Drug Safety Update (https://www.gov.uk/drug-safety-update) and Summary of Product characteristics (https://www.medicines.org.uk/emc), and the principle that the use of antibiotics should be limited or optimised where possible. Only the short-term safety of interventions in the treatment of acne vulgaris will be covered. For the long-term safety of interventions, see BNF and MHRA. Relevant legislation and national policy will also inform the guideline [see 'Developing NICE guidelines: the manual' (p. 102)].

Primary outcomes (critical outcomes)	**Critical outcomes**
	Efficacy
	• Clinician-rated improvement at treatment endpoint
	  ○ % change in acne lesion count
	  ○ change or final score on a validated acne severity scale
	We will prioritise for extraction and analysis the mean of the % change in acne lesion count, where reported together with a standard error (or a standard error can be derived). If this is not reported, mean change in lesion counts from baseline will be prioritised, as long as it is reported with a standard error and also mean and standard error of counts at baseline. If this is not reported, the mean counts and standard error at baseline and treatment endpoint will be prioritised, accounting for correlations between baseline and final counts, exploring such correlations from studies reporting change, baseline and final scores.

Field	Content
	In studies where such data on lesion counts are not reported, we will extract data on validated acne severity scale scores, if the latter are available. We will prioritise mean % change in scale if it is reported with a standard error, followed by mean change from baseline if it is reported with a standard error, and baseline mean score and standard error are available. If neither of these are reported we will extract mean scores at baseline and treatment endpoint, accounting for correlations between baseline and final scores using a correlation based on studies that report all of change, baseline and final scores. These two types of data will be synthesised, where appropriate (as explained below), to jointly estimate treatment effects on the two outcomes, to estimate a single clinician-rated measure of outcome, expressing mean % of improvement of acne symptoms. <u>Regarding mean % change in acne lesion count:</u> If summaries for total lesion count are reported, these will be extracted and used in the analysis. In studies that do not report total lesion count, but do report count of different types of lesions, we will estimate the change in total lesion count from reported data, where this is possible. If this is not possible, we will extract the change in lesion count for the following types of lesions in this hierarchy, as a proxy for total lesion count: • All inflammatory lesions (pustules, papules, nodules, cysts) • Sum of any of the types of inflammatory lesions, according to data availability • Pustules • Papules • Nodules • Cysts • Non-inflammatory lesions (comedones) <u>Regarding data on validated acne severity scale scores:</u> We will compare the relative effects on mean % change in acne scale scores and mean % change in acne lesion score in studies that report both. This will be achieved by visual inspection of a scatter plot of relative effect on the scale vs count, by scale, and also by weighted linear regression. Only scales with a sufficiently good visual fit and model fit in the regression will be included. For scales where these relative effects are found to be sufficiently linearly related, we will include the respective extracted scale score data in the NMA from studies reporting only this type of outcome, using a bivariate NMA model. For scales where relative effects measured using the two types of outcomes are not sufficiently linearly related, the extracted data will not be considered in the NMA and studies reporting only symptom scale scores on those scales (and not acne lesion count) will be excluded from the analysis. Only one acne symptom scale will be used per study. If a study reports data on more than one scale, we will prioritise data from scales according to the extent of the strength of the linear relationship between their relative effects and the relative effects obtained from change in acne lesion count. Correlations between counts of different types of acne lesions and between acne lesions and acne symptom scales will also be

Field	Content

	sought in published literature (for example Allen & Smith, 1982).
	• Participant-reported improvement at treatment endpoint
	  ○ Change in acne severity or symptoms (e.g. assessed using global acne score)
	• Prevention of scarring at any follow-up
	  ○ Final / change in number of scars from baseline
	  ○ Incidence of scarring
	
	Reference:
	Allen BS, Smith JG Jr. Various parameters for grading acne vulgaris. Archives of Dermatology 1982; 118(1): 23-5.

Secondary outcomes (important outcomes)	**Important outcomes** ***Acceptability*** • Treatment discontinuation for any reason (numbers of trial participants "leaving the study early", "leaving the study before treatment completion" or "loss to follow-up") by treatment endpoint ***Tolerability*** • Treatment discontinuation due to side effects by treatment endpoint ***Relapse*** • Relapse after treatment at follow-up ***Side effects*** The following specific short-term side effects will be assessed for comparisons of treatments within the same class or those that involve an inactive arm (e.g. placebo, no or sham treatment): - Topical treatments, oral antibiotics or combination treatments: skin irritation (e.g. burning or tingling, dryness/irritation, swelling) - Topical retinoids: sensitivity to light - Oral antibiotics: gastrointestinal side effects; thrush candidiasis - Hormonal contraceptives and hormone-modifying agents: breast tenderness; neurological side effects (headache/migraine, mood disturbance, nausea); sexual dysfunction - Hormonal contraceptives: breakthrough bleeding; mood disturbance - Hormone-modifying agents: hepatobiliary side effects. For aldosterone receptor antagonists: renal side effects - Metformin: gastrointestinal side effects - Oral isotretinoin: change in mucosal and/or cutaneous condition (e.g. new chelitis); change in participant's mood (as assessed

Field	Content
	by score on validated scale); diagnosis of any psychiatric disorder (e.g. depressive disorder); suicidality - Physical treatments: persistent skin redness of 'treated' area; changes in pigmentation (e.g. hypopigmentation) - Chemical peels: heart, kidney or liver damage; infection of 'treated' area - Comedone extraction: infection of 'treated' area; pain of 'treated' area - Energy-based devices: skin irritation
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. As the review question was selected as high priority for health economic analysis, it will be subject to dual weeding and study selection; any discrepancies above 10% of the dual weeded resources will be resolved through discussion between the first and second reviewers or by reference to a third person. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). All data extraction will quality assured by a senior reviewer. Draft excluded studies and evidence tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair. An intention-to-treat (ITT) approach will be taken and where possible ITT data will be extracted; if both ITT and completer data are reported, the former will be preferred; completer data will be used only if ITT data are not reported**.**
Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the relevant version of the Cochrane RoB tool, v2. checklist (i.e. for parallel group or individually-randomised cross-over trials), as described in Developing NICE guidelines: the manual.
Strategy for data synthesis	**Method of analysis** <u>Network meta-analysis</u> Network meta-analysis (NMAs) will be used to synthesise clinician-rated improvement, prevention of scarring, acceptability and tolerability for all eligible interventions that are connected to one or more networks of at least 3 interventions. NMA will be conducted within a Bayesian framework using Markov Chain Monte Carlo simulation techniques implemented in WinBUGS 1.4.3 (Lunn 2000; Spiegelhalter 2003). Non-informative priors will be initially used, but if the data are sparse or there are convergence problems, then we will use evidence-based priors for the between studies standard deviation (Turner 2015, Rhodes 2015). To test whether prior estimates have an impact on the results, two chains with different initial values will be run simultaneously for each analysis. Convergence will be assessed by visually inspecting the mixing of the two chains in the history plots and the Brooks Gelman-Rubin diagram in WinBUGS (Brooks 1998). For the synthesis of dichotomous outcomes (discontinuation for any reason; discontinuation due to side effects) a binomial likelihood and logit link model will be used (Dias 2013a). The output of this analysis will be expressed as log-odds ratios (LORs) with 95% credible intervals (95% CrI) between all pairs of treatments assessed. For the synthesis of rate data (incidence of scarring) a Poisson likelihood and log link will be used. The output of this analysis will be expressed as log-rate ratios (LRRs) with 95% CrIs between all pairs of treatments assessed. For the synthesis of continuous data (mean of the % change in the total lesion count) a normal likelihood will be used with an identity link for the proportionate reduction in counts at treatment endpoint relative to baseline. The output of this analysis will be

Field	Content
	expressed, for each treatment relative to the reference treatment, as the difference in the mean percentage reduction in total lesions between baseline and treatment endpoint. If some studies do not report data on total lesion counts, a bivariate NMA model will be fitted which relates the treatment effects on a clinician-related acne symptom scale to treatment effects on the mean proportionate reduction from baseline. We will also evaluate the ranking of each treatment and 95% CrI in each analysis, where a rank of 1 indicates best treatment. The goodness of fit of each model will be tested by comparing the posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, with the number of data points in the model (Dempster 1997). Smaller values of the residual deviance are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the analysis (each study arm contributes one data point) (Spiegelhalter 2002). Models will also be compared using the deviance information criterion (DIC), a measure of model fit that is equal to the sum of the posterior mean deviance and the effective number of parameters, thus penalising model fit for model complexity; lower values are preferred and typically differences of at least 3 points are considered meaningful (Dias 2013a; Spiegelhalter 2002). The posterior median between-study standard deviation, which measures the heterogeneity of treatment effects estimated by trials within contrasts, will also be used to compare models. Inconsistency between direct and indirect evidence will be explored by comparing the fit of a model assuming consistency with a model which allowed for inconsistency (also known as an unrelated mean effects model (Dias 2013b). Deviance plots, in which the posterior mean deviance of the individual data points in the inconsistency model are plotted against their posterior mean deviance in the consistency model, will be inspected in order to identify studies which may have contributed to loops of evidence where inconsistency may be present. If these analyses identify potential inconsistency, further checks will be conducted using a node-split approach implemented in R using the gemtc package in R. This method permits the direct and indirect evidence contributing to an estimate of a relative effect to be split and compared (Dias 2013b; van Valkenhoef & Kuiper, 2016). If we find evidence of inconsistency, studies contributing to loops of evidence where there may be inconsistency will be checked for data accuracy and assessment of study inclusion will be revisited against inclusion/exclusion criteria. Baseline characteristics will be checked to identify any differences in effect modifiers across studies in loops identified as potentially inconsistent. Analyses will be repeated if corrections in the data extraction or study inclusion are made. If an important effect modifier is identified, then this may be explored in subgroup analyses if sufficient evidence is available. However, if evidence of inconsistency is still present following data corrections, revisiting inclusion criteria, exploring effect modification, no further studies will be excluded from the analysis, as their results cannot be considered as less valid than those of other studies solely because of the inconsistency findings. The presence of inconsistency in the NMA will be highlighted and results will be interpreted accordingly. Sensitivity analysis: If there is sufficient evidence, we will explore bias adjustment models, where evidence from studies at high or unclear risk of bias will be down-weighted (Dias 2010; Welton 2009). Appraisal of methodological quality of the NMA: To test the robustness of the treatment recommendations based on the NMA to

Field	Content
	potential biases or sampling variation in the included evidence, we will undertake threshold analyses (Phillippo 2019). These will be carried out at two levels: (i) at a study level, assessing the influence of individual study estimates on the conclusion of the analysis and (ii) at a contrast level, where the influence of the combined evidence on each treatment contrast is considered (Caldwell 2016; Phillippo 2018; Phillippo 2019). Pairwise meta-analysis Pairwise meta-analysis will be used for all outcomes not included in NMA, i.e. participant-reported improvement, relapse and side effects. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ **References** Brooks SP, Gelman A (1998) Alternative methods for monitoring convergence of iterative simulations. Journal of Computational and Graphical Statistics, 7, 434-455. Caldwell DM, Ades AE, Dias S, Watkins S, Li T, Taske N, Naidoo B, Welton NJ (2016) A threshold analysis assessed the credibility of conclusions from network meta-analysis. Journal of Clinical Epidemiology, 80, 68-76. Dempster A (1997) The direct use of likelihood for significance testing. Statistics and Computing, 7, 247-252. Dias S, Welton NJ, Marinho VCC, Salanti G, Higgins JPT, Ades AE (2010) Estimation and adjustment of bias in randomised evidence by using Mixed Treatment Comparison Meta-analysis. Journal of the Royal Statistical Society (A), 173(3), 613-629. Dias S, Sutton AJ, Ades AE, Welton NJ (2013a) Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Medical Decision Making, 33, 607-617. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE (2013b) Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Medical Decision Making, 33, 641-656.

Field	Content
	Lunn DJ, Thomas A, Best N, Spiegelhalter D (2000) WinBUGS-A Bayesian modelling framework: Concepts, structure, and extensibility. Statistics and Computing, 10, 325-337. Phillippo DM, Dias S, Ades AE, Didelez V, Welton NJ (2018) Sensitivity of treatment recommendations to bias in network meta-analysis. Journal of the Royal Statistical Society: Series A, 181, 843-867. Phillippo DM, Dias S, Welton NJ, Caldwell DM, Taske N, Ades AE (2019) Threshold Analysis as an Alternative to GRADE for Assessing Confidence in Guideline Recommendations Based on Network Meta-analyses. Annals of Internal Medicine, 170, 538-546. Rhodes KM, Turner RM, Higgins JPT (2015) Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. Journal of Clinical Epidemiology, 68, 52-60. Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A (2002) Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B, 64, 583-616. Spiegelhalter D, Thomas A, Best N, Lunn DJ (2003) WinBUGS user manual: version 1.4. Cambridge: MRC Biostatistics Unit. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JPT (2015) Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Statistics in Medicine, 34, 984-998. van Valkenhoef G, Kuiper J (2016) gemtc: Network Meta-Analysis Using Bayesian Methods. R package version 0.8-2. Available from: https://CRAN.R-project.org/package=gemtc Welton NJ, Ades AE, Carlin, JB, Altman DG, Sterne JAC (2009) Models for potentially biased evidence in meta-analysis using empirically based priors. Journal of the Royal Statistical Society (A), 172(1), 119-136.
Analysis of sub-groups	**Severity** For all outcomes, we will conduct separate analyses for people with • mild to moderate acne vulgaris • moderate to severe acne vulgaris. We will categorise studies according to level of severity as defined in each study. The committee will be consulted to classify a study to the appropriate network/analysis if acne severity of included participants is described as moderate or it is unclear (for example it includes participants on basis of lesion counts). The committee agreed the following criteria to categorise studies into one of two severity groups, when the study population is described as having moderate acne or if the level of severity is unclear:

Field	Content

	• If the number of nodules in every study participant is at least 3, the study population will be categorised as having moderate to severe acne.
	• If study participants have only non-inflammatory lesions (regardless of their number) and no inflammatory lesions, the study population will be categorised as having mild to moderate acne.
	• If all study participants have fewer than 35 inflammatory lesions each, the study population will be categorised as having mild to moderate acne.
	• If all study participants have ≥ 35 inflammatory lesions each, the study population will be categorised as having moderate to severe acne.
	• If the number of inflammatory lesions varies across the study participants, and the mean number of inflammatory lesions at baseline is
	  ○ ≤ 30, the study population will be categorised as having mild to moderate acne
	  ○ ≥40, the study population will be categorised as having moderate to severe acne
	  ○ above 30 but below 40, the study will be excluded as the population is not possible to assign to a mild to moderate or moderate to severe level.
	• If a study does not report the mean number of inflammatory lesions at baseline, it will be excluded.
	• If a study includes all ranges of severity, from mild to severe, without providing sub-group analyses by level of acne severity, it will be excluded.
	
	Sex
	Separate NMAs will be run for decisions regarding the male and female populations, in accordance with data reported in the included studies, where only appropriate interventions for each sex are included in the network (for example, excluding hormonal contraceptives for males). We assume there is no interaction between sex and treatment effects for interventions that are suitable for both sexes.
	
	Age
	If possible, a random effects meta-regression according to age will be conducted for NMA of efficacy (% change in acne lesion count), to specify outcomes for people ≤25 years of age and those >25 years of age.
	
	In order to include studies that do not report results by age-group, we will need to estimate proportion of participants below/above 25 years of age in studies of mixed population that don't report results by age. If this is not reported, proportions in age group can be approximated if the study reports age ranges, mean age and standard deviation, median age and quartile range, etc. This requires an assumption as to the distribution of age in the study population, which can be based on inspection of the reported summaries (normal if evidence of symmetry or log-normal if skewed).
	
	We will perform this analysis by age only if at least 90% of the studies meeting inclusion criteria provide sufficient information that would allow us to estimate the proportion of participants >25 and ≤25 years of age. If we are able to follow this approach, we will exclude the remaining studies that do not provide this information.
	
	If <90% of studies meeting inclusion criteria provide relevant information on age, then we will include all studies, irrespective of

Field	Content			
	the age of their population, in the NMA of efficacy (% change in acne lesion count), but will not perform meta-regression.			
Type and method of review	☒	Intervention		
	☐	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	20 October 2019			
Anticipated completion date	13 January 2021			
Stage of review at time of this submission	**Review stage**		**Started**	**Completed**
	Preliminary searches		☑	☑
	Piloting of the study selection process		☑	☑
	Formal screening of search results against eligibility criteria		☑	☑
	Data extraction		☑	☑
	Risk of bias (quality) assessment		☑	☑
	Data analysis		☑	☑
Named contact	**5a. Named contact**			

Field	Content
	National Guideline Alliance **5b. Named contact e-mail** AcneManagement@nice.org.uk **5e. Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and National Guideline Alliance
Review team members	National Guideline Alliance
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance, which is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists. NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/gid-ng10109/documents/committee-member-list NICE Guidelines Technical Support Unit: Professor Nicky J Welton, NICE Guidelines Technical Support Unit, Department of Population Health Sciences, Bristol Medical School Miss Caitlin Daly, NICE Guidelines Technical Support Unit, Department of Population Health Sciences, Bristol Medical School
Other registration details	Not applicable
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=154100
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels,

Field	Content	
	and publicising the guideline within NICE. • Peer-reviewed publications	
Keywords	Acne; acne severity; chemical peels; energy-based devices; hormone therapy; isotretinoin; laser therapy; light therapy; management; network meta-analysis; oral antibiotics; physical; systematic review; topical antibiotics; topical retinoids; treatment.	
Details of existing review of same topic by same authors	Not applicable	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information		
Details of final publication	www.nice.org.uk	

1 *Crl: credibility interval; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; RCT: randomised controlled trial*

Appendix B – Literature search strategies

Literature search strategies for review question: For people with moderate to severe acne vulgaris what are the most effective treatment options?

Clinical search

Topical interventions (including topical retinoids)

Date of initial search: 07/08/2019

Additional terms added and searched: 10/09/2019

Last searched: 07/05/2020

Database(s): Embase Classic+Embase 1947 to 2020 May 06, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 06, 2020

Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emczd
3	acne.tw.
4	or/1-3
5	exp topical antiinfective agent/ use emczd
6	exp Anti-Infective Agents, Local/ use ppez
7	5 or 6
8	exp antibiotic agent/ use emczd
9	exp Anti-Bacterial Agents/ use ppez
10	exp anthelmintic agent/ use emczd
11	exp Anthelmintics/ use ppez
12	(antibiotic* or anti biotic* or anti bacteri* or antibacteri* or bacteriocid*).tw.
13	(anthelminti* or antihelmint?i* or anti-helmint?i* or antiparasit* or anti-parasit* or vermifug*).tw.
14	adapalene/
15	aluminum oxide/ use emczd
16	amoxicillin/
17	ampicillin/
18	avermectin/ use emczd
19	azelaic acid/
20	benzoyl peroxide plus clindamycin/ use emczd
21	benzoyl peroxide/
22	(Benzoyl Peroxide/ and Clindamycin/) use ppez
23	cefaclor/
24	cefadroxil/
25	cefalexin/ use emczd
26	Cephalexin/ use ppez
27	cefixime/
28	cefotaxime/
29	cefradine/ use emczd
30	Cephradine/ use ppez
31	ceftaroline/ use emczd
32	ceftazidime/
33	ceftriaxone/
34	cefuroxime/
35	chlorhexidine gluconate/
36	clarithromycin/
37	clindamycin/
38	dapsone/
39	doxycycline/
40	erythromycin/
41	erythromycin plus isotretinoin/ use emczd
42	flucloxacillin/ use emczd
43	Floxacillin/ use ppez
44	fusidic acid/

#	Searches
45	isotretinoin/
46	isotretinoin/ and clindamycin/
47	ivermectin/
48	lymecycline/
49	metronidazole/
50	minocycline/
51	nadifloxacin/
52	nicotinamide/ use emczd
53	Niacinamide/ use ppez
54	nitroimidazole/ use emczd
55	ozenoxacin/
56	oxytetracycline/
57	penicillin G/
58	penicillin V/
59	(phenol/ and chlorhexidine digluconate/) use emczd
60	(phenol/ and chlorhexidine/) use ppez
61	piperacillin/
62	(pleuromutilin/ or pleuromutilin antibiotic agent/) use emczd
63	praziquantel/
64	pseudomonic acid/ use emczd
65	Mupirocin/ use ppez
66	retapamulin/ use emczd
67	retinol/ use emczd
68	Vitamin A/ use ppez
69	tetracycline/
70	ticarcillin/
71	retinoic acid/ use emczd
72	tazarotene/ use emczd
73	temocillin/ use emczd
74	tretinoin/ use ppez
75	triclocarban/ use emczd
76	triclosan/
77	trimethoprim/
78	zinc acetate/
79	(adapalene or aluminum oxide or ampicillin or amoxicillin or avermectin or az?laic acid or benzylpenicillin or benzyl penicillin or benzoyl peroxide or cefaclor or cefadroxil or cefalexin or cephalexin or cefixime or cefotaxime or cefradine or ceftaroline or ceftazidime or ceftriaxone or cefuroxime or cephalexin or cephalosporin* or cephamycin* or cephradine or chlorhexidine digluconate or chlorhexidine gluconate or clarithromycin or clindamycin or dapsone or diaminodiphenyl sulfone or doxycyclin* or erythromycin or floxacillin or flucloxacillin or fucidin or fusidic acid or fusidate sodium or sodium fusidate or germolene or isotretinoi* or ivermectin or lincosamide* or lymecycline or macrolide* or metronidazole or minocycline or nadifloxacin or niacinamide or nicotinamide or nitroimidazole or ozenoxacin or oxytetracyline or penicillin* or phenol or phenoxymethylpenicillin or piperacillin or pleuromutilin or praziquantel or cysticide or pseudomonic acid or mupirocin or quinoderm or quinolon* or retapamulin or retinoi* or retinol or tazarotene or temocillin or tetracyclin* or ticarcillin or tretinoin or triclocarban or triclosan or triclozan or trimethoprim or vitamin a or vitamin b3 or zinc acetate).tw.
80	or/7-79
81	(topical or topically or cream? or emulsi* or gel? or foam? or ointment* or solution? or lotion? or pad?).tw.
82	(ointment/ or exp gel/) use emczd
83	(Ointments/ or exp Gels/) use ppez
84	skin cream/
85	(cutaneous drug administration/ or topical drug administration/) use emczd
86	(Administration, Topical/ or Administration, Cutaneous/) use ppez
87	topical drug administration.fs.
88	(cutaneous or dermal or skin or transcutaneous or transdermal or percutaneous).tw.
89	or/81-88
90	4 and 80 and 89
91	limit 90 to english language
92	Letter/ use ppez
93	letter.pt. or letter/ use emczd
94	note.pt.
95	editorial.pt.
96	Editorial/ use ppez
97	News/ use ppez
98	exp Historical Article/ use ppez
99	Anecdotes as Topic/ use ppez
100	Comment/ use ppez
101	Case Report/ use ppez
102	case report/ or case study/ use emczd
103	(letter or comment*).ti.
104	or/92-103

#	Searches
105	randomized controlled trial/ use ppez
106	randomized controlled trial/ use emczd
107	random*.ti,ab.
108	or/105-107
109	104 not 108
110	animals/ not humans/ use ppez
111	animal/ not human/ use emczd
112	nonhuman/ use emczd
113	exp Animals, Laboratory/ use ppez
114	exp Animal Experimentation/ use ppez
115	exp Animal Experiment/ use emczd
116	exp Experimental Animal/ use emczd
117	exp Models, Animal/ use ppez
118	animal model/ use emczd
119	exp Rodentia/ use ppez
120	exp Rodent/ use emczd
121	(rat or rats or mouse or mice).ti.
122	or/109-121
123	91 not 122
124	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
125	124 use ppez
126	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
127	126 use ppez
128	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
129	128 use emczd
130	125 or 127
131	129 or 130
132	Meta-Analysis/
133	exp Meta-Analysis as Topic/
134	systematic review/
135	meta-analysis/
136	(meta analy* or metanaly* or metaanaly*).ti,ab.
137	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
138	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
139	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
140	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
141	(search* adj4 literature).ab.
142	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
143	cochrane.jw.
144	((pool* or combined) adj2 (data or trials or studies or results)).ab.
145	(or/132-134,136,138-143) use ppez
146	(or/134-137,139-144) use emczd
147	or/145-146
148	network meta-analysis/
149	((network adj (MA or MAs)) or (NMA or NMAs)).tw.
150	((indirect or mixed or multiple or multi-treatment* or simultaneous) adj1 comparison*).tw.
151	or/148-150
152	131 or 147 or 151
153	123 and 152

1 Database(s): The Cochrane Library: Cochrane Database of Systematic Reviews, Issue 5 of
2 12, May 2020; Cochrane Central Register of Controlled Trials, Issue 5 of 12, May 2020

#	Searches
#1	MeSH descriptor: [Acne Vulgaris] explode all trees
#2	acne:ti,ab
#3	#1 or #2
#4	(topical or topically or cream or creams or emulsi* gel or gels or foam or foams or ointment* or solution or solutions or lotion or lotions or pad or pads):ti,ab
#5	MeSH descriptor: [Ointments] this term only
#6	MeSH descriptor: [Gels] explode all trees
#7	MeSH descriptor: [Skin Cream] this term only
#8	MeSH descriptor: [Administration, Topical] this term only
#9	MeSH descriptor: [Administration, Cutaneous] this term only
#10	(cutaneous or dermal or skin or transcutaneous or transdermal or percutaneous):ti,ab

#	Searches
#11	{or #4-#10}
#12	MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#13	MeSH descriptor: [Anthelmintics] explode all trees
#14	(antibiotic* or "anti biotic*" or "anti bacteri*" or antibacteri* or bacteriocid*):ti,ab
#15	(anthelminti* or antihelminthi* or antithelminti* or anti-helminthi* or anti-helminti* or antiparasit* or anti-parasit* or vermifug*):ti,ab
#16	MeSH descriptor: [Adapalene] this term only
#17	MeSH descriptor: [Aluminum Oxide] this term only
#18	MeSH descriptor: [Amoxicillin] this term only
#19	MeSH descriptor: [Ampicillin] this term only
#20	MeSH descriptor: [Benzoyl Peroxide] this term only
#21	MeSH descriptor: [Cefaclor] this term only
#22	MeSH descriptor: [Cefadroxil] this term only
#23	MeSH descriptor: [Cephalexin] this term only
#24	MeSH descriptor: [Cefixime] this term only
#25	MeSH descriptor: [Cefotaxime] this term only
#26	MeSH descriptor: [Cephradine] this term only
#27	MeSH descriptor: [Ceftazidime] this term only
#28	MeSH descriptor: [Ceftriaxone] this term only
#29	MeSH descriptor: [Cefuroxime] this term only
#30	MeSH descriptor: [Clarithromycin] this term only
#31	MeSH descriptor: [Clindamycin] this term only
#32	MeSH descriptor: [Dapsone] this term only
#33	MeSH descriptor: [Doxycycline] this term only
#34	MeSH descriptor: [Erythromycin] this term only
#35	MeSH descriptor: [Floxacillin] this term only
#36	MeSH descriptor: [Fusidic Acid] this term only
#37	MeSH descriptor: [Isotretinoin] this term only
#38	MeSH descriptor: [Ivermectin] this term only
#39	MeSH descriptor: [Lymecycline] this term only
#40	MeSH descriptor: [Minocycline] this term only
#41	MeSH descriptor: [Mupirocin] this term only
#42	MeSH descriptor: [Niacinamide] this term only
#43	MeSH descriptor: [Oxytetracycline] this term only
#44	MeSH descriptor: [Penicillin G] this term only
#45	MeSH descriptor: [Penicillin V] this term only
#46	MeSH descriptor: [Phenol] this term only
#47	MeSH descriptor: [Piperacillin] this term only
#48	MeSH descriptor: [Praziquantel] this term only
#49	MeSH descriptor: [Vitamin A] this term only
#50	MeSH descriptor: [Tetracycline] this term only
#51	MeSH descriptor: [Ticarcillin] this term only
#52	MeSH descriptor: [Tretinoin] this term only
#53	MeSH descriptor: [Trimethoprim] this term only
#54	MeSH descriptor: [Zinc Acetate] this term only
#55	(adapalene or aluminum oxide or ampicillin or amoxicillin or avermectin or azaelaic acid or azelaic acid or benzylpenicillin or benzyl penicillin or benzoyl peroxide or cefaclor or cefadroxil or cefalexin or cephalexin or cephalosporin* or cephamycin* or cefixime or cefotaxime or cefradine or ceftaroline or ceftazidime or ceftriaxone or cefuroxime or cephalexin or cephradine or chlorhexidine digluconate or chlorhexidine gluconate or clarithromycin or clindamycin or dapsone or diaminodiphenyl sulfone or doxycyclin* or erythromycin or floxacillin or flucloxacillin or fucidin or fusidic acid or fusidate sodium or sodium fusidate or germolene or isotretinoi* or ivermectin or lincosamide* or lymecycline or macrolide* or minocycline or mupirocin or pseudomonic acid or nadifloxacin or niacinamide or nicotinamide or nitroimidazole or ozenoxacin or oxytetracyline or penicillin* or phenol or phenoxymethylpenicillin or piperacillin or pleuromutilin or praziquantel or cysticide or quinoderm or quinolone* or retapamulin or retino* or retinol or temocillin or tetracyclin* or ticarcillin or tretinoin or trimethoprim or vitamin a or zinc acetate):ti,ab
#56	{or #12-#55}
#57	#3 and #11 and #56

1 Oral antibiotics and oral isotretinoin

2 Database(s): Embase Classic+Embase 1947 to 2020 May 06, Ovid MEDLINE(R) and Epub
3 Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 06, 2020

4 Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of
5 Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emczd

#	Searches
3	acne.tw.
4	or/1-3
5	exp antibiotic agent/ use emczd
6	exp Anti-Bacterial Agents/ use ppez
7	(antibiotic* or anti biotic* or anti bacteri* or antibacteri* or bacteriocid*).tw.
8	exp carbapenem derivative/ use emczd
9	exp Carbapenems/ use ppez
10	exp cephalosporin derivative/ use emczd
11	exp Cephalosporins/ use ppez
12	exp cephamycin derivative/ use emczd
13	exp Cephamycins/ use ppez
14	dapsone/
15	exp lincosamide/ use emczd
16	exp Lincosamide/ use ppez
17	exp macrolide/ use emczd
18	exp Macrolides/ use ppez
19	exp monobactam derivative/ use emczd
20	exp Monobactams/ use ppez
21	exp penicillin derivative/ use emczd
22	exp Penicillins/ use ppez
23	exp quinoline derived antiinfective agent/ use emczd
24	exp Quinolones/ use ppez
25	exp retinoid/ use emczd
26	exp Retinoids/ use ppez
27	exp tetracycline derivative/ use emczd
28	exp Tetracyclines/ use ppez
29	trimethoprim/
30	(carbapenem* or biapenem or doripenem or ertapenem or imipenem or meropenem or panipenem or betamipron or tebipenem).tw.
31	(cephamycin* or cephalosporin* or carbacephem or loracarbef or cefacetrile or cefaclor or cefadroxil or cefalexin or cefaloglycin or cefalonium or cefaloridine or cefalotin or cefamandole or cefapirin or cefatrizine or cefazaflur or cefazedone or cefazolin or cefbuperazone or cefcapene or cefdaloxime or cefdinir or cefditoren or cefepime or cefetamet or cefixime or cefmenoxime or cefmetazole or cefminox or cefodizime or cefonicid or cefoperazone or cefoperazone or ceforanide or cefotaxime or cefotetan or cefotiam or cefozopran or cefpiramide or cefpirome or cefpodoxime or cefprozil or cefquinome or cefradine or cefroxadine or cefsulodin or ceftaroline fosamile or ceftazidime or ceftazidime or cefteram or ceftezole or ceftibiprole or ceftibuten or ceftiolene or ceftolozane or ceftolozane or ceftraroline or ceftriaxone or cefuroxime or cefuzonam or cephamycin or depfimizole or flomoxef or latamoxef or oxacephem).tw.
32	dapsone.tw.
33	(isotretinoi* or iso tretinoin or isoretinoin or isotren or isotrex* or accutane or roaccutan* or roaccuttan* or roacuttan* or roacutan* or retinoic acid).tw.
34	(lincosamide* or clindamycin or lincomycine or linkomycine).tw.
35	(macrolide* or azithromycin or carbomycin a or clarithromycin or erythromycin or fidaxomicin or josamycin or kitasamycin or midecamycin or oleandomycin or roxithromycin or solithromycin or spiramycin or telithromycin or troleandomycin).tw.
36	(monobactam* or mono- bactam* or aztreonam).tw.
37	(penicillin* or almecillin or amoxicillin or ampicillin or azlocillin or bacampicillin or benzathine benzylpenicillin or benzylpenicillin sodium or carbenicillin or carindacillin or cloxacillin or co-amoxiclav or co-fluampicil or co-trimoxazole or dicloxacillin or epicillin or flucloxacillin or hetacillin or mecillinam or metampicillin or methicillin or mezlocillin or nafcillin or oxacillin or phenoxymethylpenicillin or piperacillin or pivampicillin or pivmecillinam hydrochloride or procaine benzylpenicillin or sultamicillin or talampicillin or temocillin or ticarcillin).tw.
38	(quinolone* or balofloxacin or besifloxacin or ciprofloxacine or clinafloxacin or delafloxacin or enoxacin or fleroxacin or gatifloxacin or gemifloxacin or grepafloxacin or levofloxacin or lomefloxacin or moxifloxacin or nadifloxacin or norfloxacin or ofloxacin or oxolinic acid or ozenoxacin or pazufloxacin or pefloxacin or prulifloxacin or rosoxacin or rufloxacin or sitafloxacin or sparfloxacin or temafloxacin or tosufloxacin).tw.
39	(tetracylcline* or chlortetracycline or demeclocycline or doxycycline or eravacycline or lymecycline or methacycline or minocycline or omadacycline or oxytetracycline or rolitetracycline or sarecycline or tetracycline or tigecycline).tw.
40	trimethoprim.tw.
41	or/5-40
42	oral drug administration/ use emczd
43	Administration, Oral/ use ppez
44	oral drug administration.fs.
45	(oral* or per os).tw.
46	or/42-45
47	4 and 41 and 46
48	Letter/ use ppez
49	letter.pt. or letter/ use emczd
50	note.pt.
51	editorial.pt.
52	Editorial/ use ppez
53	News/ use ppez

#	Searches
54	exp Historical Article/ use ppez
55	Anecdotes as Topic/ use ppez
56	Comment/ use ppez
57	Case Report/ use ppez
58	case report/ or case study/ use emczd
59	(letter or comment*).ti.
60	or/48-59
61	randomized controlled trial/ use ppez
62	randomized controlled trial/ use emczd
63	random*.ti,ab.
64	or/61-63
65	60 not 64
66	animals/ not humans/ use ppez
67	animal/ not human/ use emczd
68	nonhuman/ use emczd
69	exp Animals, Laboratory/ use ppez
70	exp Animal Experimentation/ use ppez
71	exp Animal Experiment/ use emczd
72	exp Experimental Animal/ use emczd
73	exp Models, Animal/ use ppez
74	animal model/ use emczd
75	exp Rodentia/ use ppez
76	exp Rodent/ use emczd
77	(rat or rats or mouse or mice).ti.
78	or/65-77
79	47 not 78
80	limit 79 to english language
81	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
82	81 use ppez
83	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
84	83 use ppez
85	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
86	85 use emczd
87	82 or 84
88	86 or 87
89	Meta-Analysis/
90	exp Meta-Analysis as Topic/
91	systematic review/
92	meta-analysis/
93	(meta analy* or metanaly* or metaanaly*).ti,ab.
94	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
95	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
96	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
97	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
98	(search* adj4 literature).ab.
99	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
100	cochrane.jw.
101	((pool* or combined) adj2 (data or trials or studies or results)).ab.
102	(or/89-91,93,95-100) use ppez
103	(or/91-94,96-101) use emczd
104	or/102-103
105	network meta-analysis/
106	((network adj (MA or MAs)) or (NMA or NMAs)).tw.
107	((indirect or mixed or multiple or multi-treatment* or simultaneous) adj1 comparison*).tw.
108	or/105-107
109	88 or 104 or 108
110	80 and 109

1 Database(s): The Cochrane Library: Cochrane Database of Systematic Reviews, Issue 5 of
2 12, May 2020; Cochrane Central Register of Controlled Trials, Issue 5 of 12, May 2020

#	Searches
#1	MeSH descriptor: [Acne Vulgaris] explode all trees
#2	acne:ti,ab
#3	#1 or #2

#	Searches
#4	MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#5	(antibiotic* or "anti biotic*" or "anti bacteri*" or antibacteri* or bacteriocid*):ti,ab
#6	MeSH descriptor: [Amoxicillin] this term only
#7	MeSH descriptor: [Ampicillin] this term only
#8	MeSH descriptor: [Azithromycin] this term only
#9	MeSH descriptor: [Azlocillin] this term only
#10	MeSH descriptor: [Penicillin G] this term only
#11	MeSH descriptor: [Carbenicillin] this term only
#12	MeSH descriptor: [Cefaclor] this term only
#13	MeSH descriptor: [Cefadroxil] this term only
#14	MeSH descriptor: [Cephalexin] this term only
#15	MeSH descriptor: [Cefixime] this term only
#16	MeSH descriptor: [Cefotaxime] this term only
#17	MeSH descriptor: [Cephradine] this term only
#18	MeSH descriptor: [Ceftazidime] this term only
#19	MeSH descriptor: [Ceftriaxone] this term only
#20	MeSH descriptor: [Chlortetracycline] this term only
#21	MeSH descriptor: [Clarithromycin] this term only
#22	MeSH descriptor: [Clindamycin] this term only
#23	MeSH descriptor: [Cloxacillin] this term only
#24	MeSH descriptor: [Amoxicillin-Potassium Clavulanate Combination] this term only
#25	MeSH descriptor: [Trimethoprim, Sulfamethoxazole Drug Combination] this term only
#26	(amoxicillin or ampicillin or azithromycin or azlocillin or bacampicillin or benzylpenicillin sodium or "penicillin g" or biapenem or carbenicillin or carbomycin or cefaclor or cefadroxil or cefalexin or cephalexin or cefixime or cefotaxime or cephotaxim* or cefradine or cephradine or ceftaroline or ceftazidime or ceftriaxone or cefuroxime or chlortetracyline or clarithromycin or clindamycin or cloxacillin or co amoxiclav or coamoxiclav or co fluampcil or cofluampcil or co trimoxazole or cotrimoxazole):ti,ab
#27	MeSH descriptor: [Demeclocycline] this term only
#28	MeSH descriptor: [Dicloxacillin] this term only
#29	MeSH descriptor: [Doripenem] this term only
#30	MeSH descriptor: [Doxycycline] this term only
#31	MeSH descriptor: [Ertapenem] this term only
#32	MeSH descriptor: [Erythromycin] this term only
#33	MeSH descriptor: [Fidaxomicin] this term only
#34	MeSH descriptor: [Floxacillin] this term only
#35	(demeclocycline or dicloxacillin or doripenem or doxycycline or epicillin or eravacycline or ertapenem or erythromycin or fidaxomicin or floxacillin or flucloxacillin):ti,ab
#36	MeSH descriptor: [Imipenem] this term only
#37	MeSH descriptor: [Cilastatin, Imipenem Drug Combination] this term only
#38	MeSH descriptor: [Josamycin] this term only
#39	MeSH descriptor: [Kitasamycin] this term only
#40	MeSH descriptor: [Lymecycline] this term only
#41	MeSH descriptor: [Meropenem] this term only
#42	MeSH descriptor: [Methacycline] this term only
#43	MeSH descriptor: [Methicillin] this term only
#44	MeSH descriptor: [Mezlocillin] this term only
#45	MeSH descriptor: [Miocamycin] this term only
#46	MeSH descriptor: [Nafcillin] this term only
#47	(hetacillin or imipenem or isotretinoi* or josamycin* or kitasamycin or leucomycin or lymecycline or meropenem or metampicillin or methampicillin or metacycline or methacycline or methicillin or mezlocillin or midecamycin or minocycline or miocamycin* or miokamycin* or nafcillin):ti,ab
#48	MeSH descriptor: [Oleandomycin] this term only
#49	MeSH descriptor: [Oxacillin] this term only
#50	MeSH descriptor: [Oxytetracycline] this term only
#51	MeSH descriptor: [Penicillin V] this term only
#52	MeSH descriptor: [Piperacillin] this term only
#53	MeSH descriptor: [Piperacillin, Tazobactam Drug Combination] this term only
#54	MeSH descriptor: [Amdinocillin Pivoxil] this term only
#55	MeSH descriptor: [Rolitetracycline] this term only
#56	MeSH descriptor: [Roxithromycin] this term only
#57	MeSH descriptor: [Spiramycin] this term only
#58	MeSH descriptor: [Talampicillin] this term only
#59	MeSH descriptor: [Tetracycline] this term only
#60	MeSH descriptor: [Ticarcillin] this term only
#61	MeSH descriptor: [Tigecycline] this term only
#62	MeSH descriptor: [Trimethoprim] this term only
#63	MeSH descriptor: [Troleandomycin] this term only
#64	(oleandomycin or omadacycline or "PTK-0796" or oxacillin* or oxytetracycline or panipenem or betamipron or carbenin or phenoxymethylpenicillin or "penicillin v" or piperacillin or pivmeillinam or amdinocillin pivoxil or retinoi* or rolitetracycline or roxithromycin or sarecycline or solithromycin or spiramycin or talampicillin or tebipenem or

#	Searches
	telithromycin or temocillin or tetracylin* or ticarcillin or timentin or tigecycline or trimethoprim or troleandomycin):ti,ab
#65	{or #4-#64}
#66	#3 and #65
#67	MeSH descriptor: [Administration, Oral] explode all trees
#68	(oral or per os):ti,ab
#69	#67 or #68
#70	#66 and #69

1 Hormonal interventions

2 Database(s): Embase Classic+Embase 1947 to 2020 May 06, Ovid MEDLINE(R) and Epub
3 Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 06, 2020

4 Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of
5 Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emczd
3	acne.tw.
4	or/1-3
5	exp aldosterone antagonist/ use emczd
6	exp Mineralocorticoid Receptor Antagonists/ use ppez
7	spironolactone/
8	hydroflumethiazide plus spironolactone/ use emczd
9	canrenone/
10	eplerenone/
11	furosemide plus spironolactone/ use emczd
12	(aldactone or spironolactone or canrenone or co-flumactone or coflumactone or eplerenon* or furosemide).tw.
13	or/5-12
14	exp alpha adrenergic receptor blocking agent/ use emczd
15	exp Adrenergic alpha-Antagonists/ use ppez
16	alfuzosin/ use emczd
17	doxazosin/
18	indoramin/
19	prazosin/
20	tamsulosin/
21	dutasteride plus tamsulosin/ use emczd
22	solifenacin plus tamsulosin/ use emczd
23	terazosin/ use emczd
24	(alfuzosin or doxazosin or uroprost or indoramin or prazosin or tamsulosin or terazosin).tw.
25	or/14-24
26	exp steroid 5alpha reductase inhibitor/ use emczd
27	exp 5-alpha Reductase Inhibitors/ use ppez
28	dutasteride/
29	finasteride/
30	(5a reductase inhibitor* or 5-alpha reductase inhibitor* or dutastaride or finasteride).tw.
31	or/26-30
32	exp antiandrogen/ use emczd
33	exp Androgen Antagonists/ use ppez
34	metformin/
35	abiraterone acetate/
36	apalutamide/ use emczd
37	bicalutamide/ use emczd
38	cyproterone acetate plus ethinylestradiol/ use emczd
39	cyproterone acetate/
40	enzalutamide/ use emczd
41	flutamide/
42	(antiandrogen* or anti-androgen* or androgen antagonist* or abiraterone acetate or apalutamide or bicalutamide or cocyprindiol or co-cyprindiol or cyproterone acetate or enzalutamide or flutamide or metformin).tw.
43	or/32-42
44	exp oral contraceptive agent/ use emczd
45	exp Contraceptives, Oral, Combined/ use ppez
46	exp gestagen/ use emczd
47	exp Progestins/ use ppez
48	(chlormadinone acetate plus ethinylestradiol/ or desogestrel plus ethinylestradiol/ or dienogest plus ethinylestradiol/ or drospirenone plus ethinylestradiol/ or dydrogesterone plus estradiol/ or estradiol plus levonorgestrel/ or estradiol plus nomegestrol acetate/ or estradiol plus norethisterone acetate/ or ethinylestradiol plus etonogestrel/ or ethinylestradiol plus gestodene/ or ethinylestradiol plus levonorgestrel/ or ethinylestradiol plus norelgestromin/ or

#	Searches
	ethinylestradiol plus norethisterone/ or ethinylestradiol plus norgestimate/) use emczd
49	Ethinyl Estradiol-Norgestrel Combination/ use ppez
50	(Ethinyl Estradiol/ use ppez and (Chlormadinone Acetate/ or Desogestrel/ or Levonorgestrel/ or Norethindrone/ or Norgestrel/)) use ppez
51	(Mestranol/ and (Norethindrone/ or Norethynodrel/)) use ppez
52	(Estradiol/ and (Dydrogesterone/ or Levonorgestrel/ or Medroxyprogesterone Acetate/ or Norethindrone/)) use ppez
53	((oral* adj contracept*) or progest?gen* or gestagen* or progestin*).tw.
54	((ethinyl?estradiol or ethinyl estradiol or ethinyl oestradiol) adj3 (chlormadinone acetate or desogestrel or dienogest or drospirenone or etonogestrel or gestodene or levonorgestrel or nomogestrol or norelgestromin* or norethindrone or norethisterone or norgestimate or norgestrel)).tw.
55	(mestranol adj3 (norethindrone or norethisterone or noretynodrel or norethynodrel)).tw.
56	((estradiol or oestradiol) adj3 (dienogest or dydrogesterone or levonorgestrel or medroxyprogesterone acetate or nomegestrol or norethindrone or norethisterone)).tw.
57	or/44-56
58	or/13,25,31,43,57
59	4 and 58
60	limit 59 to english language
61	Letter/ use ppez
62	letter.pt. or letter/ use emczd
63	note.pt.
64	editorial.pt.
65	Editorial/ use ppez
66	News/ use ppez
67	exp Historical Article/ use ppez
68	Anecdotes as Topic/ use ppez
69	Comment/ use ppez
70	Case Report/ use ppez
71	case report/ or case study/ use emczd
72	(letter or comment*).ti.
73	or/61-72
74	randomized controlled trial/ use ppez
75	randomized controlled trial/ use emczd
76	random*.ti,ab.
77	or/74-76
78	73 not 77
79	animals/ not humans/ use ppez
80	animal/ not human/ use emczd
81	nonhuman/ use emczd
82	exp Animals, Laboratory/ use ppez
83	exp Animal Experimentation/ use ppez
84	exp Animal Experiment/ use emczd
85	exp Experimental Animal/ use emczd
86	exp Models, Animal/ use ppez
87	animal model/ use emczd
88	exp Rodentia/ use ppez
89	exp Rodent/ use emczd
90	(rat or rats or mouse or mice).ti.
91	or/78-90
92	60 not 91
93	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
94	93 use ppez
95	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
96	95 use ppez
97	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
98	97 use emczd
99	94 or 96
100	98 or 99
101	Meta-Analysis/
102	exp Meta-Analysis as Topic/
103	systematic review/
104	meta-analysis/
105	(meta analy* or metanaly* or metaanaly*).ti,ab.
106	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
107	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
108	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
109	(search strategy or search criteria or systematic search or study selection or data extraction).ab.

#	Searches
110	(search* adj4 literature).ab.
111	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
112	cochrane.jw.
113	((pool* or combined) adj2 (data or trials or studies or results)).ab.
114	(or/101-103,105,107-112) use ppez
115	(or/103-106,108-113) use emczd
116	or/114-115
117	network meta-analysis/
118	((network adj (MA or MAs)) or (NMA or NMAs)).tw.
119	((indirect or mixed or multiple or multi-treatment* or simultaneous) adj1 comparison*).tw.
120	or/117-119
121	100 or 116 or 120
122	92 and 121

1 Database(s): The Cochrane Library: Cochrane Database of Systematic Reviews, Issue 5 of
2 12, May 2020; Cochrane Central Register of Controlled Trials, Issue 5 of 12, May 2020

#	Searches
#1	MeSH descriptor: [Acne Vulgaris] explode all trees
#2	acne*:ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees
#5	MeSH descriptor: [Spironolactone] this term only
#6	MeSH descriptor: [Eplerenone] this term only
#7	(aldactone or spironolactone or co-flumactone or coflumactone or eplerenon* or furosemide):ti,ab
#8	{or #4-#7}
#9	MeSH descriptor: [Adrenergic alpha-Antagonists] explode all trees
#10	MeSH descriptor: [Doxazosin] this term only
#11	MeSH descriptor: [Indoramin] this term only
#12	MeSH descriptor: [Prazosin] this term only
#13	MeSH descriptor: [Tamsulosin] this term only
#14	(alfuzosin or doxazosin or uroprost or indoramin or prazosin or tamsulosin or terazosin):ti,ab
#15	{or #9-#14}
#16	MeSH descriptor: [5-alpha Reductase Inhibitors] explode all trees
#17	MeSH descriptor: [Dutasteride] this term only
#18	MeSH descriptor: [Finasteride] this term only
#19	("5a reductase inhibitor*" or "5-alpha reductase inhibitor*" or dutastaride or finasteride):ti,ab
#20	{or #16-#19}
#21	MeSH descriptor: [Androgen Antagonists] explode all trees
#22	MeSH descriptor: [Metformin] this term only
#23	MeSH descriptor: [Abiraterone Acetate] this term only
#24	MeSH descriptor: [Cyproterone Acetate] this term only
#25	MeSH descriptor: [Flutamide] this term only
#26	(antiandrogen* or "anti androgen*" or "androgen antagonist*" or "abiraterone acetate" or apalutamide or bicalutamide or cocyprindiol or "co cyprindiol" or "cyproterone acetate" or enzalutamide or flutamide or metformin):ti,ab
#27	{or #21-#26}
#28	MeSH descriptor: [Contraceptives, Oral, Combined] explode all trees
#29	MeSH descriptor: [Progestins] explode all trees
#30	MeSH descriptor: [Ethinyl Estradiol-Norgestrel Combination] this term only
#31	MeSH descriptor: [Ethinyl Estradiol] this term only
#32	MeSH descriptor: [Estradiol] this term only
#33	MeSH descriptor: [Mestranol] this term only
#34	((oral* next contracept*) or progestogen* or progestagen* or gestagen* or progestin*):ti,ab
#35	((ethinylestradiol or ethinyloestradiol or ethinyl estradiol or ethinyl oestradiol) near/3 (chlormadinone acetate or desogestrel or dienogest or drospirenone or etonogestrel or gestodene or levonorgestrel or nomogestrol or norelgestromin* or norethindrone or norethisterone or norgestimate or norgestrel)):ti,ab
#36	((estradiol or oestradiol) near/3 (dienogest or dydrogesterone or levonorgestrel or medroxyprogesterone acetate or nomegestrol or norethindrone or norethisterone)):ti,ab
#37	(mestranol near/3 (norethindrone or norethisterone or noretynodrel or norethynodrel)):ti,ab
#38	{or #28-#37}
#39	#8 or #15 or #20 or #27 or #38
#40	#3 and #39

3

1 Physical interventions

2 Database(s): Embase Classic+Embase 1947 to 2019 August 12, Ovid MEDLINE(R) and
3 Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 06,
4 2020

5 Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of
6 Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emczd
3	acne.tw.
4	or/1-3
5	chemexfoliation/
6	(amino acid/ or 2 hydroxyacid/) use emczd
7	(Amino Acids/ or Hydroxy Acids/) use ppez
8	glycolic acid/ use emczd
9	Glycolates/ use ppez
10	lactic acid/
11	mandelic acid/ use emczd
12	Mandelic Acids/ use ppez
13	pyruvic acid/
14	salicylic acid/
15	trichloroacetic acid/
16	(chemical adj1 (exfoliat* or peel* or resurfac*)).tw.
17	(chemoexfoliat* or chemexfoliat* or chemo exfoliat*).tw.
18	((amino or glycol* or lactic or mandelic or pyruvic or salicylic or trichloroa?cetic or salicylic-mandelic or alpha hydroxy or "amino fruit") adj acid*).tw.
19	(hydroxyacid* or hydroxy acid*).tw.
20	((Jessner* or phenol or pheno or Baker-Gordon) adj (peel* or solution*)).tw.
21	or/5-20
22	comedo/th use emczd
23	((blackhead* or comedo* or whitehead*) adj (extract* or remov*)).tw.
24	triamcinolone acetonide/
25	(adrenal cortex hormone* or triamcinolone acetonide).tw.
26	or/22-25
27	exp laser/
28	exp phototherapy/
29	exp photodynamic therapy/
30	exp photochemotherapy/
31	exp photolysis/
32	exp sunlight/
33	exp photosensitizing agent/
34	radiofrequency/ or radiofrequency ablation/
35	aminolevulinic acid/
36	methylene blue/
37	aminolevulinic acid methyl ester/
38	(or/27-37) use emczd
39	exp Lasers/
40	exp Phototherapy/
41	exp Laser Therapy/
42	exp Photochemotherapy/
43	exp Photolysis/
44	exp Sunlight/
45	exp Ultraviolet Therapy/
46	exp Photosensitizing Agents/
47	exp Radiofrequency Therapy/
48	Aminolevulinic Acid/
49	Methylene Blue/
50	(or/39-49) use ppez
51	(laser* or light therap* or light treatment* or aminolevulinic acid or blue light* or red light* or intense pulsed light* or IPL or methyl aminolevulinate or methylene blue gel or microneedl* or micro needl* or photochemical therap* or photochemical treatment* or photo chemical therap* or photo chemical treatment* or photochemotherap* or photodynamic therap* photodynamic treatment* or photo dynamic therap* or photo dynamic treatment* or photolysis or photopneumatic therap* or photopneumatic treatment* or photo pneumatic therap* or photo pneumatic treatment* or photosensiti?ing agent* or photo-sensiti?ing agent* or phototherap* or photo-therap* or photothermal therap* or photothermal treatment* or photo-thermal therap* or photo-thermal treatment* or radiofrequenc* or radio frequenc* or smoothbeam or sunlight or ultraviolet).tw.

#	Searches
52	or/21,26,38,50-51
53	4 and 52
54	Letter/ use ppez
55	letter.pt. or letter/ use emczd
56	note.pt.
57	editorial.pt.
58	Editorial/ use ppez
59	News/ use ppez
60	exp Historical Article/ use ppez
61	Anecdotes as Topic/ use ppez
62	Comment/ use ppez
63	Case Report/ use ppez
64	case report/ or case study/ use emczd
65	(letter or comment*).ti.
66	or/54-65
67	randomized controlled trial/ use ppez
68	randomized controlled trial/ use emczd
69	random*.ti,ab.
70	or/67-69
71	66 not 70
72	animals/ not humans/ use ppez
73	animal/ not human/ use emczd
74	nonhuman/ use emczd
75	exp Animals, Laboratory/ use ppez
76	exp Animal Experimentation/ use ppez
77	exp Animal Experiment/ use emczd
78	exp Experimental Animal/ use emczd
79	exp Models, Animal/ use ppez
80	animal model/ use emczd
81	exp Rodentia/ use ppez
82	exp Rodent/ use emczd
83	(rat or rats or mouse or mice).ti.
84	or/71-83
85	53 not 84
86	limit 85 to english language
87	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
88	87 use ppez
89	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
90	89 use ppez
91	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
92	91 use emczd
93	88 or 90
94	92 or 93
95	Meta-Analysis/
96	exp Meta-Analysis as Topic/
97	systematic review/
98	meta-analysis/
99	(meta analy* or metanaly* or metaanaly*).ti,ab.
100	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
101	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
102	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
103	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
104	(search* adj4 literature).ab.
105	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
106	cochrane.jw.
107	((pool* or combined) adj2 (data or trials or studies or results)).ab.
108	(or/95-97,99,101-106) use ppez
109	(or/97-100,102-107) use emczd
110	or/108-109
111	network meta-analysis/
112	((network adj (MA or MAs)) or (NMA or NMAs)).tw.
113	((indirect or mixed or multiple or multi-treatment* or simultaneous) adj1 comparison*).tw.
114	or/111-113
115	94 or 110 or 114
116	86 and 115

Database(s): The Cochrane Library: Cochrane Database of Systematic Reviews, Issue 5 of 12, May 2020; Cochrane Central Register of Controlled Trials, Issue 5 of 12, May 2020

#	Searches
#1	MeSH descriptor: [Acne Vulgaris] explode all trees
#2	acne*:ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Chemexfoliation] this term only
#5	MeSH descriptor: [Amino Acids] this term only
#6	MeSH descriptor: [Hydroxy Acids] this term only
#7	MeSH descriptor: [Glycolates] this term only
#8	MeSH descriptor: [Lactic Acid] this term only
#9	MeSH descriptor: [Mandelic Acids] this term only
#10	MeSH descriptor: [Pyruvic Acid] this term only
#11	MeSH descriptor: [Salicylic Acid] this term only
#12	MeSH descriptor: [Trichloroacetic Acid] this term only
#13	(chemical near/1 (exfoliat* or peel* or resurfac*)):ti,ab
#14	(chemoexfoliat* or chemexfoliat* or chemo exfoliat*):ti,ab
#15	((amino or glycol* or lactic or mandelic or pyruvic or salicylic or trichloroaecetic or trichloroacetic or "salicylic mandelic" or "alpha hydrox" or "amino fruit") next acid*):ti,ab
#16	(hydroxyacid* or "hydroxy acid*").ti,ab
#17	((Jessner* or phenol or pheno or "Baker Gordon") next (peel* or solution*)).ti,ab
#18	{or #4-#17}
#19	((blackhead* or comedo* or whitehead*) near/2 (extract* or remov*)):ti,ab
#20	MeSH descriptor: [Triamcinolone Acetonide] this term only
#21	("adrenal cortex hormone*" or "triamcinolone acetonide").ti,ab
#22	{or #19-#21}
#23	MeSH descriptor: [Lasers] explode all trees
#24	MeSH descriptor: [Phototherapy] explode all trees
#25	MeSH descriptor: [Photochemotherapy] explode all trees
#26	MeSH descriptor: [Photochemotherapy] explode all trees
#27	MeSH descriptor: [Photolysis] explode all trees
#28	MeSH descriptor: [Sunlight] explode all trees
#29	MeSH descriptor: [Photosensitizing Agents] explode all trees
#30	MeSH descriptor: [Radiofrequency Therapy] explode all trees
#31	MeSH descriptor: [Aminolevulinic Acid] this term only
#32	MeSH descriptor: [Methylene Blue] this term only
#33	MeSH descriptor: [Ultraviolet Therapy] explode all trees
#34	(laser* or light therap* or light treatment* or aminolevulinic acid or blue light* or red light* or intense pulsed light* or IPL or methyl aminolevulinate or methylene blue gel or microneedl* or micro needl* or photochemical therap* or photochemical treatment* or photo chemical therap* or photo chemical treatment* or photochemotherap* or photodynamic therap* photodynamic treatment* or photo dynamic therap* or photo dynamic treatment* or photolysis or photopneumatic therap* or photopneumatic treatment* or photo pneumatic therap* or photo pneumatic treatment* or photosensitising agent* or photosensitizing agent* or photo-sensitising agent* or photo-sensitizing agent* or phototherap* or photo-therap* or photothermal therap* or photothermal treatment* or photo-thermal therap* or photo-thermal treatment* or radiofrequenc* or radio frequenc* or smoothbeam or sunlight or ultraviolet):ti,ab
#35	{or #23-#34}
#36	#18 or #22 or #35
#37	#3 and #18

Health Economics search

Date of initial search: 12/12/2018

Date of updated search: 06/05/2020

Database{s): Embase 1980 to 2020 May 05, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 05, 2020

Multifile database codes: emez = Embase; ppez = MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emez
3	acne.tw.
4	or/1-3

#	Searches
5	Economics/
6	Value of life/
7	exp "Costs and Cost Analysis"/
8	exp Economics, Hospital/
9	exp Economics, Medical/
10	Economics, Nursing/
11	Economics, Pharmaceutical/
12	exp "Fees and Charges"/
13	exp Budgets/
14	(or/5-13) use ppez
15	health economics/
16	exp economic evaluation/
17	exp health care cost/
18	exp fee/
19	budget/
20	funding/
21	(or/15-20) use emez
22	budget*.ti,ab.
23	cost*.ti.
24	(economic* or pharmaco?economic*).ti.
25	(price* or pricing*).ti,ab.
26	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
27	(financ* or fee or fees).ti,ab.
28	(value adj2 (money or monetary)).ti,ab.
29	or/22-27
30	14 or 21 or 29
31	4 and 30
32	limit 31 to english language
33	limit 32 to yr="2004 -Current"
34	remove duplicates from 33

Date of initial search: 12/12/2018

Date of updated search: 06/05/2020

Databases(s): NIHR Centre for Reviews and Dissemination: Health Technology Assessment Database (HTA) and the NHS Economic Evaluation Database (NHS EED)

#	Searches
1	MeSH DESCRIPTOR Acne Vulgaris EXPLODE ALL TREES
2	(acne) IN NHSEED, HTA FROM 2004 TO 2018
3	#1 OR #2

Search for health utility values

Date of initial search: 29/01/2019

Date of updated search: 06/05/2020

Database{s): Embase 1980 to 2020 May 05, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 05, 2020

Multifile database codes: emez = Embase; ppez = MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emez
3	acne.tw.
4	or/1-3
5	Quality-Adjusted Life Years/ use ppez
6	Sickness Impact Profile/
7	quality adjusted life year/ use emez
8	"quality of life index"/ use emez
9	(quality adjusted or quality adjusted life year*).tw.
10	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
11	(illness state* or health state*).tw.
12	(hui or hui2 or hui3).tw.
13	(multiattibute* or multi attribute*).tw.

#	Searches
14	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
15	utilities.tw.
16	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
17	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
18	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
19	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
20	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
21	Quality of Life/ and ec.fs.
22	Quality of Life/ and (health adj3 status).tw.
23	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
24	(quality of life or qol).tw. and cost benefit analysis/ use emez
25	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
26	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
27	cost benefit analysis/ use emez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
28	*quality of life/ and (quality of life or qol).ti.
29	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
30	quality of life/ and health-related quality of life.tw.
31	Models, Economic/ use ppez
32	economic model/ use emez
33	or/5-32
34	4 and 33
35	limit 34 to english language
36	limit 35 to yr="2004 -Current"
37	remove duplicates from 36

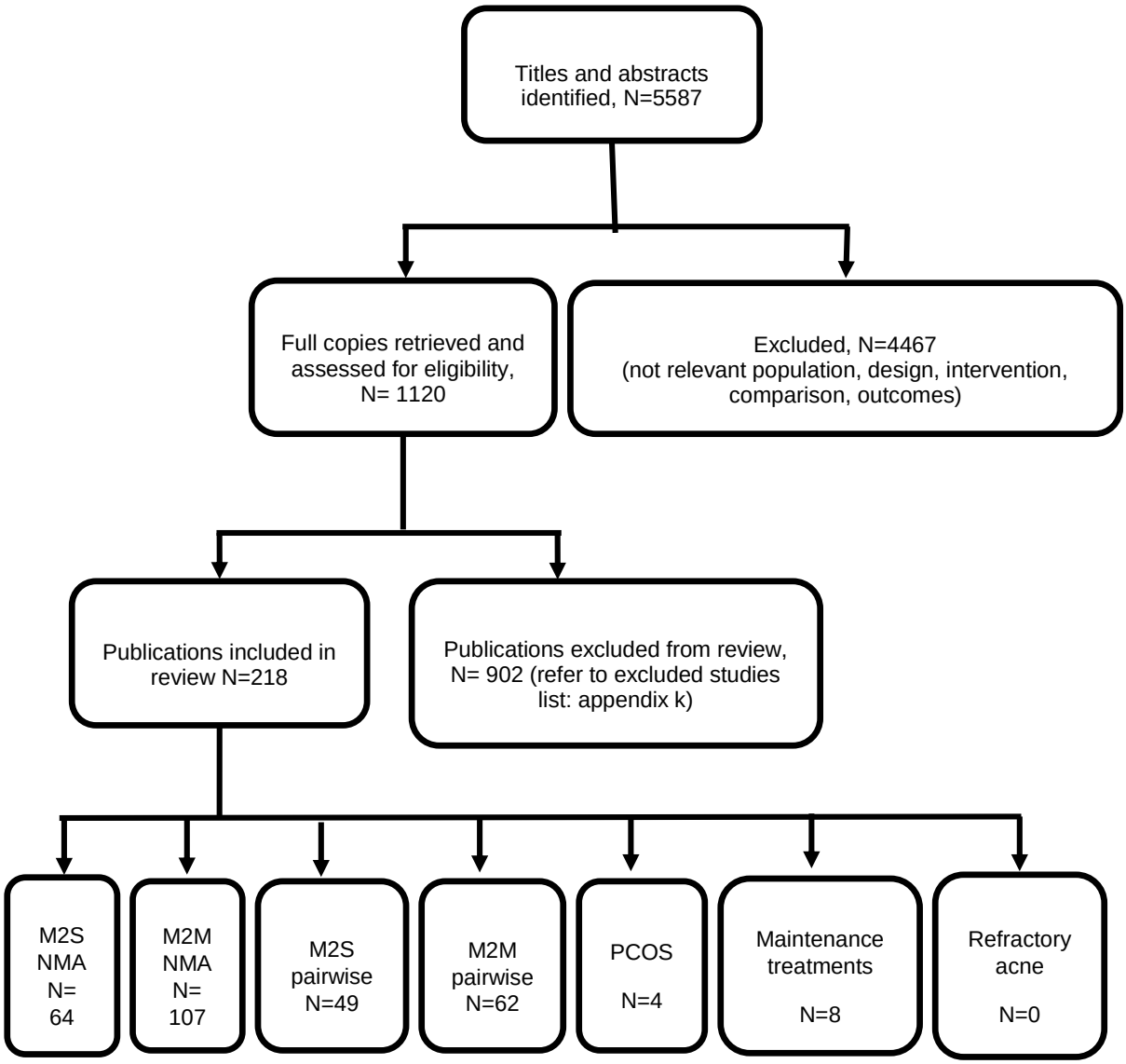
1

2

Appendix C – Clinical evidence study selection

Study selection for: For people with moderate to severe acne vulgaris what are the most effective treatment options?

Figure 4: Study selection flow chart



1 Appendix D – Clinical evidence tables

2 Evidence tables for review question: For people with moderate to severe acne vulgaris what are the most effective treatment 3 options?

4 **Table 7: Clinical evidence tables (for data extraction see supplement 8)**

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Bossuyt, L. B., J.,Richert, B.,Cromphaut, P.,Mitchell, T.,Al Abadie, M.,Henry, I.,Bewley, A.,Poyner, T.,Mann, N.,Czernielewski, J.Lymecycline in the treatment of acne: An efficacious, safe and cost-effective alternative to minocycline. 2003. European Journal of Dermatology **Trial ID** Bossuyt 2003 **Country** Europe **Study type** RCT **Source of funding** Galderma Belgilux N.V./S.A. and Galderma UK Limited. **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	N=134 **Characteristics** **Sex** mixed **age (mean±SD)** 18.6 **age (min/max)** 12/29 **age (other information)** LYME mean age 18.6 (range 13 - 29), MINO mean age 18.6 (range 12 - 29) **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Leeds Grading Scale, Cunliffe **Inclusion details** Males or females aged between 12 and 30 years. Participants with at least 15 and at most 120 inflammatory facial lesions (papules, pustules, nodules) including at most 2 facial nodules (diameter >1 cm), a maximum of 60 non-inflammatory facial	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** LYME-oral 300mg **Intervention: arm 2** MINO-oral 100mg **Coded intervention: arm 1** LYME-oral **Coded intervention: arm 2** MINO-oral	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;not reported if participants were blinded; ITT analysis was done; 8% protocol deviations in LYME arm vs 1.5% in MINO arm **3. Missing outcome data (efficacy)** Some concerns;22% withdrawals / loss to follow-up - balanced between arms; 1.5% due to lack of efficacy; ITT used; **4. Outcome measurement (efficacy)** Low;investigator-masked **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	lesions (open and closed comedones) and an acne severity grade between 1 and 5 (Leeds grading scale). Women of childbearing age were required to use contraception during the study and for 1 month after completing the trial. Women on oral contraceptives were to have been using the same method for 3 months prior to enrolment, or for at least 12 months for contraceptive pills constraining cyproterone acetate. Use of cosmetics was permitted during the course of the study, but contraceptives and cosmetics had to be listed as concomitant medication. **Exclusion details** Pregnancy or lactating women. Participants with acne conglobata, acne fulminans or secondary acne. Participants using topical anti-acne or anti-inflammatory drugs or antibiotics, with the exception of short-courses of penicillin during the previous 6 months. **Number included** **Number randomised: arm 1** 66 **Number randomised: arm 2** 68 **Number completed: arm 1** 52			

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 2 52			
Study details **Reference** Braathen, L. R.Topical clindamycin versus oral tetracycline and placebo in acne vulgaris. 1984. Scandinavian Journal of Infectious Diseases **Trial ID** Braathen 1984 **Country** Norway **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** completers	N=na **Characteristics** **Sex** mixed **age (mean±SD)** 20 **age (min/max)** 16/35 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Participants with moderate to severe acne vulgaris. **Exclusion details** Participants with a history of gastrointestinal disease. Participants who had received systemic or topical antibiotics, systemic or topical steroids, or androgenic drugs within 30 days of entering the study. .Females who were pregnant, or had been on oral contraceptives for less than 3 months, or had changed oral	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** CLIND-topical 1% + PLC-oral **Intervention: arm 2** TETRA-oral 500mg bid + Vehicle **Intervention: arm 3** PLC-oral + Vehicle **Coded intervention: arm 1** CLIND-topical + PLC-oral **Coded intervention: arm 2** TETRA-oral + Vehicle **Coded intervention: arm 3** PLC-oral + Vehicle	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;double-blinded but not clear who was blinded; no ITT analysis **3. Missing outcome data (efficacy)** High;12% excluded from analysis for unclear reasons - not clear if balanced between arms; no ITT **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	contraceptive within the previous 3 months. **Number included** **Number randomised: arm 1** na **Number randomised: arm 2** na **Number randomised: arm 3** na **Number completed: arm 1** 29 **Number completed: arm 2** 29 **Number completed: arm 3** 29			
Study details **Reference** Chen, X. S., H.,Chen, S.,Zhang, J.,Niu, G.,Liu, X.Clinical efficacy of 5-aminolevulinic acid photodynamic therapy in the treatment of moderate to severe facial acne vulgaris. 2015. Experimental and Therapeutic Medicine **Trial ID** Chen 2015 **Country** China **Study type** RCT **Source of funding** Not reported.	N=50 **Characteristics** **Sex** mixed **age (min/max)** 18/33 **age (other information)** ALA-PDT mean age=23.57; control=24.12 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Participants with moderate (acne with inflammatory papules and pustules) to severe (acne with inflammatory	**Interventions** **Treatment duration (weeks)** 3 **Treatment duration category** 0 to <6 weeks **Treatment intensity** Total 4 sessions, once every week **Number of arms** 2 **Split face design** No **Intervention: arm 1** 5ALA 5% photodynamic therapy **Intervention: arm 2** Sham treatment **Coded intervention: arm 1** 5ALA-RED-PDT	**Results** **Treatment discontinuation for any reason** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;no information provided; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** Low;1 patient withdrew for unreported reason **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting**

Study details	Participants	Interventions	Outcomes and results	Comments
Analysis method **Intention to treat or completers analysis** completers	papules, nodules, cysts and scars) facial acne vulgaris. **Exclusion details** Use of topical antibiotics within 2 weeks of the study or intake of systemic oral antibiotics within 4 weeks of the study.Use of systemic retinoids within 6 months of the study. Porphyria or facial atopic dermatitis. Pregnancy or lactation. History of keloid or photosensitivity disorders. Photosensitive eczema or autoimmune diseases. Use of anti-acne medication such as prophylactics, glucocorticoid and photosensitisers. **Number included** **Number randomised: arm 1** 25 **Number randomised: arm 2** 25 **Number completed: arm 1** 24 **Number completed: arm 2** 23	**Coded intervention: arm 2** PLC-physical		Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns
Study details **Reference** Cunliffe, W. J. M., J.,Alirezai, M.,George, S. A.,Coutts, I.,Roseeuw, D. I.,Hachem, J. P.,Briantais, P.,Sidou, F.,Soto, P.Is combined oral and topical therapy better than oral	N=242 **Characteristics** **Sex** mixed **age (mean±SD)** 18.9±4.7 **age (min/max)** 12/45	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design**	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects**	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;not reported if participants were blinded; ITT

Study details	Participants	Interventions	Outcomes and results	Comments
therapy alone in patients with moderate to moderately severe acne vulgaris? A comparison of the efficacy and safety of lymecycline plus adapalene gel 0.1%, versus lymecycline plus gel vehicle. 2003. Journal of the American Academy of Dermatology **Trial ID** Cunliffe 2003 **Country** Europe **Study type** RCT **Source of funding** Galderma International (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	**age (other information)** LYME+ADAP=19.3 (5.4); LYME+VEH=18.6 (4) **Inclusion/exclusion criteria** **Used validated acne scale** yes **Acne scale** Leeds Revised Grading Scale **Inclusion details** Males and females aged 12 to 30 years with moderate to moderately severe inflammatory acne vulgaris. Global severity grade ranging from 4 to 10 on the Leeds Revised Acne Grading System and at least 15 inflammatory facial lesions (no more than 3 nodules) and at least 20 non-inflammatory facial lesions. Participants taking certain topical and systemic treatments were required to complete specified washout periods before entering the study. **Exclusion details** Participants with acne conglobata, acne fulminans, secondary acne, severe nodulocystic acne requiring treatment with isotretinoin, or other dermatologic conditions requiring interfering topical or systemic treatment. Pregnancy or women planning pregnancy or nursing. Men with beards or	No **Intervention: arm 1** LYME 300mg + ADAP 0.1% gel **Intervention: arm 2** LYME 300 mg + Vehicle gel **Coded intervention: arm 1** LYME-oral + ADAP-topical **Coded intervention: arm 2** LYME-oral + Vehicle	See supplement 8 **Clinician rated improvement in acne** See supplement 8	analysis was done **3. Missing outcome data (efficacy)** Some concerns;more than 5% withdrawals - balanced between arms **4. Outcome measurement (efficacy)** Low;investigator-blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	other facial hair likely to interfere with study assessments. **Number included** **Number randomised: arm 1** 118 **Number randomised: arm 2** 124 **Number completed: arm 1** 106 **Number completed: arm 2** 111			
Study details **Reference** Degreef, H. V., B. G.Double-blind evaluation of miconazole-benzoyl peroxide combination for the topical treatment of acne vulgaris. 1982b. Dermatologica **Trial ID** Degreef 1982b **Country** Belgium **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** completers	N=105 **Characteristics** **Sex** mixed **age group** =25 years **age (median)** 15 **age (min/max)** 12/24 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unknown, 5-point scale **Inclusion details** Participants with moderate to severe facial acne. **Exclusion details** Not reported. **Number included** **Number randomised: arm 1**	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** BPO 5%/MICO 2% cream **Intervention: arm 2** BPO 5% cream **Coded intervention: arm 1** BPO-topical + MICO-topical **Coded intervention: arm 2** BPO-topical	**Results** **Treatment discontinuation for any reason** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Low;double-blinded; it looks like participants were blinded; no ITT analysis **3. Missing outcome data (efficacy)** Low;less than 5% withdrawals - balanced between arms **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	52 **Number randomised: arm 2** 53 **Number completed: arm 1** 51 **Number completed: arm 2** 51			
Study details **Reference** Dhawan, S. S. G., J.Clindamycin phosphate 1.2%-benzoyl peroxide (5% or 2.5%) plus tazarotene cream 0.1% for the treatment of acne. 2013. Cutis **Trial ID** Dhawan 2013 **Country** United States **Study type** RCT **Source of funding** Stiefel, a GlaxoSmithKline company (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** not reported	N=40 **Characteristics** **Sex** mixed **age (mean±SD)** 21.9±8.34 **age (min/max)** 12.3/45.9 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Static Global Assessment (ISGA)/Investigator's global severity Assessment **Inclusion details** Males and females aged 12 to 45 years. Participants with grade 3 or higher according to the investigator static global assessment (ISGA) (3=moderate; 4=severe; 5=very severe). 20 to 50 papules and pustules (inflammatory lesions), 30 to 100 open and closed comedones (non-inflammatory	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** BPO 5%/CLIND 1.2% gel + TAZ 0.1% cream **Intervention: arm 2** BPO 2.5%/CLIND 1.2% gel + TAZ 0.1% cream **Coded intervention: arm 1** BPO-topical + CLIND-topical + TAZ-topical **Coded intervention: arm 2** BPO-topical + CLIND-topical + TAZ-topical	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;insufficient information provided on allocation concealment **2. Deviation from intervention** Low;likely participants were blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;12.5% withdrawals/lost to FU unclear reasons - not clear if balanced between arms; ITT done **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Low **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	lesions), 1 or fewer small nodular lesions, no facial cystic lesions. **Exclusion details** **Number included** **Number randomised: arm 1** 20 **Number randomised: arm 2** 20 **Number completed: arm 1** na **Number completed: arm 2** na			
Study details **Reference** Dhir, R. G., N. P.,Agarwal, R.,More, Y. E.Oral isotretinoin is as effective as a combination of oral isotretinoin and topical anti-acne agents in nodulocystic acne. 2008. Indian Journal of Dermatology, Venereology & Leprology **Trial ID** Dhir 2008 **Country** India **Study type** RCT **Source of funding** None (no conflicts of interest). **Analysis method** **Intention to treat or**	N=60 **Characteristics** **Sex** mixed **age (other information)** 10-15 yrs-old, n=3 16-20, n=23 21-25, n=26 26-30, n=5 >30, n=3 **Inclusion/exclusion criteria** **Used validated acne scale** no	**Interventions** **Treatment duration (weeks)** 24 **Treatment duration category** 24+ weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** ISO=120.Daily=0.5 + CLIND 1% during daytime + ADAP 0.1% at bed time **Intervention: arm 2** ISO=120.Daily=0.5 **Coded intervention: arm 1** ISO=120.Daily=0.5-oral + CLIND-topical + ADAP-topical **Coded intervention: arm 2** ISO=120.Daily=0.5-oral	**Results** **Treatment discontinuation for any reason** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** High;participants and personnel were not blinded; no ITT analysis **3. Missing outcome data (efficacy)** High;17% withdrawals unclear reasons (not A.E.s)- balanced between arms; no ITT **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if

Study details	Participants	Interventions	Outcomes and results	Comments
completers analysis completers	**Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Participants with nodulocystic acne. **Exclusion details** Pregnant and lactating females. Participants with abnormal lipid profiles, significant hepatic dysfunction and an underlying psychiatric disorder. **Number included** **Number randomised: arm 1** 30 **Number randomised: arm 2** 30 **Number completed: arm 1** 25 **Number completed: arm 2** 25			trial protocol was registered **6. Overall bias** High
Study details **Reference** Dobson, R. L. B., B. S.Topical erythromycin solution in acne. Results of a multiclinic trial. 1980. Journal of the American Academy of Dermatology **Trial ID** Dobson 1980 **Country** United States **Study type**	N=253 **Characteristics** **Sex** mixed **age (other information)** no age info reported **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details**	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** ERYTH 1.5% solution **Intervention: arm 2**	**Results** **Treatment discontinuation for any reason** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;double-blinded but not clear who was blinded; no ITT analysis **3. Missing outcome data (efficacy)** High;21% withdrawals - imbalanced between arms &

Study details	Participants	Interventions	Outcomes and results	Comments
RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** completers	Participants with moderate to severe acne vulgaris of the face (at least 10 papules or pustules, one or more comedones, and not more than 5 nodulocystic lesions). No concurrent illness and not receiving any anti-acne treatment (topical or systemic) for at least 2 weeks prior to study entry. **Exclusion details** Not reported. **Number included** **Number randomised: arm 1** 127 **Number randomised: arm 2** 126 **Number completed: arm 1** 109 **Number completed: arm 2** 90	Vehicle **Coded intervention: arm 1** ERYTH-topical **Coded intervention: arm 2** Vehicle		due to lack of efficacy (2 X more in the vehicle arm); no ITT **4. Outcome measurement (efficacy)** Some concerns;double-blinded but not clear who was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High
Study details **Reference** Dogra, S., Sumathy, T. K., Nayak, C., Ravichandran, G., Vaidya, P. P., Mehta, S., Mittal, R., Mane, A., Charugulla, S. N.Efficacy and safety comparison of combination of 0.04% tretinoin microspheres plus 1% clindamycin versus their monotherapy in patients	N=750 **Characteristics** **Sex** mixed **age (mean±SD)** 21.2 **age (median)** 20 **age (min/max)** 12/48	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** Fixed dose tretinoin 0.04%	**Results** **Treatment discontinuation for any reason** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;random allocation software used - but no further information given **2. Deviation from intervention** Low;double-blinded but not clear who was blinded; ITT analysis was done **3. Missing outcome data**

Study details	Participants	Interventions	Outcomes and results	Comments
with acne vulgaris: a phase 3, randomized, double-blind study. 2020. Journal of Dermatological Treatment **Trial ID** Dogra 2020 **Country** India **Study type** RCT **Source of funding** Dr. Reddy's Laboratories Ltd, India. **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	**Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Static Global Assessment (ISGA)/Investigator's global severity Assessment **Inclusion details** Participants aged >/=12 years.Facial acne (inflammatory lesion count [papulesþpustules] count between >20 to <50; non-inflammatory lesion count [openþclosed comedones] between >20 to <100, and nodules [inflammatory lesion 5mm in diameter] 2) and Investigator's Static Global Assessment (ISGA) score of 3 (moderate) or 4 (severe) **Exclusion details** Patients with a known allergy or sensitivity to study drug, or who were concomitantly using any potentially irritating over-the-counter products that contained benzoyl peroxide, a-hydroxy acids, salicylic acid, retinol or glycolic acids, or who required concurrent use of topical (antimicrobials, anti-acne drugs, anti-inflammatory agents, corticosteroids, retinoids) or systemic (corticosteroids, antimicrobials,	(microsphere) + clindamycin 1.0% gel, o.d. **Intervention: arm 2** Tretinoin gel 0.025%, o.d. **Intervention: arm 3** Clindamycin gel 1.0%, o.d. **Coded intervention: arm 1** TRET-topical+CLIND-topical **Coded intervention: arm 2** TRET-topical **Coded intervention: arm 3** CLIND-topical		**(efficacy)** Some concerns;10% discontinued in total **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Low **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	retinoids) medication and not willing to undergo the specified washout period **Number included** **Number randomised: arm 1** 300 **Number randomised: arm 2** 300 **Number randomised: arm 3** 150 **Number completed: arm 1** 277 **Number completed: arm 2** 267 **Number completed: arm 3** 133			
Study details **Reference** Dreno, B. K., R.,Talarico, S.,Torres Lozada, V.,Rodríguez-Castellanos, M. A.,Gómez-Flores, M.,De Maubeuge, J.,Berg, M.,Foley, P.,Sysa-Jedrzejowska, A.,et al.,Combination therapy with adapalene-benzoyl peroxide and oral lymecycline in the treatment of moderate to severe acne vulgaris: a multicentre, randomized, double-blind controlled study. 2011. British journal of dermatology **Trial ID** Dreno 2011	N=378 **Characteristics** **Sex** mixed **age (mean±SD)** 18.9±4.5999999999999996 **age (min/max)** 12/35 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Participants of any race or sex and aged between 12 and 35 years.	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** ADAP 0·1%/BPO 2·5% gel + LYME 300 mg **Intervention: arm 2** LYME 300 mg + Vehicle **Coded intervention: arm 1** ADAP-topical + BPO-topical + LYME-oral **Coded intervention: arm 2**	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Low;double-blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;more than 5% withdrawals - balanced between arms **4. Outcome measurement (efficacy)** Low;investigators blinded **5. Selective reporting** Some concerns;not reported if

Study details	Participants	Interventions	Outcomes and results	Comments
Country Europe/Maxico/Brazil/Australia **Study type** RCT **Source of funding** Galderma (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	.Moderate to severe acne vulgaris (defined by the Investigator's Global Assessment: IGA score of 3 or 4 on a scale from 0 to 5). Minimum of 20 inflammatory lesions, between 30 and 120 non-inflammatory lesions, and no more than 3 nodulocystic lesions on the face excluding the nose area. Females of childbearing potential had to have a negative urine pregnancy test before and during the study. **Exclusion details** Participants with acne conglobata, acne fulminans (secondary acne) or other dermatological conditions which could interfere with treatment or evaluation. **Number included** **Number randomised: arm 1** 191 **Number randomised: arm 2** 187 **Number completed: arm 1** 178 **Number completed: arm 2** 174	Vehicle + LYME-oral		trial protocol was registered **6. Overall bias** Some concerns
Study details **Reference**	N=218 **Characteristics**	**Interventions** **Treatment duration (weeks)**	**Results** **Treatment**	**Cochrane RoB Tool v2.0** **1. Randomisation**

Study details	Participants	Interventions	Outcomes and results	Comments
Dubertret, L. A., M.,Rostain, G.,Lahfa, M.,Forsea, D.,Dimitrie Niculae, B.,Simola, M.,Horvath, A.,Mizzi, F.The use of lymecycline in the treatment of moderate to severe acne vulgaris: A comparison of the efficacy and safety of two dosing regimens. 2003. European Journal of Dermatology **Trial ID** Dubertret 2003 **Country** Europe **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	**Sex** mixed **age (min/max)** 14/39 **age (other information)** mean age was 20.4, 21.2 & 20.5 yrs for LYME 300mg, LYME 150mg and PLC groups **Inclusion/exclusion criteria** **Used validated acne scale** yes **Acne scale** Leeds Revised Grading Scale **Inclusion details** Males and females aged between 16 and 40 years. Acne vulgaris with a minimum of 15 inflammatory facial lesions and a global severity of at least grade 3 on the Leeds Revised Acne Grading System. **Exclusion details** **Number included** **Number randomised: arm 1** 111 **Number randomised: arm 2** 107 **Number randomised: arm 3** 53 **Number completed: arm 1** 105 **Number completed: arm 2** 88 **Number completed: arm 3**	12 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** LYME-oral 300mg od + PLC-oral **Intervention: arm 2** LYME-oral 150mg bid **Intervention: arm 3** PLC-oral bid **Coded intervention: arm 1** LYME-oral + PLC-oral **Coded intervention: arm 2** LYME-oral **Coded intervention: arm 3** PLC-oral	**discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	Some concerns;no information provided **2. Deviation from intervention** Low;double-blinded; participants likely blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;12% withdrawals (unclear reasons) - imbalanced between arms (more in lymecycline arm); ITT used **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	45			
Study details **Reference** Eichenfield, L.F., Jarratt, M.,Schlessinger, J.,Kempers, S.,Manna, V.,Hwa, J.,Liu, Y.,Graeber, M.Adapalene 0.1% lotion in the treatment of acne vulgaris: Results from two placebo-controlled, multicenter, randomized double-blind, clinical studies. 2010b. Journal of Drugs in Dermatology **Trial ID** Eichenfield 2010b **Country** United States **Study type** RCT **Source of funding** Galderma Research & Development (conflicts of interest were reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	N=1075 **Characteristics** **Sex** mixed **age (mean±SD)** 19.1487441860465±6.89 **age (min/max)** 12/63.9 **age (other information)** mean (SD) combines study 1 and study 2, article reports combined data for both studies by group: ADAP age=19.3 (6.9), median=16.7, range 12-53.8, <18, n=665, 18-64, n=403 ; Veh age=19 (6.9), median=16.8, range 12-63.9, <19, n=679, 18-64, n=394 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Males and females of any race/ethnicity aged 12 years or older. Minimum of 20, but not more than 50, papules and pustules in total on the face and a minimum of 30, but not more than 100, non-inflammatory lesions (open comedones and closed	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** ADAP 0.1% lotion **Intervention: arm 2** Vehicle **Coded intervention: arm 1** ADAP-topical **Coded intervention: arm 2** Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information about allocation sequence provided **2. Deviation from intervention** Low;double-blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;13% withdrawals (both trials combined) - balanced between arms; ITT used **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	comedones) on the face (excluding the nose). Participants with an Investigator's Global Assessment (IGA) of 3 (moderate; more than half of the face involved. Many comedones, papules and pustules. One small nodule may be present) or 4 (severe; entire face is involved. Covered with comedones, numerous papules and pustules. Few nodules/cysts may or may not be present). **Exclusion details** **Number included** **Number randomised: arm 1** 533 **Number randomised: arm 2** 542 **Number completed: arm 1** 471 **Number completed: arm 2** 460			
Study details **Reference** Feldman, S. R. W., C. P.,Alio Saenz, A. B.The efficacy and tolerability of tazarotene foam, 0.1%, in the treatment of acne vulgaris in 2 multicenter, randomized, vehicle-controlled, double-blind studies. 2013.	N=744 **Characteristics** **Sex** mixed **age (mean±SD)** 18.400269179004±6.0598000000000001 **age (min/max)** 12/44	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Low **2. Deviation from intervention** Low;double-blinded; study center,

Study details	Participants	Interventions	Outcomes and results	Comments
Journal of Drugs in Dermatology: JDD **Trial ID** Feldman 2013;Trial 1 **Country** North America **Study type** RCT **Source of funding** Stiefel, a GlaxoSmithKline company (conflicts of interest were reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	**age (other information)** TAZ: 12-17, n=223, 18-25, n=104, 26-35, n=38, 36-45, n=6; VEH: 12-17, n=227, 18-25, n=99, 26-35, n=33, 36-45, n=13 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Static Global Assessment (ISGA)/Investigator's global severity Assessment **Inclusion details** Males and females aged between 12 and 45 years, in good general health and agreed to use a medically-acceptable form of contraception throughout the study. .Moderate to severe acne vulgaris: Investigator's Static Global Assessment (ISGA) score =3 at baseline; lesion counts of 25 to 50 facial inflammatory lesions (papules plus pustules), including nasal lesions, with no more than one facial nodular lesion (<5 mm) and no cystic lesions, and 30 to 125 facial non-inflammatory lesions (open and closed comedones), excluding nasal	**Intervention: arm 1** TAZ 0.1% foam **Intervention: arm 2** Vehicle **Coded intervention: arm 1** TAZ-topical **Coded intervention: arm 2** Vehicle	**Clinician rated improvement in acne** See supplement 8	study monitors, sponsor personnel were blinded to the treatment assignments. ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;14% discontinued (unclear how many due to inefficacy)-imbalanced between arms (more in tazarotene foam arm) **4. Outcome measurement (efficacy)** Low **5. Selective reporting** Low **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	lesions. Provide consent. **Exclusion details** History of suspected intolerance to tazarotene or any of the ingredients of the study products. Participants taking certain topical and systemic treatments were required to undergo specified washout periods. **Number included** **Number randomised: arm 1** 372 **Number randomised: arm 2** 372 **Number completed: arm 1** 307 **Number completed: arm 2** 333			
Study details **Reference** Feldman, S. R. W., C. P.,Alio Saenz, A. B.The efficacy and tolerability of tazarotene foam, 0.1%, in the treatment of acne vulgaris in 2 multicenter, randomized, vehicle-controlled, double-blind studies. 2013. Journal of Drugs in Dermatology: JDD **Trial ID** Feldman 2013;Trial 2 **Country** North America **Study type**	N=742 **Characteristics** **Sex** mixed **age (mean±SD)** 19.2±6.6463999999999999 **age (min/max)** 12/45 **age (other information)** TAZ: 12-17, n=205, 18-25, n=117, 26-35, n=35, 36-45, n=16; VEH: 12-17, n=205, 18-25, n=108, 26-35, n=37, 36-45, n=19 **Inclusion/exclusion criteria**	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** TAZ 0.1% foam **Intervention: arm 2** Vehicle **Coded intervention: arm 1** TAZ-topical	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Low **2. Deviation from intervention** Low;double-blinded; study center, study monitors, sponsor personnel were blinded to the treatment assignments. ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;14%

Study details	Participants	Interventions	Outcomes and results	Comments
RCT **Source of funding** Stiefel, a GlaxoSmithKline company (conflicts of interest were reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	**Used validated acne scale** no **Acne scale** Investigator's Static Global Assessment (ISGA)/Investigator's global severity Assessment **Inclusion details** Males and females aged between 12 and 45 years, in good general health and agreed to use a medically-acceptable form of contraception throughout the study. .Moderate to severe acne vulgaris: Investigator's Static Global Assessment (ISGA) score =3 at baseline; lesion counts of 25 to 50 facial inflammatory lesions (papules plus pustules), including nasal lesions, with no more than one facial nodular lesion (<5 mm) and no cystic lesions, and 30 to 125 facial non-inflammatory lesions (open and closed comedones), excluding nasal lesions. Provide consent. **Exclusion details** History of suspected intolerance to tazarotene or any of the ingredients of the study products. Participants taking certain topical and	**Coded intervention: arm 2** Vehicle		discontinued (unclear how many due to inefficacy)-imbalanced between arms (more in tazarotene foam arm) **4. Outcome measurement (efficacy)** Low **5. Selective reporting** Low **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	systemic treatments were required to undergo specified washout periods. **Number included** **Number randomised: arm 1** 373 **Number randomised: arm 2** 369 **Number completed: arm 1** 307 **Number completed: arm 2** 334			
Study details **Reference** Fluckiger, R. F., H. J.,Rufli, T.Efficacy and tolerance of a miconazole-benzoyl peroxide cream combination versus a benzoyl peroxide gel in the topical treatment of acne vulgaris. 1988. Dermatologica **Trial ID** Fluckiger 1988 **Country** Switzerland **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** completers	N=58 **Characteristics** **Sex** mixed **age (mean±SD)** 18 **age (min/max)** 15/30 **age (other information)** BPO mean age=18.8; BPO + MICO mean age =17.7 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Participants with moderately severe to severe forms of acne vulgaris. Participants not receiving any treatment 4 weeks prior to study entry.	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** BPO 5% cream **Intervention: arm 2** BPO 5%/MICO 2% cream **Coded intervention: arm 1** BPO-topical **Coded intervention: arm 2** BPO-topical + MICO-topical	**Results** **Treatment discontinuation for any reason** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Low;single-blinded - participants; no ITT analysis **3. Missing outcome data (efficacy)** High;12% discontinued - imbalanced between arms (more in BPO-MCZ arm) **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Exclusion details Any accompanying treatment. **Number included** **Number randomised: arm 1** 29 **Number randomised: arm 2** 29 **Number completed: arm 1** 27 **Number completed: arm 2** 25			
Study details **Reference** Fugere, P. P.-S., R. K.,Lussier-Cacan, S.,Davignon, J.,Farquhar, D.Cyproterone acetate/ethinyl estradiol in the treatment of acne. A comparative dose-response study of the estrogen component. 1990. Contraception **Trial ID** Fugere 1990 **Country** Canada **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** completers	N=73 **Characteristics** **Sex** female **age (mean±SD)** 22.9260273972603±3.2639999999999998 **age (min/max)** 17/35 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Cook **Inclusion details** Women in good health aged between 18 and 35 years. Moderate to severe androgen-dependent acne vulgaris (defined as presence of comedones, papules and macules on at least half of the face. Previous treatment	**Interventions** **Treatment duration (weeks)** 48 **Treatment duration category** 24+ weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** CPA 2mg + EE 0.035 mg (Diane-35) **Intervention: arm 2** CPA 2mg + EE 0.05 mg (Diane-50) **Coded intervention: arm 1** CPA-oral + EE-oral **Coded intervention: arm 2** CPA-oral + EE-oral	**Results** **Treatment discontinuation for any reason** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Low;double-blinded - clear that participants were blinded; no ITT analysis **3. Missing outcome data (efficacy)** High;23% withdrawals - not clear if balanced between arms; no ITT used **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias**

Study details	Participants	Interventions	Outcomes and results	Comments
	withdrawn within 6 weeks of starting study treatments. **Exclusion details** Not reported. **Number included** **Number randomised: arm 1** 40 **Number randomised: arm 2** 33 **Number completed: arm 1** 37 **Number completed: arm 2** 25			High
Study details **Reference** Gollnick, H. P. G., K.,Zaumseil, R. P.Comparison of combined azelaic acid cream plus oral minocycline with oral isotretinoin in severe acne. 2001. European Journal of Dermatology **Trial ID** Gollnick 2001 **Country** Germany **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** ITT	N=85 **Characteristics** **Sex** male **age (mean±SD)** 19 **age (min/max)** 15/31 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Leeds Grading Scale, Cunliffe **Inclusion details** Males over the age of 16 years. Participants with severe inflammatory facial acne (at least grade 4 using the Cunliffe's classification (Leeds scale)); at least 2 deep inflammatory lesions (nodes,	**Interventions** **Treatment duration (weeks)** 26 **Treatment duration category** 24+ weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** AZE-topical 20% cream + MINO-oral 50mg bid **Intervention: arm 2** ISO<120.Daily=0.5 **Coded intervention: arm 1** AZE-topical + MINO-oral **Coded intervention: arm 2** ISO<120.Daily=0.5-oral	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** High;open-labeled **3. Missing outcome data (efficacy)** Some concerns;more than 5% withdrawals - imbalanced between arms (more in AA/Mino arm); all participants were included in the efficacy analysis **4. Outcome measurement (efficacy)** High;open-labeled **5. Selective reporting** Some concerns;not reported if trial protocol was registered

Study details	Participants	Interventions	Outcomes and results	Comments
Method of ITT imputation not reported	cysts or nodules) and other papules and pustules. No treatment with any systemic treatment for at least 4 weeks prior to the start of the study (or for isotretinoin, 12 months), use of topical treatment had to have been discontinued at least 2 weeks prior to the start of the study. For inclusion in phase II of the study, participants must have achieved a decrease of at least 75% in the number of deep inflammatory lesions in phase I of the study and in whom the efficacy of treatment had been rated as 'very good'. **Exclusion details** Women. Participants with milder (comedonal or papulopustular acne) or more severe (acne fulminans, acne tetrade) forms of acne. Photosensitivity. Participants with contraindications to isotretinoin or minocycline and hypersensitivity to the substances contained in the study treatment. **Number included** **Number randomised: arm 1** 50 **Number randomised: arm 2** 35 **Number completed: arm 1** 44			**6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 2 33			
Study details **Reference** Gratton, D. R., G. P.,Guertin-Larochelle, S.,Maddin, S. W.,Leneck, C. M.,Warner, J.,Collins, J. P.,Gaudreau, P.,Bendl, B. J.Topical clindamycin versus systemic tetracycline in the treatment of acne. Results of a multiclinic trial. 1982. Journal of the American Academy of Dermatology **Trial ID** Gratton 1982 **Country** Canada **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** completers	N=245 **Characteristics** **Sex** mixed **age (min/max)** 18/35 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Participants with moderate to severe acne (defined as presence of a minimum of 12 to 70 inflammatory papules and pustules, and a maximum of 6 nodulocystic lesions on the face above the jawline). **Exclusion details** Participants with a history of gastrointestinal disease. Participants who had received systemic or topical antibiotics, systemic or topical steroids, or androgenic drugs within 30 days of starting study medication.	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** CLIND 1% solution + PLC capsule **Intervention: arm 2** PLC capsule + PLC solution **Coded intervention: arm 1** CLIND-topical + PLC-oral **Coded intervention: arm 2** PLC-oral + PLC-topical	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Low;double-blinded; likely that participants were blinded; no ITT analysis **3. Missing outcome data (efficacy)** High;17% discontinued - imbalanced between arms (more in placebo arm); no ITT **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	.Females who had been on oral contraceptives for 3 months, or made a change in oral contraceptives within the previous 3 months; pregnancy. **Number included** **Number randomised: arm 1** 121 **Number randomised: arm 2** 124 **Number completed: arm 1** 105 **Number completed: arm 2** 97			
Study details **Reference** Greenwood, R. B., L.,Burke, B.,Cunliffe, W. J.Acne: Double blind clinical and laboratory trial of tetracycline, oestrogen-cyproterone acetate, and combined treatment. 1985. British Medical Journal **Trial ID** Greenwood 1985 **Country** United Kingdom **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** completers	N=92 **Characteristics** **Sex** female **age (min/max)** 16/30 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Leeds Grading Scale, Cunliffe **Inclusion details** Women with moderate or moderately severe acne who had already tried antibiotics for their acne. **Exclusion details** Not reported. **Number included** **Number randomised: arm 1**	**Interventions** **Treatment duration (weeks)** 26 **Treatment duration category** 24+ weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** CPA 2mg/EE 0.05 mg + TETRA 500 mg bid **Intervention: arm 2** CPA 2mg/EE 0.05 mg + PLC capsule **Intervention: arm 3** TETRA 500 mg bid + PLC capsule **Coded intervention: arm 1** CPA-oral + EE-oral + TETRA-	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Low;double-blinded; likely that participants were blinded; not clear if ITT analysis was done **3. Missing outcome data (efficacy)** High;33% withdrawals - balanced between arms. 3% due to inefficacy; No ITT **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if

Study details	Participants	Interventions	Outcomes and results	Comments
	37 **Number randomised: arm 2** 30 **Number randomised: arm 3** 25 **Number completed: arm 1** 25 **Number completed: arm 2** 21 **Number completed: arm 3** 16	oral **Coded intervention: arm 2** CPA-oral + EE-oral + PLC-oral **Coded intervention: arm 3** TETRA-oral + PLC-oral		trial protocol was registered **6. Overall bias** High
Study details **Reference** Gruber, D. M. S., M. O.,Joura, E. A.,Kokoschka, E. M.,Heinze, G.,Huber, J. C.Topical cyproterone acetate treatment in women with acne: A placebo- controlled trial. 1998a. Archives of Dermatology **Trial ID** Gruber 1998a **Country** Austria **Study type** RCT **Source of funding** Supported by Schering Wien Ges. M.b.H. (manuscript translation) and Schering Berlin (provision of cyproterone acetate assays). **Analysis method**	N=32 **Characteristics** **Sex** female **age group** >25 years **age (mean±SD)** 30.3 **age (min/max)** 26/38 **age (other information)** Oral CPA age=29.4 (range 26-37); Topical CPA age 31.3 (range 26-38); PLC topical age=30.3 (range26-38) **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Leeds Grading Scale, Cunliffe **Inclusion details** Women with moderate to severe acne who consulted the	**Interventions** **Treatment duration (weeks)** 13 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** CPA 2mg/EE 0.035 mg **Intervention: arm 2** PLC-lotion **Coded intervention: arm 1** CPA-oral + EE-oral **Coded intervention: arm 2** PLC-topical	**Results** **Treatment discontinuation for any reason** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;not reported if participants/personnel were blinded; no ITT analysis was done **3. Missing outcome data (efficacy)** High;11% withdrawals - balanced between arms; no ITT **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered

Study details	Participants	Interventions	Outcomes and results	Comments
Intention to treat or completers analysis completers	endocrinology outpatient department for a hormonal evaluation and treatment of their acne. Using barrier contraception during study treatment. Acne treatment had been stopped 6 weeks prior to study commencement. **Exclusion details** Participants with medical contraindications to the study treatment or unwilling to smoke less than 5 cigarettes daily. **Number included** **Number randomised: arm 1** 14 **Number randomised: arm 2** 18 **Number completed: arm 1** 12 **Number completed: arm 2** 16			**6. Overall bias** High
Study details **Reference** Hong, J. S. J., J. Y.,Yoon, J. Y.,Suh, D. H.Acne treatment by methyl aminolevulinate photodynamic therapy with red light vs. intense pulsed light. 2013. International Journal of Dermatology **Trial ID** Hong 2013 **Country** Korea, Republic of	N=44 **Characteristics** **Sex** mixed **age (min/max)** 19/35 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Leeds Grading Scale, Cunliffe **Inclusion details**	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Treatment intensity** Total 3 sessions, once every 2 weeks. Endpoint 4-wks after last session. **Number of arms** 2 **Split face design** Yes	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;Unit of randomisation was side of face; no information provided about randomisation method or allocation concealement **2. Deviation from intervention** Some concerns;investigator/ participant blinding not reported; no ITT; unlikely there was a carry over effect of

Study details	Participants	Interventions	Outcomes and results	Comments
Study type RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** completers	Males and females with active acne lesions and Fitzpatrick skin phototypes IV to V; acne grade at least grade 2 (Cunliffe acne grading system). **Exclusion details** History of keloid, photosensitive disorders. Taking medication such as oral contraceptives, oral antibiotics, and topical agents within 4 weeks, treatment with oral isotretinoin within the past 6 months. Pregnant and/or lactating women. **Number included** **Number randomised: arm 1** 22 **Number randomised: arm 2** 22 **Number completed: arm 1** 20 **Number completed: arm 2** 20	**Intervention: arm 1** MAL 16%-RED PDT **Intervention: arm 2** MAL 16%-IPL-PDT **Coded intervention: arm 1** MAL-RED-PDT **Coded intervention: arm 2** MAL-IPL-PDT		treatment **3. Missing outcome data (efficacy)** Some concerns;10% withdrawals - balanced between arms; withdrawals not related to efficacy **4. Outcome measurement (efficacy)** Low;assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns
Study details **Reference** Horfelt, C. F., J.,Frohm-Nilsson, M.,Wiegleb Edstrom, D.,Wennberg, A. M.Topical methyl aminolaevulinate photodynamic therapy for treatment of facial acne vulgaris: Results of a randomized, controlled study. 2006. British Journal of	N=60 **Characteristics** **Sex** mixed **age (median)** 18 **age (min/max)** 15/28 **age (other information)** MAL-PDT median age=18 (range 15-28).	**Interventions** **Treatment intensity** Total 2 sessions, once every 2 weeks. Endpoint 4-wks after last session. **Number of arms** 2 **Split face design** Yes **Intervention: arm 1** MAL 16%-PDT	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;Unit of randomisation was side of face; no information provided about randomisation method or allocation concealement **2. Deviation from intervention** Low;investigator/ participant blinding; ITT used

Study details	Participants	Interventions	Outcomes and results	Comments
Dermatology **Trial ID** Horfelt 2006 **Country** Sweden **Study type** RCT **Source of funding** PhotoCure ASA, Norway (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	PL median age=18 (range 15-28) **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Leeds Grading Scale, Cunliffe **Inclusion details** Participants with moderate to severe inflammatory facial acne; moderate defined as at least 10 inflammatory lesions (papules and pustules) and 15 to 100 non-inflammatory lesions (open and closed comedones), excluding the nose. Acne treatments discontinued up to 3 months prior to the study. **Exclusion details** Not stated. **Number included** **Number randomised: arm 1** 30 **Number randomised: arm 2** 30 **Number completed: arm 1** 27 **Number completed: arm 2** 27	**Intervention: arm 2** PL **Coded intervention: arm 1** MAL-RED-PDT **Coded intervention: arm 2** PLC-physical		**3. Missing outcome data (efficacy)** Some concerns;10% withdrawals - balanced between arms; withdrawals not related to efficacy **4. Outcome measurement (efficacy)** Low;assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns
Study details **Reference** Ioannides, D. R.,	N=80 **Characteristics** **Sex**	**Interventions** **Treatment duration (weeks)** 12	**Results** **Treatment discontinuation for**	**Cochrane RoB Tool v2.0** **1. Randomisation** Low

Study details	Participants	Interventions	Outcomes and results	Comments
D.,Katsambas, A.Topical adapalene gel 0.1% vs. isotretinoin gel 0.05% in the treatment of acne vulgaris: A randomized open-label clinical trial. 2002. British Journal of Dermatology **Trial ID** Ioannides 2002 **Country** Greece **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** completers	mixed **age (min/max)** 15/35 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, lesion type x severity scale 0-100 **Inclusion details** Participants with 15 to 80 facial non-inflammatory lesions (open and closed comedones), 10 to 50 inflammatory lesions (papules and pustules) and no more than 3 nodulocystic lesions. No other cutaneous disease on the face. No use of any other topical treatment for 14 days, systemic antibiotics for 30 days, or systemic retinoids for at least 6 months prior to start of study treatment. Women who were not pregnant or lactating, and had discontinued oral contraception at least 3 months before study entry. **Exclusion details** Not reported. **Number included** **Number randomised: arm 1** 40 **Number randomised: arm 2** 40 **Number completed: arm 1**	**Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** ADAP 0.1% gel **Intervention: arm 2** ISO 0.05% gel **Coded intervention: arm 1** ADAP-topical **Coded intervention: arm 2** ISO-topical	**any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8	**2. Deviation from intervention** High;open label; no ITT analysis was done **3. Missing outcome data (efficacy)** High;9% discontinued - balanced between arms; 6% due to inefficacy; no ITT **4. Outcome measurement (efficacy)** High;open-labeled **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	36 **Number completed: arm 2** 31			
Study details **Reference** Jackson, J. M. F., J. J.,Almekinder, J. L.A randomized, investigator-blinded trial to assess the antimicrobial efficacy of a benzoyl peroxide 5%/ clindamycin phosphate 1% gel compared with a clindamycin phosphate 1.2%/tretinoin 0.025% gel in the topical treatment of acne vulgaris. 2010. Journal of Drugs in Dermatology: JDD **Trial ID** Jackson 2010 **Country** United States **Study type** RCT **Source of funding** Not reported (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** not reported	N=54 **Characteristics** **Sex** mixed **age (mean±SD)** 16.9±5.9 **age (IQR)** BPO/CLIND, median age=15.8 (IQR=13.5-18.5. CLIND/TRET=13.9-17 **age (other information)** BPO/CLIND median age=15.8 (IQR 13.5-18.5). CLIND/TRET median age=15.6 (IQR 13.9-17). **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Males and females of any race, aged 12 years or older. Moderate to moderately severe	**Interventions** **Treatment duration (weeks)** 16 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** BPO 5%/CLIND 1% gel **Intervention: arm 2** CLIND 1%/TRET 0.025% gel **Coded intervention: arm 1** BPO-topical + CLIND-topical **Coded intervention: arm 2** CLIND-topical + TRET-topical	**Results** **Treatment discontinuation for any reason** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;participants not blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;more than 5% withdrawals **4. Outcome measurement (efficacy)** Low;Assessors blinded **5. Selective reporting** Low;All the outcomes listed in the registered protocol were all reported **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	and stable facial acne vulgaris characterised by 15 to 100 facial inflammatory lesions; 15 to 100 facial non-inflammatory lesions, and =2 facial nodules and/or cysts. P. acnes counts of =104 colony-forming units per square centimetre of skin (CFU/cm2) of which no more than 104 CFU/cm2 were erythromycin or clindamycin resistant. Women of childbearing age were required to have a negative urine pregnancy test prior to study enrolment and practice a reliable method of contraceptive during the study. Women taking oestrogens/oral contraceptives =90 days before study baseline could continue with this during the study provided they did not discontinue or alter use during the study. Washout periods and restrictions adhered to for topical and systemic treatments: topical facial treatments, including retinoids, anti-acne products and corticosteroids (2 weeks); topical antibiotics and systemic corticosteroids (4 weeks); systemic antibiotics (6 weeks) and systemic retinoids (6 months). **Exclusion details** Women taking oestrogens/oral			

Study details	Participants	Interventions	Outcomes and results	Comments
	contraceptives =90 days before study baseline. **Number included** **Number randomised: arm 1** 27 **Number randomised: arm 2** 27 **Number completed: arm 1** 25 **Number completed: arm 2** 24			
Study details **Reference** Jones, E. L. C., A. F.Topical erythromycin vs blank vehicle in a multiclinic acne study. 1981. Archives of Dermatology **Trial ID** Jones 1981 **Country** United States **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** completers	N=175 **Characteristics** **Sex** mixed **age (other information)** ERYTH 13-20, n=31; 21-30, n=46; 31-40, n=3; 41+, n=1; not known=0. Vehicle 13-20, n=29; 21-30, n=39; 31-40, n=6; 41+, n=0; not known=1. **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Males and females aged 12 years or older, seeking medical care for acne or recruited volunteers, but	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** BPO 5%/ERYTH 3% gel **Intervention: arm 2** Vehicle **Coded intervention: arm 1** BPO-topical + ERYTH-topical **Coded intervention: arm 2** Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;double-blinded but not clear who was blinded; not clear if ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;more than 5% withdrawals - balanced between arms **4. Outcome measurement (efficacy)** Some concerns;not clear if blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	otherwise in good general health. Facial acne grades 2 or 3 on the severity scale (grade 2: a moderate number of comedones, papules, and small cysts, occasional pustules, and inflammation; grade 3: a great number of lesions with deeper and larger cysts and minimal scarring). Minimum of 10 papular inflammatory acne lesions in the facial area. Participants could be pregnant or of childbearing age. Unresponsive to treatment with oral tetracycline hydrochloride, topical benzoyl peroxide, and tretinoin. **Exclusion details** Children aged <12 years of age. Participants could not be planning to move within 12 weeks. Use of concomitant antibiotics given for systemic effect or another topical acne treatment, unless it was possible to discontinue such treatment 3 weeks before the start of the study. **Number included** **Number randomised: arm 1** 90 **Number randomised: arm 2** 85 **Number completed: arm 1** 81			

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 2 75			
Study details **Reference** Jones, T. M., L.,Monroe, E.,Weiss, J.,Levy, S.A multicentre, double-blind, parallel-group study to evaluate 3% erythromycin/5% benzoyl peroxide dual-pouch pack for acne vulgaris. 2002. Clinical Drug Investigation **Trial ID** Jones 2002 **Country** United States **Study type** RCT **Source of funding** Dermick Laboratories, US. **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** not reported	N=223 **Characteristics** **Sex** mixed **age (mean±SD)** 18.5±5.8 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Physician's Global Assessment (PGA)/Physician's Global Acne Severity Score **Inclusion details** Male and females aged =13 years. Moderate to moderately severe acne vulgaris (overall acne severity score =1.5 on the Physician's Global Acne Severity Scale, 15 to 80 inflammatory lesions, 20 to 140 comedones, and =2 nodules or cysts measuring greater than 5mm. The comedo count did not include the nasal and nasolabial fold area). Treatment with systemic antibiotics known to affect acne and systemic corticosteroids should be discontinued 4 weeks prior to	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** BPO 5%/ERYTH 3% gel (dual pouch pack) **Intervention: arm 2** Vehicle **Coded intervention: arm 1** BPO-topical + ERYTH-topical **Coded intervention: arm 2** Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Low;double-blinded & ITT analysis **3. Missing outcome data (efficacy)** Some concerns;Unclear how many discontinued during the trial **4. Outcome measurement (efficacy)** Low;Assessors blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	study commencement, and 6 months for oral retinoids. A 2-week washout period was required for topical antibiotics and/or anti-acne medication, topical corticosteroids, and topical retinoids. **Exclusion details** Pregnant or lactating women. Participants with beards or long sideburns. Participants with cystic acne or any other diseases affecting their condition or interfering with treatment evaluation. **Number included** **Number randomised: arm 1** 112 **Number randomised: arm 2** 111 **Number completed: arm 1** 112 **Number completed: arm 2** 110			
Study details **Reference** Khanna, N.Treatment of acne vulgaris with oral tetracylines. 1993. Indian journal of dermatology, venerology and leprology **Trial ID** Khanna 1993 **Country** India	N=44 **Characteristics** **Sex** mixed **age group** =25 years **age (min/max)** 14/24 **Inclusion/exclusion criteria** **Used validated acne scale** no	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** TETRA 500 mg po bid	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;No detials on methods **2. Deviation from intervention** High;No blinding; no ITT **3. Missing outcome data (efficacy)** High;Withdrawals of 23% - some due to lack of efficacy &

Study details	Participants	Interventions	Outcomes and results	Comments
Study type RCT **Source of funding** None (no conflicts of interest). **Analysis method** **Intention to treat or completers analysis** completers **Method of ITT imputation** not reported	**Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Males and females with moderately severe acne (defined when acne lesion score (ALS) was 30 to 70) and severe acne (defined as ALS score of more than 70). Participants who had taken oral antibiotics were included in the study after 1 month discontinuation of the antibiotics. **Exclusion details** Participants with acne conglobata. Pregnant women or women using oral contraceptives. Participants with obvious endocrinopathy. **Number included** **Number randomised: arm 1** 21 **Number randomised: arm 2** 23 **Number completed: arm 1** 15 **Number completed: arm 2** 19	**Intervention: arm 2** MINO 50 mg po bid **Coded intervention: arm 1** TETRA-oral **Coded intervention: arm 2** MINO-oral		imbalanced between groups **4. Outcome measurement (efficacy)** High;not blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High
Study details **Reference** Kim, T. I. A., H. J.,Kang, I. H.,Jeong, K. H.,Kim, N. I.,Shin, M. K.Nonablative fractional	N=32 **Characteristics** **Sex** mixed **age (mean±SD)**	**Interventions** **Treatment duration (weeks)** 16 **Treatment duration category** 12 to <24 weeks	**Results** **Treatment discontinuation for any reason** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information about allocation concealment provided

Study details	Participants	Interventions	Outcomes and results	Comments
laser-assisted daylight photodynamic therapy with topical methyl aminolevulinate for moderate to severe facial acne vulgaris: Results of a randomized and comparative study. 2017. Photodermatology Photoimmunology and Photomedicine **Trial ID** Kim 2017 **Country** Korea, Republic of **Study type** RCT **Source of funding** Galderma Research & Development (no conflicts of interest). **Analysis method** **Intention to treat or completers analysis** completers	24.75±3.5999999999999996 **age (min/max)** 19/45 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Participants aged between 19 and 45 years. Active acne lesions and Fitzpatrick skin phototypes III to IV; acne severity grade 3 or 4 according to the IGA. **Exclusion details** History of photosensitive disorders. Use of medications such as oral isotretinoin for 3 months and oral contraceptives or antibiotics for 4 weeks, topical treatments or facial procedures for 4 weeks. Pregnant or lactating women. Participants were prohibited from using oral or topical medications for treatment of acne during the study. **Number included** **Number randomised: arm 1** 16 **Number randomised: arm 2** 16 **Number completed: arm 1** 14	**Treatment intensity** Total 2 sessions, once every 2 weeks. FU visits at 2, 6, 10 and 14 wks after last session. **Number of arms** 2 **Split face design** No **Intervention: arm 1** MAL 16%-DL PDT **Intervention: arm 2** NAFL + MAL 16%-DL PDT **Coded intervention: arm 1** MAL-DL-PDT **Coded intervention: arm 2** NAFL + MAL-DL-PDT	**Clinician rated improvement in acne** See supplement 8	**2. Deviation from intervention** Some concerns;Not reported if participants were blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** High;more than 5% withdrawals - balanced between arms **4. Outcome measurement (efficacy)** Low **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 2 14			
Study details **Reference** Kircik, L.Community-based trial results of combination clindamycin 1 %-benzoyl peroxide 5% topical gel plus tretinoin microsphere Gel 0.04% or 0.1% or adapalene gel 0.1 % in the treatment of moderate to severe acne. 2007. Cutis **Trial ID** Kircik 2007 **Country** United States **Study type** RCT **Source of funding** Stiefel Laboratories (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** not reported	N=353 **Characteristics** **Sex** mixed **age (mean±SD)** 20.4±na **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Static Global Assessment (ISGA)/Investigator's global severity Assessment **Inclusion details** Participants with moderate to severe acne. **Exclusion details** Not reported. **Number included** **Number randomised: arm 1** 118 **Number randomised: arm 2** 118 **Number randomised: arm 3** 117 **Number completed: arm 1** 118 **Number completed: arm 2** 118 **Number completed: arm 3** 117	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Treatment intensity** 3 **Number of arms** 2 **Split face design** No **Intervention: arm 1** BPO 5%/CLIND 1% gel + TRET 0.04% gel **Intervention: arm 2** BPO 5%/CLIND 1% gel + ADAP 0.1% gel **Intervention: arm 3** BPO 5%/CLIND 1% gel + TRET 0.1% gel **Coded intervention: arm 1** BPO-topical + CLIND-topical + TRET-tropical **Coded intervention: arm 2** BPO-topical + CLIND -topical + ADAP-topical **Coded intervention: arm 3** BPO-topical + CLIND-topical + TRET-tropical	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;not reported if participants were blinded **3. Missing outcome data (efficacy)** Low;No withrawals / loss to follow-up **4. Outcome measurement (efficacy)** Low **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Kircik, L. G., L.,Thiboutot, D.,Tanghetti, E.,Wilson, D.,Dhawan, S.,Parr, L.Comparing a novel solubilized benzoyl peroxide gel with benzoyl peroxide/clindamycin: Final data from a multicenter, investigator-blind, randomized study. 2009a. Journal of Drugs in Dermatology **Trial ID** Kircik 2009a **Country** United States **Study type** RCT **Source of funding** Not reported (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** not reported	N=147 **Characteristics** **Sex** mixed **age (mean±SD)** 21.4±8.4 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Males or females of any race, aged 12 years or older. Moderate to severe stable, non-rapidly progressing facial acne vulgaris characterised by 20 to 60 facial inflammatory lesions; 20 to 60 facial non-inflammatory lesions and =2 facial nodules and/or cysts. Women of childbearing potential were required to have a negative urine pregnancy test at baseline and use a reliable method of contraceptive during the study period. **Exclusion details** Pregnancy, nursing or lack of contraceptive use. Known sensitivity to any of the test medications or their components, potentially	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** BPO 5%/CLIND 1% gel + TRET 0.04% gel **Intervention: arm 2** CLIND 1.2%/TRET 0.025% gel + BPO 5% wash **Coded intervention: arm 1** BPO-topical + CLIND-topical + TRET-tropical **Coded intervention: arm 2** BPO-topical + CLIND-topical + TRET-tropical	**Results** **Treatment discontinuation for any reason** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;not reported if participants were blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;more than 5% withdrawals - balanced between arms **4. Outcome measurement (efficacy)** Low **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	complicating medical histories (such as history of enteritis, especially pseudomembranous colitis or antibiotic-associated colitis). Non-compliance with washout periods for treatments such as topical and systemic acne medications, antibiotics, retinoids, BPO and corticosteroids). Skin conditions that might interfere with the diagnosis or evaluation of acne, procedures complementary to treatment of facial acne within 14 days of baseline and compliance issues. **Number included** **Number randomised: arm 1** 73 **Number randomised: arm 2** 74 **Number completed: arm 1** 59 **Number completed: arm 2** 65			
Study details **Reference** Kuhlman, D. S. C., J. P.A comparison of clindamycin phosphate 1 percent topical lotion and placebo in the treatment of acne vulgaris. 1986. Cutis **Trial ID**	N=na **Characteristics** **Sex** mixed **age (min/max)** 12/30 **Inclusion/exclusion criteria** **Used validated acne scale** no	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;double-blinded but not clear who was blinded **3. Missing outcome data**

Study details	Participants	Interventions	Outcomes and results	Comments
Kuhlman 1986 **Country** United States **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** completers	**Acne scale** None **Inclusion details** Men and women aged 12 to 30 years. Moderate to severe acne vulgaris defined as 12 to 70 inflammatory papules and no more than 6 cystic lesions on the face above the jawline. **Exclusion details** Participants sensitive to clindamycin. Pregnant or nursing women. Participants with chronic bowel disease or frequent periodic diarrhoea. Participants requiring additional acne treatment, those who had received systemic antibiotics, steroids, or androgens within the past 30 days or topical acne medications within the past 14 days, and participants who had started or stopped using oral contraceptives in the past 60 days. **Number included** **Number randomised: arm 1** na **Number randomised: arm 2** na **Number completed: arm 1** 21 **Number completed: arm 2** 14	**Intervention: arm 1** CLIND 1% lotion **Intervention: arm 2** Vehicle **Coded intervention: arm 1** CLIND-topical **Coded intervention: arm 2** Vehicle		**(efficacy)** High;not reported how many participants were randomised to each arm; not reported how many withdrew **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Leyden, J. B., W.,Drake, L.,Dunlap, F.,Goldman, M. P.,Gottlieb, A. B.,Heffernan, M. P.,Hickman, J. G.,Hordinsky, M.,Jarrett, M.,et al.,A systemic type I 5 alpha-reductase inhibitor is ineffective in the treatment of acne vulgaris. 2004. Journal of the american academy of dermatology **Trial ID** Leyden 2004 **Country** United States **Study type** RCT **Source of funding** Merck Research Laboratories (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** completers	N=na **Characteristics** **Sex** mixed **age (other information)** no age nor sex data reported **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Participants with moderately severe acne with a minimum of 20 inflammatory lesions. **Exclusion details** Not reported. **Number included** **Number randomised: arm 1** na **Number randomised: arm 2** na **Number completed: arm 1** 34 **Number completed: arm 2** 37	**Interventions** **Treatment duration (weeks)** 13 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** MINO 100 mg + PL **Intervention: arm 2** PL **Coded intervention: arm 1** MINO-oral + PLC-oral **Coded intervention: arm 2** PLC-oral	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Low;Participant & investigator blinded; no ITT **3. Missing outcome data (efficacy)** High;not reported how many participants withdrew (only results for completers). 269 included in safety analysis - only 182 in efficacy analysis **4. Outcome measurement (efficacy)** Low;Assessor blinded **5. Selective reporting** High;Some of the specified outcomes not reported **6. Overall bias** High
Study details **Reference** Mei, X. S., W.,Piao, Y.Effectiveness of photodynamic therapy with topical 5-aminolevulinic acid and intense pulsed light in Chinese acne vulgaris	N=41 **Characteristics** **Sex** mixed **age (mean±SD)** 24 **Inclusion/exclusion criteria** **Used validated acne scale**	**Interventions** **Treatment intensity** Total 4 sessions, once every week. Assessments 1-wk after each session so have assumed endpoint is at 4th treatment (see table1) **Number of arms**	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** High;Allocation not concealed **2. Deviation from intervention** Low;Participants & investigators blinded **3. Missing outcome data**

Study details	Participants	Interventions	Outcomes and results	Comments
patients. 2013. Photodermatology Photoimmunology and Photomedicine **Trial ID** Mei 2013 **Country** China **Study type** RCT **Source of funding** Not reported (no conflicts of interest). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** not reported	no **Acne scale** Global Acne Severity Scale (GEA Scale) **Inclusion details** Chinese people aged over 18 years. Participants with II–IV facial acne according to Pillsbury grade and Fitzpatrick skin type II–IV. **Exclusion details** Participants exposed to systemic retinoid treatment in the last 6 months, systemic antibiotics treatment or contraceptive and photosensitive drugs in the previous month, local acne drug treatment in the last 2 weeks. Participants with a tendency to form keloids or with a history of photosensitivity. Pregnant or breastfeeding women. **Number included** **Number randomised: arm 1** 21 **Number randomised: arm 2** 20 **Number completed: arm 1** 21 **Number completed: arm 2** 20	2 **Split face design** No **Intervention: arm 1** 5ALA 10%-IPL-PDT **Intervention: arm 2** IPL-PT + Vehicle **Coded intervention: arm 1** 5ALA-IPL-PDT **Coded intervention: arm 2** IPL + Vehicle		**(efficacy)** Low;No withrawals / loss to follow-up. **4. Outcome measurement (efficacy)** Low;Assessor blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High
Study details **Reference**	N=90 **Characteristics**	**Interventions** **Treatment duration (weeks)**	**Results** **Treatment**	**Cochrane RoB Tool v2.0** **1. Randomisation**

Study details	Participants	Interventions	Outcomes and results	Comments
Miller, J. A. W., F. T.,Dowd, P. M.Anti-androgen treatment in women with acne: A controlled trial. 1986b. British Journal of Dermatology **Trial ID** Miller 1986b **Country** United Kingdom **Study type** RCT **Source of funding** Schering Chemicals Ltd. **Analysis method** **Intention to treat or completers analysis** completers	**Sex** female **age (min/max)** 16/36 **age (other information)** CPA/EE mean age=24.2 (range 18-34); NOR/EE mean age 24.2 (range 18-36); CPA mean age=22.8 (range 16-30) **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Leeds Grading Scale, Cunliffe **Inclusion details** Women aged between 16 and 36 years. Moderate to severe acne (graded according to Burke & Cunliffe, 1984). Any acne medication (other than contraceptive pill) stopped 6 weeks prior to study participation. Oral contraception was continued until the commencement of the trial. **Exclusion details** Participants with medical contraindications to the study treatment. Current smokers (more than 5 cigarettes daily). **Number included** **Number randomised: arm 1** 28 **Number randomised: arm 2** 32	26 **Treatment duration category** 24+ weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** CPA 2mg/EE 0.05 mg (days 5-25) + PL (days 5-14) **Intervention: arm 2** NOR 1mg/EE 0.05mg (days 5-25) + PL (days 5-14) **Intervention: arm 3** CPA 50mg (days 5-14), then EE 0.05 mg (days 5-25) **Coded intervention: arm 1** CPA-oral + EE-oral + PLC-oral **Coded intervention: arm 2** NOR-oral + EE-oral + PLC-oral **Coded intervention: arm 3** CPA-oral + EE-oral	**discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8	Some concerns;no information provided **2. Deviation from intervention** Some concerns;double-blinded but not clear who was blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** High;Withdrawal imbalanced between groups (more in Diane and placebo arm) and more than 5% **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number randomised: arm 3 30 **Number completed: arm 1** 24 **Number completed: arm 2** 26 **Number completed: arm 3** 26			
Study details **Reference** Nicklas, C. R., R.,Cardenas, C.,Hasson, A.Comparison of efficacy of aminolaevulinic acid photodynamic therapy vs. adapalene gel plus oral doxycycline for treatment of moderate acne vulgaris-A simple, blind, randomized, and controlled trial. 2019. Photodermatology Photoimmunology and Photomedicine **Trial ID** Nicklas 2019 **Country** Chile **Study type** RCT **Source of funding** Research Department, Universidad Catolica de Chile. **Analysis method** **Intention to treat or completers analysis** ITT	N=46 **Characteristics** **Sex** mixed **age (other information)** 5ALA-PDT median age=21 (IQR 18-21); ADAP+DOXY median age=21 (IQR 18-25) **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Participants with moderately severe inflammatory acne vulgaris defined by Leeds revised acne grading system with modifications as numerous papules and pustules (40 to 100) usually with many comedones (40 to 100) and occasional (up to 5) larger, deeper nodular inflamed lesions on the face. Males and females aged 18 to 30 years. Phototype according	**Interventions** **Treatment duration (weeks)** 6 **Treatment duration category** 6 to <12 weeks **Treatment intensity** Total 2 sessions of 5ALA-PDT, once every 2 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** 5ALA 20%-PDT **Intervention: arm 2** ADAP 0.1% gel + DOXY 100 mg **Coded intervention: arm 1** 5ALA-RED-PDT **Coded intervention: arm 2** ADAP-topical + DOXY-oral	**Results** **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information about allocation concealment provided **2. Deviation from intervention** Some concerns;not reported if participants were blinded **3. Missing outcome data (efficacy)** Low;all participants completed the study **4. Outcome measurement (efficacy)** Low **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
Method of ITT imputation not reported	to Fitzpatrick skin type I to IV with facial acne vulgaris. No other acne treatments permitted during study. **Exclusion details** Participants with photosensitivity disorder, autoimmune diseases, infectious diseases (HIV, herpes, TB), allergy or intolerance to tetracycline antibiotics, taking topical medication within 3 months and/or systemic treatment within the past 6 months. Pregnant or lactating women **Number included** **Number randomised: arm 1** 23 **Number randomised: arm 2** 23 **Number completed: arm 1** 23 **Number completed: arm 2** 23			
Study details **Reference** Paithankar DY, Sakamoto FH, Farinelli WA, et al.Acne Treatment Based on Selective Photothermolysis of Sebaceous Follicles with Topically Delivered Light-	N=48 **Characteristics** **Sex** mixed **age (mean±SD)** 21.2 **age (min/max)** 16/30	**Interventions** **Treatment intensity** Total 3 treatments, at 2 week intervals **Number of arms** 2 **Split face design** No	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;methods not reported **2. Deviation from intervention** Some concerns;Unclear whether blinded; no ITT

Study details	Participants	Interventions	Outcomes and results	Comments
Absorbing Gold Microparticles. 2015. J Invest Dermatol. **Trial ID** Paithankar 2015;Trial 1 **Country** Poland **Study type** RCT **Source of funding** Sebacia, Duluth, GA (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** completers	**Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Males and females aged 16 to 35 years of age. Moderate-to-severe inflammatory facial acne; IGA scores 3 to 4 with at least 25 total papules and pustules present on face Fitzpatrick skin phototype I to III. **Exclusion details** Use of systemic medications for acne, oral retinoid treatment, or treatment with Intense Pulsed Lights or lasers within the past 12 months. **Number included** **Number randomised: arm 1** 23 **Number randomised: arm 2** 25 **Number completed: arm 1** 21 **Number completed: arm 2** 25	**Intervention: arm 1** GOLDMP + PDL **Intervention: arm 2** No treatment **Coded intervention: arm 1** GOLDMP **Coded intervention: arm 2** No treatment		**3. Missing outcome data (efficacy)** High;Withdrawal imbalanced between groups, &>5%, unclear reasons for missing data; no ITT **4. Outcome measurement (efficacy)** High;Assessor blinded scores pooled with unblinded scores **5. Selective reporting** Low;Trial protocol was registered (both trials 1 & 2 under the same number) **6. Overall bias** High
Study details **Reference** Pariser, D. M. T., D. M.,Clark, S. D.,Jones, T. M.,Liu, Y.,Graeber, M.The efficacy	N=214 **Characteristics** **Sex** mixed **age (mean±SD)**	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks	**Results** **Treatment discontinuation for any reason** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;reported only that medication was dispensed by a third party to protect

Study details	Participants	Interventions	Outcomes and results	Comments
and safety of adapalene gel 0.3% in the treatment of acne vulgaris: A randomized, multicenter, investigator-blinded, controlled comparison study versus adapalene gel 0.1% and vehicle. 2005. Cutis **Trial ID** Pariser 2005 **Country** United States **Study type** RCT **Source of funding** Galderma Research & Development (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** baseline assigned?	17.3±5.07 **age (median)** 16 **age (min/max)** 12/45 **Inclusion/exclusion criteria** **Used validated acne scale** yes **Acne scale** Leeds Revised Grading Scale **Inclusion details** Participants aged 12 to 40 years. Moderate to moderately severe acne vulgaris; minimum of 20 inflammatory facial lesions (not >2 nodules/cysts), 20 non-inflammatory facial lesions; global facial severity grade 4 to 10 according to the Leeds Revised Acne Grading System. Washout periods for certain topical and systemic treatments were required. Negative urine pregnancy test results required at screening and at the final visit for women of childbearing potential. **Exclusion details** Not reported. **Number included** **Number randomised: arm 1** 70 **Number randomised: arm 2** 70 **Number randomised: arm 3** 74	**Number of arms** 3 **Split face design** No **Intervention: arm 1** ADAP 0.3% gel **Intervention: arm 2** ADAP 0.1% gel **Intervention: arm 3** Vehicle **Coded intervention: arm 1** ADAP-topical **Coded intervention: arm 2** ADAP-topical **Coded intervention: arm 3** Vehicle	**Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	blinding **2. Deviation from intervention** Some concerns;not reported if participants were blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;Withdrawal imbalanced between groups (21% in the adapalene gel 0.3% arm, only 7% in the adapalene 0.1% gel arm) **4. Outcome measurement (efficacy)** Low;investigator-blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 1 55 **Number completed: arm 2** 65 **Number completed: arm 3** 62			
Study details **Reference** Pariser, D. M. R., P.,Cook-Bolden, F. E.,Korotzer, A.An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 3.75% for the once-daily treatment of moderate to severe acne vulgaris. 2014. Journal of Drugs in Dermatology **Trial ID** Pariser 2014 **Country** United States **Study type** RCT **Source of funding** Valeant Pharmaceuticals North America LLC. **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** MI MCMC	N=498 **Characteristics** **Sex** mixed **age (mean±SD)** 18.7±5.82 **age (median)** 17 **age (min/max)** 12/40 **age (other information)** Sig. diff (p=0.02) between age of groups **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Evaluator's Global Severity Scale (EGSS) **Inclusion details** Males and females of any race and ethnicity, aged 12 to 40 years. Moderate to severe acne vulgaris (a score of 3 or 4 on the Global Severity Score (EGSS), presenting with 20 to 40 inflammatory lesions (papules, pustules, and	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** BPO 3.75%/CLIND 1.2% gel **Intervention: arm 2** Vehicle **Coded intervention: arm 1** BPO-topical + CLIND-topical **Coded intervention: arm 2** Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;insufficient information provided on allocation concealment **2. Deviation from intervention** Low;double-blinded & ITT analysis **3. Missing outcome data (efficacy)** Some concerns;Withdrawal imbalanced between groups, &>5% **4. Outcome measurement (efficacy)** Low **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	nodules), 20 to 100 non-inflammatory lesions (open and closed comedones), and =2 nodules. Women of childbearing age were required to have a negative urine pregnancy test and to agree to use an effective form of contraception during the study period. A washout period of up to 1 month was required for participants who used previous prescription and over-the-counter acne treatments (including, topical (face) and systemic treatments: topical astringents and abrasives (1 week); topical anti-acne products, including soaps containing antimicrobials, and known comedogenic products (2 weeks); topical retinoids, retinol, and systemic acne treatments (4 weeks); and systemic retinoids (6 months). **Exclusion details** Not reported. **Number included** **Number randomised: arm 1** 253 **Number randomised: arm 2** 245 **Number completed: arm 1** 234 **Number completed: arm 2** 213			

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Pariser, D. M. E., L. F.,Bukhalo, M.,Waterman, G.,Jarratt, M.,Bhatia, A.,Greenstein, D.,Hamzavi, F.,Kantor, J.,Speelman, P. N.,Murakawa, G. J.,Tichy, E.,Zaengelin, A.,Frankel, E.,Werschler, W.Photodynamic therapy with methyl aminolaevulinate 80 mg g⁻¹ for severe facial acne vulgaris: A randomized vehicle-controlled study. 2016. British Journal of Dermatology **Trial ID** Pariser 2016 **Country** United States **Study type** RCT **Source of funding** Photocure ASA, Norway (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	N=153 **Characteristics** **Sex** mixed **age (min/max)** 12/36 **age (other information)** MAL-PDT median age=17 (range 12-36), <18 years-old, n=59; Vehicle median age=17 (range 12-35), <18 years-old, n=31 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Males and females aged 12 to 35 years. Severe facial acne vulgaris (defined by an IGA rating score of 4); 27 to 75 inflammatory lesions (papules, pustules and no more than 3 nodules) and 20 to 100 non-inflammatory lesions (open and closed comedones) on the face; Fitzpatrick skin types I to VI. Confirmed using standardised clinical photographs. Females of childbearing potential were required to use appropriate contraception (same product and dose if using an oral	**Interventions** **Treatment intensity** Total 4 sessions, once every 2 weeks. Endpoint is 6-wks after last treatment. **Number of arms** 2 **Split face design** No **Intervention: arm 1** MAL 8%-RED-PDT **Intervention: arm 2** Vehicle-RED-PDT **Coded intervention: arm 1** MAL-RED-PDT **Coded intervention: arm 2** Vehicle + RED	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Low **2. Deviation from intervention** Low;double-blinded; according to the study protocol it is quadruple-blinded (participant, care provider, investigator, outcomes assessor); ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;16% withdrawals - imbalanced between arms as 12 out of 17 in the active arm discontinued due to adverse events and none in the other arm **4. Outcome measurement (efficacy)** Low **5. Selective reporting** Low **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	contraceptive) for at least 14 days before the first treatment and during the study. **Exclusion details** Participants with acne conglobata, acne fulminans, secondary acne, melanoma or dysplastic naevi in the treatment area. Facial har that might interfere with study assessments. Participants with porphyria, cutaneous photosensitivity or known allergy to methyl aminolaevulinate, components of the cream or similar photosensitisers. Participants with moderate-to-very-severe facial acne scarring. Pregnant or nursing females. Systemic acne treatment (oral antibiotics within 1 month or oral isotretinoin within 6 months); topical treatments (other than medicated cleansers) within 14 days; facial procedures (for example, dermabrasion, chemical or laser peels); exposure to ultraviolet radiation (other than sunlight) within 1 month and concomitant hormonal therapy for acne were prohibited. **Number included** **Number randomised: arm 1** 100 **Number randomised: arm 2**			

Study details	Participants	Interventions	Outcomes and results	Comments
	53 **Number completed: arm 1** 83 **Number completed: arm 2** 46			
Study details **Reference** Peacock, C. E. P., C.,Ryan, B. E.,Mitchell, A. D.Topical clindamycin (Dalacin T) compared to oral minocycline (Minocin 50) in treatment of acne vulgaris. A randomized observer-blind controlled trial in three university student health centres. 1990. Clinical Trials Journal **Trial ID** Peacock 1990 **Country** United Kingdom **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** completers	N=na **Characteristics** **Sex** mixed **age (mean±SD)** 21 **age (min/max)** 18/34 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Males and females aged 16 to 35 years of age attending student health centres at 4 universities. Moderate to severe acne, defined as having a minimum of 12 and a maximum of 100 inflammatory lesions, with no more than 6 nodulocystic lesions above the jawline. **Exclusion details** Participants taking prescribed treatment for acne within 14 days of study start, receiving systemic antibiotics, corticosteroids or androgens	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** CLIND-topical 1% bid **Intervention: arm 2** MINO-oral 50mg bid **Coded intervention: arm 1** CLIND-topical **Coded intervention: arm 2** MINO-oral	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;insufficient information provided on allocation concealment **2. Deviation from intervention** Some concerns;Participants were blinded but the dispensing nurses were not; no ITT **3. Missing outcome data (efficacy)** Some concerns;>10% did not complete - unclear how many due to lack of efficacy **4. Outcome measurement (efficacy)** Low;"observers" were blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	within 14 days of the start of study treatment; participants who had started or stopped oral contraception within 31 days of study treatment. Participants in any other trial or previously enrolled in the study. Participants with known allergy to tetracyclines or clindamycin. .Participants with a history of chronic bowel disease, diarrhoea or a past history of antibiotic associated colitis, participants with any serious or uncontrolled illness. Pregnant or nursing women, or women not using reliable contraceptive methods. **Number included** **Number randomised: arm 1** na **Number randomised: arm 2** na **Number completed: arm 1** 42 **Number completed: arm 2** 38			
Study details **Reference** Peck, G. L. O., T. G.,Butkus, D.Isotretinoin versus placebo in the treatment of cystic acne. 1982a. Journal of the	N=33 **Characteristics** **Sex** mixed **age (mean±SD)**	**Interventions** **Treatment duration (weeks)** 4 **Treatment duration category** 0 to <6 weeks	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Low **2. Deviation from intervention**

Study details	Participants	Interventions	Outcomes and results	Comments
American Academy of Dermatology **Trial ID** Peck 1982a **Country** United States **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** completers	23 **age (other information)** 32 of the 33 included participants had a mean age of 23 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Volunteers with at least 10 inflamed deep dermal or subcutaneous acne cysts or nodules of at least 4 mm diameter. History of minimal response to treatment with oral and topical antibiotics, oral vitamin A, topical vitamin A acid, topical benzoyl peroxide, x-irradiation, oral contraceptives, oral dapsone, intralesional injections of corticosteroids, oral prednisone, surgical drainage, applications of liquid nitrogen, photochemotherapy with psoralen and long-wave ultraviolet light, and other acne treatments. Discontinuation of conventional acne treatment for at least 1 month prior to study entry. No other acne treatment (topical or systemic) permitted during 4-month study treatment period. **Exclusion details**	**Number of arms** 2 **Split face design** No **Intervention: arm 1** ISO<120.Daily=0.5 **Intervention: arm 2** PLC-oral **Coded intervention: arm 1** ISO<120.Daily=0.5-oral **Coded intervention: arm 2** PLC-oral		Low;double-blinded - likely that participants were blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;not clear how many participants discontinued **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	Pregnant women and women of childbearing potential refusing use of birth control methods. Use of oral contraceptives. **Number included** **Number randomised: arm 1** 16 **Number randomised: arm 2** 17 **Number completed: arm 1** 16 **Number completed: arm 2** 17			
Study details **Reference** Sami, N. A. A., A. T.,Badawi, A. M.Phototherapy in the treatment of acne vulgaris. 2008. Journal of drugs in dermatology : JDD **Trial ID** Sami 2008 **Country** Egypt **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** ITT	N=45 **Characteristics** **Sex** mixed **age (mean±SD)** 29 **age (min/max)** 20/38 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Burton **Inclusion details** Males and females with moderate to severe facial acne according to Burton classification. **Exclusion details** Participants with a history of	**Interventions** **Treatment duration (weeks)** 4 **Treatment duration category** 0 to <6 weeks **Treatment intensity** Trial continued until 90% lesion clearance observed but 1-mo data available. Total sessions at 1-mo are 4, 4 and 8, respectively, for PDL (1 session, once a week), IPL (1 session, once a week) and BR-LED (2 sessions every week) groups **Number of arms** 3 **Split face design** No **Intervention: arm 1** 595 nm PDL PT	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;methods not reported **2. Deviation from intervention** Some concerns;Not reported if participants were blinded **3. Missing outcome data (efficacy)** Some concerns;not clear if/how many participants discontinued **4. Outcome measurement (efficacy)** Low **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	topical acne treatment or systemic antibiotics within the past 2 weeks, or use of systemic steroids, systemic retinoids, or anti-inflammatory drugs within the past 6 months. History of photosensitivity. Pregnancy. **Number included** **Number randomised: arm 1** 15 **Number randomised: arm 2** 15 **Number randomised: arm 3** 15 **Number completed: arm 1** 15 **Number completed: arm 2** 15 **Number completed: arm 3** 15	**Intervention: arm 2** 550 nm-1200 nm IPL PT **Intervention: arm 3** BR-LED PT **Coded intervention: arm 1** PDL **Coded intervention: arm 2** IPL **Coded intervention: arm 3** BR-LED		
Study details **Reference** Schmidt, N. G., E. H.Clindamycin 1.2% tretinoin 0.025% gel versus clindamycin gel treatment in acne patients: A focus on fitzpatrick skin types. 2011. Journal of Clinical and Aesthetic Dermatology **Trial ID** Schmidt 2011 **Country** United States **Study type**	N=2010 **Characteristics** **Sex** mixed **age (mean±SD)** 19.0501492537313±7.250747 0119521908 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Evaluator's Global Severity Scale (EGSS)	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** CLIND 1.2%/TRET 0.025% gel **Intervention: arm 2** CLIND 1.2% gel	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information about allocation concealment provided **2. Deviation from intervention** Some concerns;double-blinded but not clear who was blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;16% withdrawals - balanced

Study details	Participants	Interventions	Outcomes and results	Comments
RCT **Source of funding** Not reported (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	**Inclusion details** Males and females aged over 12 years. Facial acne vulgaris with 20 to 50 inflammatory lesions (papules and pustules), 20 to 100 non-inflammatory lesions (open and closed comedones), and not more than 2 nodules; Evaluators Global Severity Score (EGSS) of moderate or severe. Willing to undergo the specified washout periods for topical antibiotics and other topical antibacterial drugs (2 weeks); facial anti-inflammatory agents and corticosteroids (4 weeks); retinoids, including retinol (4 weeks). Had undergone the specified washout periods of systemic treatments including corticosteroids and intramuscular injections (4 weeks); antibiotics (4 weeks); other systemic acne treatments (4 weeks); systemic retinoids (6 months). **Exclusion details** Participated in a similar study within 30 days of enrolment or participating in another study. Facial dermatological conditions that could hinder or obstruct clinical evaluations. Use of other non-acne topical medication that could interfere with study treatment. Pregnant,	**Coded intervention: arm 1** CLIND-topical + TRET-topical **Coded intervention: arm 2** CLIND-topical		between arms (unclear how many due to inefficacy); ITT used **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	nursing, planning a pregnancy, or became pregnant during the trial. Non-compliance with washout criteria for topical or systemic treatment. **Number included** **Number randomised: arm 1** 1008 **Number randomised: arm 2** 1002 **Number completed: arm 1** 859 **Number completed: arm 2** 838			
Study details **Reference** Shalita, A. R. S., J. G.,Parish, L. C.,Sofman, M. S.,Chalker, D. K.Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. 1995. International Journal of Dermatology **Trial ID** Shalita 1995 **Country** United States **Study type** RCT **Source of funding** Supported in part by Genderm Corporation, Lincolnshire, IL. **Analysis method** **Intention to treat or**	N=76 **Characteristics** **Sex** mixed **age (mean±SD)** 21.3 **age (min/max)** 13/35 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Men and women aged 13 to 35 years. Moderate inflammatory acne vulgaris (defined by the presence of at least 15 papules and/or pustules on the face); severity grade according	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Number of arms** 2 **Coded intervention: arm 1** NICO-topical **Coded intervention: arm 2** CLIND-topical	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;double-blinded but not clear who was blinded; no ITT analysis was done **3. Missing outcome data (efficacy)** High;22% withdrawals - balanced between arms (unclear how many due to inefficacy); no ITT **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting**

Study details	Participants	Interventions	Outcomes and results	Comments
completers analysis completers	to Allen and Smith's modification of the Cook et al. procedure. Withdrawal of treatments, including topical acne preparations, topical antimicrobial agents, medicated cosmetics, soaps or shampoos, and radiation therapy, topical corticosteroids, and investigational drugs at least 2 weeks before study enrolment; systemic antimicrobials corticosteroids at least 12 weeks before study; and oral isotretinoin at least 2 years prior to study enrolment. Oral contraceptives were permitted as long as they had been used continuously for at least 3 months prior to study and the dosage schedule was not expected to change during the study. **Exclusion details** Participants with primarily comedonal acne. Pregnant or lactating women. Participants with more than 3 nodular lesions on the face; active skin disease other than inflammatory acne vulgaris. History of allergy to study treatments. Previous history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. **Number included**			Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number randomised: arm 1 38 **Number randomised: arm 2** 38 **Number completed: arm 1** 29 **Number completed: arm 2** 30			
Study details **Reference** Sklar, J. L. J., C.,Rizer, R.,Gans, E. H.Evaluation of Triaz 10% Gel and Benzamycin in acne vulgaris. 1996. Journal of dermatological treatment **Trial ID** Sklar 1996 **Country** United States **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** completers	N=94 **Characteristics** **Sex** mixed **age (min/max)** 16/30 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Males and females aged 16 to 30 years. Moderate to moderately severe, papular-pustular, facial acne vulgaris with a minimum number of inflamed lesions. Willingness to co-operate and adhere to study criteria. Absence of interfering medical and dermatological conditions and medications. Absence of pregnancy and avoidance of interference from oral contraceptives. **Exclusion details**	**Interventions** **Treatment duration (weeks)** 13 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** BPO-topical 5%/ ERYTH-topical 3% **Intervention: arm 2** BPO-topical 10% **Intervention: arm 3** Vehicle **Coded intervention: arm 1** BPO-topical + ERYTH-topical **Coded intervention: arm 2** BPO-topical **Coded intervention: arm 3** Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;participants not blinded; ITT not used **3. Missing outcome data (efficacy)** Some concerns;5% discontinued **4. Outcome measurement (efficacy)** Low;Investigator blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	Not reported. **Number included** **Number randomised: arm 1** 30 **Number randomised: arm 2** 32 **Number randomised: arm 3** 32 **Number completed: arm 1** 28 **Number completed: arm 2** 30 **Number completed: arm 3** 28			
Study details **Reference** Stein Gold, L. ,. C., L. E.,Johnson, L. A.,Gottschalk, R. W.Is switching retinoids a sound strategy for the treatment of acne vulgaris?. 2008. Journal of drugs in dermatology : JDD **Trial ID** Stein Gold 2008 **Country** United States **Study type** RCT **Source of funding** Not reported (conflicts of interest reported). **Analysis method** **Intention to treat or**	N=201 **Characteristics** **Sex** mixed **age (mean±SD)** 19 **age (other information)** ADAP mean age=18.5; ADAP then TAZ, mean age=19.4. **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Males and females aged between 12 and 35 years. .15 to 100 non-inflammatory	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** ADAP 0.1% gel **Intervention: arm 2** ADAP 0.1% gel for 6 weeks then TAZ 0.1% cream for 6 weeks **Coded intervention: arm 1** ADAP-topical **Coded intervention: arm 2** ADAP-topical / TAZ-topical	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;not reported if participants were blinded; ITT analysis was done **3. Missing outcome data (efficacy)** High;more than 5% withdrawals; not clear how balanced between arms; no reasons reported **4. Outcome measurement (efficacy)** Low **5. Selective reporting** Some concerns;not reported if

Study details	Participants	Interventions	Outcomes and results	Comments
completers analysis ITT **Method of ITT imputation** LOCF	lesions, at least 20 inflammatory lesions, and no more than 3 nodules. **Exclusion details** Participants with severe nodulocystic acne. Pregnant, nursing, or planning a pregnancy during the study. Participants with facial hair that would interfere with study assessments. Washout periods <4 weeks for topical acne treatments or <6 months for systemic treatment. Participants with other dermatologic conditions requiring interfering treatment. **Number included** **Number randomised: arm 1** 101 **Number randomised: arm 2** 100			trial protocol was registered **6. Overall bias** High
Study details **Reference** Stein Gold, L.,, C., A.,Eichenfield, L.,Tan, J.,Jorizzo, J.,Kerrouche, N.,Dhuin, J. C.Effective and safe combination therapy for severe acne vulgaris: a randomized, vehicle-controlled, double-blind study of adapalene 0.1%-benzoyl peroxide 2.5% fixed-dose combination gel with doxycycline hyclate 100 mg.	N=459 **Characteristics** **Sex** mixed **age (mean±SD)** 18.4±5.41 **age (min/max)** 12/39 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** ADAP 0.1%/BPO 2.5% gel + DOXY 100 mg **Intervention: arm 2**	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Low;double-blinded - likely that participants wer eblinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;more than 5% withdrawals; balanced

Study details	Participants	Interventions	Outcomes and results	Comments
2010. Cutis; cutaneous medicine for the practitioner **Trial ID** Stein Gold 2010 **Country** North America **Study type** RCT **Source of funding** Galderma Research & Development (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** not reported	Assessment scale (IGA) **Inclusion details** Males and females of any race, aged 12 to 35 years. Severe facial acne vulgaris (IGA score of 4); minimum of 20 inflammatory lesions, 30 to 120 non-inflammatory lesions, and no more than 3 nodulocystic lesions. Specified washout periods were required for participants using topical and oral acne treatments. **Exclusion details** Participants with acne conglobata, acne fulminans (secondary acne), or other dermatologic conditions that interfere with treatment. Pregnancy, breastfeeding or women planning a pregnancy during the study. **Number included** **Number randomised: arm 1** 232 **Number randomised: arm 2** 227 **Number completed: arm 1** 211 **Number completed: arm 2** 201	DOXY 100 mg + Vehicle **Coded intervention: arm 1** ADAP-topical + BPO-topical + DOXY-oral **Coded intervention: arm 2** DOXY-oral + Vehicle		between arms **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns
Study details **Reference** Stein Gold, L. F. J., M. T.,Bucko, A. D.,Grekin, S.	N=434 **Characteristics** **Sex** mixed	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category**	**Results** **Treatment discontinuation for any reason**	**Cochrane RoB Tool v2.0** **1. Randomisation** Low **2. Deviation from**

Study details	Participants	Interventions	Outcomes and results	Comments
K.,Berlin, J. M.,Bukhalo, M.,Weiss, J. S.,Berk, D. R.,Chang-Lin, J. E.,Lin, V.,et al.,Efficacy and Safety of Once-Daily Dapsone Gel, 7.5% for Treatment of Adolescents and Adults With Acne Vulgaris: first of Two Identically Designed, Large, Multicenter, Randomized, Vehicle-controlled Trials. 2016. Journal of drugs in dermatology **Trial ID** Stein Gold 2016 **Country** United States **Study type** RCT **Source of funding** Galderma Research & Development (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** MI (no other details reported)	**age (mean±SD)** 19.5785288270378±6.996407 1856287422 **age (min/max)** 12/57 **age (other information)** ADAP 0.3%, range 12-57; ADAP 0.1%, range 12-49; Vehicle, range=12-36 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Males and females. Moderate to severe inflammatory facial acne, that is a score of 3 (moderate) or 4 (severe) on the IGA, the presence of 20 to 100 inflammatory lesions, 30 to 150 non-inflammatory lesions (including the nose), and up to 2 nodules on the face. A urine pregnancy test was required for females at baseline and throughout the study. **Exclusion details** Participants with acne conglobata, acne fulminans, nodulocystic acne, or acne requiring systemic treatment. **Number included** **Number randomised: arm 1** 217	12 to <24 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** ADAP 0.3%/BPO 2.5% gel **Intervention: arm 2** ADAP 0.1%/BPO 2.5% gel **Intervention: arm 3** Vehicle **Coded intervention: arm 1** ADAP-topical + BPO-topical **Coded intervention: arm 2** ADAP-topical + BPO-topical **Coded intervention: arm 3** Vehicle	See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**intervention** Low;double-blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;10% withdrawals - balanced between arms; ITT used **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Low **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	Number randomised: arm 2 217 **Number randomised: arm 3** 69 **Number completed: arm 1** 197 **Number completed: arm 2** 192 **Number completed: arm 3** 61			
Study details **Reference** Stewart, D. M. T., H. M.,Weiss, J. S.,Plott, R. T.Dose-ranging efficacy of new once-daily extended-release minocycline for acne vulgaris. 2006. Cutis; cutaneous medicine for the practitioner **Trial ID** Stewart 2006 **Country** United States **Study type** RCT **Source of funding** Not reported (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	N=174 **Characteristics** **Sex** mixed **age (mean±SD)** 17.7 **age (min/max)** 17/19 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Participants aged 12 to 30 years, weighing between 39.1 kg and 102.3 kg (86 to 225 lb). Diagnosed with moderate to severe facial acne vulgaris; at least 20 and no more than 100 inflammatory facial lesions and <5 facial nodules or cysts. Females of childbearing potential must have had a	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** MINO-oral 2mg/kg/day **Intervention: arm 2** MINO-oral 3mg/kg/day **Intervention: arm 3** PLC-oral **Coded intervention: arm 1** MINO-oral **Coded intervention: arm 2** MINO-oral **Coded intervention: arm 3** PLC-oral	**Results** **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;methods not reported **2. Deviation from intervention** Low;double-blind;ITT **3. Missing outcome data (efficacy)** High;>20% discontinued - unclear how many were due to lack of efficacy - or which arm they were in **4. Outcome measurement (efficacy)** Low;described as double-blind, without further details **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	negative urine pregnancy test result (25 µg/mL sensitivity), be using contraception and will to continue on contraception during the study. Participants or parent/guardian consent provided. **Exclusion details** Participants sensitive to minocycline or any of the components. Pregnancy. Males with facial hair. Use of supplements containing aluminium, calcium, iron, or magnesium, or vitamin A. Prior history of complicating illnesses or medications. **Number included** **Number randomised: arm 1** 59 **Number randomised: arm 2** 60 **Number randomised: arm 3** 55 **Number completed: arm 1** na **Number completed: arm 2** na **Number completed: arm 3** na			
Study details **Reference**	N=na **Characteristics**	**Interventions** **Treatment duration (weeks)**	**Results** **Clinician rated**	**Cochrane RoB Tool v2.0** **1. Randomisation**

Study details	Participants	Interventions	Outcomes and results	Comments
Strauss, J. S. R., R. P.,Shalita, A. R.,Konecky, E.,Pochi, P. E.,Comite, H.,Exner, J. H.Isotretinoin therapy for acne: Results of a multicenter dose-response study. 1984a. Journal of the American Academy of Dermatology **Trial ID** Strauss 1984a **Country** United States **Study type** RCT **Source of funding** Not reported. **Analysis method** **Intention to treat or completers analysis** Completers	**Sex** mixed **age (other information)** Mean age 23.3,23.1 & 22.2 in the 3 groups (no SDs reported) **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Participants with treatment-resistant, severe nodulocystic acne; minimum of 10 inflammatory nodulocystic acne lesions at least 4 mm in diameter on the face, back, or chest. Off all treatment for at least 1 month. Female participants were required to have negative pregnancy test within 2 weeks prior to starting treatment. **Exclusion details** Not reported. **Number included** **Number randomised: arm 1** na **Number randomised: arm 2** na **Number randomised: arm 3** na **Number completed: arm 1** 46 **Number completed: arm 2** 46	20 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** ISO<120.Daily<0.5 (0.1 mg/kg daily for 140 days) **Intervention: arm 2** ISO<120.Daily=0.5 (0.5 mg/kg daily for 140 days) **Intervention: arm 3** ISO=120.Daily=0.5 (1 mg/kg daily for 140 days) **Coded intervention: arm 1** ISO<120.Daily<0.5-oral **Coded intervention: arm 2** ISO<120.Daily=0.5-oral **Coded intervention: arm 3** ISO=120.Daily=0.5-oral	**improvement in acne** See supplement 8	Some concerns;no information about allocation concealment provided **2. Deviation from intervention** High;study was double-blinded in the beginning; then "The protocol design allowed participating people to be retreated with isotretinoin in an open study beginning at least 8 weeks after the completion of the first course of therapy if optimal improvement (less than a 95% reduction in lesions) had not been achieved in the first course." No ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;6% withdrawals in 2 out of 3 arms; no reasons provided; no ITT **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 3 49			
Study details **Reference** Tan, J. H., S.,Vender, R.,Barankin, B.,Gooderham, M.,Kerrouche, N.,Audibert, F.,Lynde, C.A treatment for severe nodular acne: A randomized investigator-blinded, controlled, noninferiority trial comparing fixed-dose adapalene/benzoyl peroxide plus doxycycline vs. oral isotretinoin. 2014. British Journal of Dermatology **Trial ID** Tan 2014 **Country** Canada **Study type** RCT **Source of funding** Galderma (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	N=266 **Characteristics** **Sex** mixed **age (mean±SD)** 19.4±4.8 **age (min/max)** 12/41 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Participants of any race, aged 12 to 35 years. **Exclusion details** Pregnancy. **Number included** **Number randomised: arm 1** 133 **Number randomised: arm 2** 133 **Number completed: arm 1** 105 **Number completed: arm 2** 116	**Interventions** **Treatment duration (weeks)** 20 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** DOXY 200 mg + ADAP 0.1%/BPO 2.5% gel **Intervention: arm 2** ISO=120.Daily=0.5 (wk 1-4 0.5 mg), then ISO=120.Daily=0.5 (wk 5-20 1.0 mg) **Coded intervention: arm 1** DOXY-oral + ADAP-topical + BPO-topical **Coded intervention: arm 2** ISO=120.Daily=0.5-oral	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Low **2. Deviation from intervention** Some concerns;not reported if participants were blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;13% withdrawals (2% due to inefficacy) balanced between arms **4. Outcome measurement (efficacy)** Low **5. Selective reporting** Low **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Tan, J. T., D.,Popp, G.,Gooderham, M.,Lynde, C.,Del Rosso, J.,Weiss, J.,Blume-Peytavi, U.,Weglovska, J.,Johnson, S.,Parish, L.,Witkowska, D.,Sanchez Colon, N.,Alio Saenz, A.,Ahmad, F.,Graeber, M.,Stein Gold, L.Randomized phase 3 evaluation of trifarotene 50 mug/g cream treatment of moderate facial and truncal acne. 2019. Journal of the American Academy of Dermatology **Trial ID** Tan 2019;Trial 1 **Country** US/Canada/Europe/Russia **Study type** RCT **Source of funding** Nestle Skin Health Care, Galderma Research & Development, LLC, US (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** MI (no further details reported)	N=1208 **Characteristics** **Sex** mixed **age (mean±SD)** 19.4±6.41 **age (median)** 18 **age (min/max)** 9/58 **age (other information)** <18, n=592; =18, n=616. data for groups also reported **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Participants aged 9 years and older. Moderate facial acne (defined as IGA score of 3 on the face [=20 inflammatory lesions and =25 non-inflammatory lesions]), and moderate truncal acne (defined as a Physician's Global Assessment [PGA] score of 3 at screening and baseline [=20 inflammatory lesions and 20 to <100 non-inflammatory	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** TRIF 0.05 mg/g **Intervention: arm 2** Vehicle **Coded intervention: arm 1** TRIF-topical **Coded intervention: arm 2** Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information about allocation concealment provided **2. Deviation from intervention** Low;double-blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;11% withdrawals (reasons unclear)-balanced between arms; ITT used **4. Outcome measurement (efficacy)** Low;likely blinded **5. Selective reporting** Low **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	lesions on the areas of the trunk within reach for self-application]). For participants aged 9 to 11 years, the inclusion criteria relating to truncal acne were optional owing to the relative rarity of this (compared with facial involvement) in this age group. **Exclusion details** Participants with severe forms of acne; more than 1 nodule o the face; more than 1 nodule on the trunk; presence of acne cysts. Beards or facial hair that could interfere with study evaluations. Presence of tattoos that could interfere with study assessments. Uncontrolled or serious disease or medical condition; clinically significant abnormal laboratory values; known or suspected allergies or sensitivities to the planned study treatments. Lactating women or women planning pregnancy during the study. Prohibited treatments and washout periods of 1 to 4 weeks were specified for use of antiacne treatments (prescription and over-the counter), non-steroidal anti-inflammatory drugs,			

Study details	Participants	Interventions	Outcomes and results	Comments
	corticosteroids, and antibiotics (but 6 months for use of oral retinoids and immunomodulators). **Number included** **Number randomised: arm 1** 612 **Number randomised: arm 2** 596 **Number completed: arm 1** 540 **Number completed: arm 2** 535			
Study details **Reference** Tanghetti, E. A., W.,Solomon, B.,Loven, K.,Shalita, A.Tazarotene versus tazarotene plus clindamycin/benzoyl peroxide in the treatment of acne vulgaris: a multicenter, double-blind, randomized parallel-group trial. 2006. Journal of drugs in dermatology : JDD **Trial ID** Tanghetti 2006 **Country** United States **Study type** RCT **Source of funding** Not reported (conflicts of interest reported). **Analysis method**	N=121 **Characteristics** **Sex** mixed **age (mean±SD)** 20 **age (min/max)** 12 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Participants aged at least 12 years of age. Stable moderate to severe facial inflammatory acne vulgaris (defined as 15 to 60 papules plus pustules, 10 to 100 comedos, and no more than 2 nodulocystic lesions	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** TAZ 0.1% cream + Vehicle gel **Intervention: arm 2** BPO 5%/CLIND 1% gel + TAZ 0.1% cream **Coded intervention: arm 1** TAZ-topical + Vehicle **Coded intervention: arm 2** BPO-topical + CLIND-topical + TAZ	**Results** **Treatment discontinuation for any reason** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;Double blind but not clear if participants were blinded; no ITT **3. Missing outcome data (efficacy)** High;Around 20% discontinued - insufficient information on reasons **4. Outcome measurement (efficacy)** Some concerns;not clear **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
Intention to treat or completers analysis ITT **Method of ITT imputation** not reported	with a maximum diameter of 5 mm). Washout periods required: 2 weeks for topical acne treatments, 30 days for systemic antibiotics and investigational drugs, 12 weeks for oestrogens/birth control pills if previously used for <12 weeks, and 6 months for oral retinoids. **Exclusion details** Participants with acne known to be resistant to oral antibiotics. Pregnancy, breastfeeding or of childbearing potential and not using reliable contraception. **Number included** **Number randomised: arm 1** 61 **Number randomised: arm 2** 60 **Number completed: arm 1** 50 **Number completed: arm 2** 52			
Study details **Reference** Tanghetti, E. D., S.,Torok, H.,Kircik, L.Tazarotene 0.1 percent cream plus clindamycin 1 percent gel versus tretinoin 0.025 percent gel plus clindamycin 1 percent gel in the treatment of facial	N=150 **Characteristics** **Sex** mixed **age (mean±SD)** 21 **age (min/max)** 12/58 **Inclusion/exclusion criteria**	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No	**Results** **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;not reported if participants were blinded; ITT analysis was done

Study details	Participants	Interventions	Outcomes and results	Comments
acne vulgaris. 2007. Dermatology Online Journal **Trial ID** Tanghetti 2007 **Country** United States **Study type** RCT **Source of funding** Allergan Inc, US. **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** not reported	**Used validated acne scale** no **Acne scale** None **Inclusion details** Participants aged at least 12 years old. .Facial acne vulgaris; 15 to 60 papules plus pustules, 10 to 100 comedones, and no more than 2 nodulocystic lesions (with a diameter no more than 5 mm). Washout periods required: 14 days for topical antibiotics and anti-acne treatments, 30 days for systemic antibiotics and investigational drugs, 12 weeks for oestrogens/birth control pills if used for <12 weeks before study entry, and 12 months for oral retinoids. **Exclusion details** Known resistance to oral antibiotics; known hypersensitivity to lincomycin. History of enteritis; recent alcohol or drug abuse; any skin disorder that might interfere with the diagnosis or evaluation of acne vulgaris; any uncontrolled systemic disease. Any cosmetic or surgical procedures complementary to the	**Intervention: arm 1** CLIND 1% gel + TAZ 0.1% cream **Intervention: arm 2** CLIND 1% gel + TRET 0.025% gel **Coded intervention: arm 1** CLIND-topical + TAZ-topical **Coded intervention: arm 2** CLIND-topical + TRET-topical		**3. Missing outcome data (efficacy)** Some concerns;10% withdrawals - not clear if balanced between arms **4. Outcome measurement (efficacy)** Low **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	treatment of acne in the preceding 15 days; participation in an investigational drug study in the preceding 30 days. Pregnancy or breastfeeding, and not using a reliable method of contraception. **Number included** **Number randomised: arm 1** 75 **Number randomised: arm 2** 75			
Study details **Reference** Tanghetti, E. K., L.,Wilson, D.,Dhawan, S.Solubilized benzoyl peroxide versus benzoyl peroxide/clindamycin in the treatment of moderate acne. 2008. Journal of drugs in dermatology: JDD **Trial ID** Tanghetti 2008 **Country** United States **Study type** RCT **Source of funding** Supported by Obagi Medical Products Inc. (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis**	N=46 **Characteristics** **Sex** mixed **age (mean±SD)** 21 **age (min/max)** 11/45 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Participants aged between 11 to 45 years of age. Moderate facial acne vulgaris; 25 to 100 non-inflammatory lesions, 25 to 100 inflammatory lesions, up to 2 nodulocystic lesions. Willing to refrain from using non-study acne medications,	**Interventions** **Treatment duration (weeks)** 4 **Treatment duration category** 0 to <6 weeks **Number of arms** 2 **Split face design** Yes **Intervention: arm 1** BPO 5% gel **Intervention: arm 2** BPO 5%/CLIND 1% gel **Coded intervention: arm 1** BPO-topical **Coded intervention: arm 2** BPO-topical + CLIND-topical	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;not reported if participants were blinded **3. Missing outcome data (efficacy)** Low;all participants completed the study **4. Outcome measurement (efficacy)** Low;investigator-blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
ITT **Method of ITT imputation** not reported	moisturisers, sunscreens, fragrances, aftershaves, and make-up on the face (oil-free non-comedogenic make-up, mascara, eyeshadow, and lipstick were allowed). Willing to avoid excessive exposure to the sun and the use of tanning booths. Washout periods required: 1 week for medicated facial cleansers; 2 weeks for topical alpha-hydroxy acids, anti-acne medications, topical retinoids, topical and systemic antibiotics, and topical and systemic steroids; 3 months for oestrogens/birth control pills (unless used for at least 3 months); and 6 months for systemic retinoids. **Exclusion details** Participants who had undergone a facial cosmetic procedure in the past 6 months. Allergic to BPO, clindamycin, lincomycin, salicylic acid, sunscreens or other ingredients in the study products. Papulopustular rosacea or other skin diseases on the face (other than acne) that could interfere with study assessments; facial sunburn at study baseline. Males with facial hear that could interfere with study assessments. Uncontrolled systemic disease or infection with HIV; history of			

Study details	Participants	Interventions	Outcomes and results	Comments
	regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Concurrent facial use of other medicated products. Participation in an investigational study in the previous 30 days. **Number included** **Number randomised: arm 1** 23 **Number randomised: arm 2** 23 **Number completed: arm 1** 23 **Number completed: arm 2** 23			
Study details **Reference** Tanghetti, E. A. K., L. H.,Green, L. J.,Guenin, E.,Harris, S.,Martin, G.,Pillai, R.A Phase 2, Multicenter, Double-Blind, Randomized, Vehicle-Controlled Clinical Study to Compare the Safety and Efficacy of a Novel Tazarotene 0.045% Lotion and Tazarotene 0.1% Cream in the Treatment of Moderate-to-Severe Acne Vulgaris. 2019. Journal of drugs in dermatology : JDD **Trial ID** Tanghetti 2019 **Country**	N=210 **Characteristics** **Sex** mixed **age (mean±SD)** 22.1332857142857±9.2005769230769214 **age (min/max)** 12 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Evaluator's Global Severity Scale (EGSS) **Inclusion details** Participants of any gender, race and ethnicity, aged 12	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** TAZ 0.045% lotion **Intervention: arm 2** TAZ 0.1% cream **Intervention: arm 3** Lotion vehicle or cream vehicle (arms combined) **Coded intervention: arm 1** TAZ-topical	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Low;double-blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;10% withdrawals - imbalanced between arms **4. Outcome measurement (efficacy)** Low;likely blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered

Study details	Participants	Interventions	Outcomes and results	Comments
United States **Study type** RCT **Source of funding** Ortho Dermatologics funded Konic Limited's activities relating to the manuscript (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	years or older. Participants with moderate to severe acne; EGSS score of 3 (moderate) or 4 (severe); 20 to 40 inflammatory lesions (papules, pustules, and nodules), 20 to 100 non-inflammatory lesions (open and closed comedones), and 2 nodules or less. Women of childbearing potential were required to have a negative urine pregnancy test at and agree to use a reliable method of contraceptive during the study period. Washout period of 1 month required for participants who previously used prescription and over-the-counter acne treatments, and 6 months for systemic retinoids. **Exclusion details** Not reported. **Number included** **Number randomised: arm 1** 69 **Number randomised: arm 2** 72 **Number randomised: arm 3** 69 **Number completed: arm 1** 65 **Number completed: arm 2** 63 **Number completed: arm 3** 61	**Coded intervention: arm 2** TAZ-topical **Coded intervention: arm 3** Vehicle		**6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Thiboutot, D. J., M.,Rich, P.,Rist, T.,Rodriguez, D.,Levy, S.A randomized, parallel, vehicle-controlled comparison of two erythromycin/benzoyl peroxide preparations for acne vulgaris. 2002. Clinical Therapeutics **Trial ID** Thiboutot 2002 **Country** United States **Study type** RCT **Source of funding** Dermik Laboratories, US. **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** Unclear	N=245 **Characteristics** **Sex** mixed **age (mean±SD)** 19.9 **age (min/max)** 12/46 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Physician's Global Assessment (PGA)/Physician's Global Acne Severity Score **Inclusion details** Males and females aged >12 years of age. Moderate to moderately severe acne; 15 to 80 facial inflammatory lesions, 20 to 140 facial comedones (not including the nose or nasolabial area), <2 nodules or cysts >5 mm, and a minimum Physician's Global Acne Severity score of 1.5. **Exclusion details** Not reported. **Number included** **Number randomised: arm 1** 124 **Number randomised: arm 2** 121 **Number randomised: arm 3** 42 **Number randomised: arm 4**	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Number of arms** 4 **Split face design** No **Intervention: arm 1** BPO 5%/ERYTH 3% gel **Intervention: arm 2** BPO 5%/ERYTH 3% jar **Intervention: arm 3** Vehicle gel **Intervention: arm 4** Vehicle Jar **Coded intervention: arm 1** BPO-topical + ERYTH-topical **Coded intervention: arm 2** BPO-topical + ERYTH-topical **Coded intervention: arm 3** Vehicle **Coded intervention: arm 4** Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;insufficient information provided **2. Deviation from intervention** Low;Double blind; ITT **3. Missing outcome data (efficacy)** Low **4. Outcome measurement (efficacy)** Low **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	40 **Number completed: arm 1** 115 **Number completed: arm 2** 110 **Number completed: arm 3** 33 **Number completed: arm 4** 35			
Study details **Reference** Thiboutot, D. M. S., A. R.,Yamauchi, P. S.,Dawson, C.,Arsonnaud, S.,Kang, S.Combination therapy with adapalene gel 0.1% and doxycycline for severe acne vulgaris: a multicenter, investigator-blind, randomized, controlled study. 2005. Skinmed **Trial ID** Thiboutot 2005 **Country** United States **Study type** RCT **Source of funding** Galderma Research & Development, US (conflicts of interest reported). **Analysis method** **Intention to treat or completers analysis** ITT	N=467 **Characteristics** **Sex** mixed **age (mean±SD)** 17.8471092077088±4.361806451612904 **age (min/max)** 12/36 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Global Acne Severity Scale (GEA Scale) **Inclusion details** Males and females with severe facial acne (global severity score of at least 4 on a scale ranging from 0 [clear] to 5 [very severe]); minimum of 15 inflammatory lesions and 15 to 100 non-inflammatory facial lesions. Washout periods were required for participants taking	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** ADAP 0.1% gel + DOXY 100 mg **Intervention: arm 2** DOXY 100 mg + Vehicle **Coded intervention: arm 1** ADAP-topical + DOXY-oral **Coded intervention: arm 2** DOXY-oral + Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information about allocation sequence provided **2. Deviation from intervention** Some concerns;not reported if participants were blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;18% withdrawals - imbalanced between arms; ITT used; <1% due to inefficacy **4. Outcome measurement (efficacy)** Low **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
Method of ITT imputation not reported	certain topical and systemic treatments. **Exclusion details** Acne requiring isotretinoin treatment or other dermatologic conditions requiring interfering treatment. Pregnancy, nursing or planning a pregnancy. Men with facial hair that would interfere with evaluations. **Number included** **Number randomised: arm 1** 238 **Number randomised: arm 2** 229 **Number completed: arm 1** 186 **Number completed: arm 2** 196			
Study details **Reference** Webster, G. F., Leyden, J. J., & Gross, J. A.Results of a Phase III, double-blind, randomized, parallel-group, non-inferiority study evaluating the safety and efficacy of isotretinoin-Lidose in patients with severe recalcitrant nodular acne. 2014. Journal of Drugs in Dermatology **Trial ID** Webster 2014 **Country**	N=925 **Characteristics** **Sex** mixed **age (mean±SD)** 20.8±7.2 **age (min/max)** 12/52 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details**	**Interventions** **Treatment duration (weeks)** 20 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** Isotretinoin-(lidose formulation) ISO<120.Daily=0.5 **Intervention: arm 2** ISO<120.Daily=0.5	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information about allocation sequence provided **2. Deviation from intervention** Low;ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns;14% discontinued -balanced between arms. ITT used. Unclear how many related to efficacy

Study details	Participants	Interventions	Outcomes and results	Comments
North America **Study type** RCT **Source of funding** Cipher Pharmaceuticals Inc, Canada (conflicts of interest reported).	Participants with severe calcitrant nodular acne, compatible with isotretinoin treatment; 10 or more facial and/or truncal nodular lesions. No prior exposure to systemic isotretinoin or other retinoids. Aged between 12 and 54 years and weighing between 40 and 110 kg. **Exclusion details** Pregnancy, breastfeeding, or high risk of becoming pregnant or considering breastfeeding during study treatment. Concurrent or history of GI disease, skin conditions that may interfere with study assessments, psychosis or psychotic symptoms, reported suicidal behaviour, carcinoma, liver or kidney disease, pseudotumour cerebri, rheumatoid arthritis or vitamin D depletion disease, and paediatric participants with 25-hydroxyvitamin D levels <20 ng/ml. **Number included** **Number randomised: arm 1** 464 **Number randomised: arm 2** 461 **Number completed: arm 1** 394 **Number completed: arm 2** 401	**Coded intervention: arm 1** ISO<120.Daily=0.5-oral **Coded intervention: arm 2** ISO<120.Daily=0.5-oral		**4. Outcome measurement (efficacy)** Low **5. Selective reporting** Low **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Xu, X. Z., Y.,Zhao, Z.,Zhang, X.,Liu, P.,Li, C.Efficacy of photodynamic therapy combined with minocycline for treatment of moderate to severe facial acne vulgaris and influence on quality of life. 2017. Medicine (United States) **Trial ID** Xu 2017 **Country** China **Study type** RCT **Source of funding** Not reported (no conflicts of interest). **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** not reported	N=95 **Characteristics** **Sex** mixed **age (median)** 24 **age (min/max)** 15/35 **age (other information)** MINO + PDT median age=24 (range 16-35); MINO median age 24 (range 15-35) **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Males and females aged 15 to 35 years attending a Department of Dermatology, China. Moderate to severe facial acne vulgaris defined by IGA scale of 3 or 4; =10 inflammatory lesions (papules, pustules, or nodules) and =10 non-inflammatory lesions (open and closed comedones) on the face. **Exclusion details** Participants with acne fulminans, acne conglobata, secondary acne, or dysplastic naevi in the treatment area.	**Interventions** **Treatment duration (weeks)** 4 **Treatment duration category** 0 to <6 weeks **Treatment intensity** Total 4 sessions, once every week. Endpoint 4 wks after last session **Number of arms** 2 **Split face design** No **Intervention: arm 1** MINO 100 mg + 5ALA 5%-RED LED-PDT **Intervention: arm 2** MINO 100 mg **Coded intervention: arm 1** MINO-oral + 5ALA-RED-PDT **Coded intervention: arm 2** MINO-oral	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information about allocation sequence provided **2. Deviation from intervention** Some concerns;not reported if investigators/participants were blinded **3. Missing outcome data (efficacy)** High;not reportedif/how many participants discontinued **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was published **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Systemic acne treatment with oral isotretinoin within 6 months or oral antibiotics in the past 1 month; history of facial procedures such as dermabrasion, chemical, or laser peels; phototherapy within 1 month; topical treatments other than medicated cleansers within 14 days. Pregnant or nursing females. History of photosensitive diseases, porphyria, or porphyrin sensitivity. **Number included** **Number randomised: arm 1** 48 **Number randomised: arm 2** 47 **Number completed: arm 1** 48 **Number completed: arm 2** 47			
Study details **Reference** Yin, R. H., F.,Deng, J.,Yang, X. C.,Yan, H.Investigation of optimal aminolaevulinic acid concentration applied in topical aminolaevulinic acid-photodynamic therapy for treatment of moderate to severe acne: A pilot study in	N=180 **Characteristics** **Sex** mixed **age (mean±SD)** 24.975±6.85 **age (min/max)** 18/38 **Inclusion/exclusion criteria**	**Interventions** **Treatment duration (weeks)** 4.29 **Treatment duration category** 0 to <6 weeks **Treatment intensity** Total 4 sessions, once every 10 days. Fu at 2, 4, 12 and 24 wks after last session,	**Results** **Treatment discontinuation due to side effects** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention** Some concerns;"single-blind": not clear if investigators or participants were blinded; not

Study details	Participants	Interventions	Outcomes and results	Comments
Chinese subjects. 2010. British Journal of Dermatology **Trial ID** Yin 2010 **Country** China **Study type** RCT **Source of funding** Not reported (no conflicts of interest). **Analysis method** **Intention to treat or completers analysis** completers	**Used validated acne scale** no **Acne scale** None **Inclusion details** Chines participants attending a Department of Dermatology in China. Facial inflammatory acne vulgaris (moderate to severe grade according to Pillsbury et al.); Fitzpatrick skin type III and IV. Underwent aminolaevulinic acid-photodynamic therapy treatment and following up from June 2007 to January 2009. **Exclusion details** Participants who had used topical retinoic acid, glucocorticosteroids, antibiotics and other drugs within 2 weeks. Use of medication that may exacerbate or alleviate acne. Planned pregnancy, pregnancy or lactating women. History of photosensitivity disorder. Participants planning prolonged exposure to sunlight. Participants with herpes simplex outbreak. **Number included** **Number randomised: arm 1** 45 **Number randomised: arm 2** 45 **Number randomised: arm 3**	assumed 2 wks to be appropriate FU **Number of arms** 5 **Split face design** No **Intervention: arm 1** 5ALA 5%-PDT **Intervention: arm 2** 5ALA 10%-PDT **Intervention: arm 3** 5ALA 15%-PDT **Intervention: arm 4** 5ALA 20%-PDT **Coded intervention: arm 1** 5ALA-RED-PDT **Coded intervention: arm 2** 5ALA-RED-PDT **Coded intervention: arm 3** 5ALA-RED-PDT **Coded intervention: arm 4** 5ALA-RED-PDT		reported if ITT analysis was done **3. Missing outcome data (efficacy)** Low;1 participant dropped out due to a severe adverse event **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was published **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	45 **Number randomised: arm 4** 45 **Number completed: arm 1** 45 **Number completed: arm 2** 45 **Number completed: arm 3** 45 **Number completed: arm 4** 44			
Study details **Reference** Zhang, L. W., Y.,Zhang, Y.,Liu, X.,Wang, B.,Wang, P.,Zhang, G.,Wang, X.Topical 5-aminolevulinic photodynamic therapy with red light vs intense pulsed light for the treatment of acne vulgaris: A spilit face, randomized, prospective study. 2017. Dermato-endocrinology **Trial ID** Zhang 2017 **Country** China **Study type** RCT **Source of funding** Shanghai Municipal Commission of Health and Family Planning and Guide support project in western medicine of Shanghai	N=24 **Characteristics** **Sex** mixed **age (mean±SD)** 21.75±2.9889999999999999 **age (min/max)** 18/27 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** EU Acne Guidelines **Inclusion details** Males and females aged between 18 and 40 years. Acne lesions on the forehead and on both sides of the face and clinically diagnosed with acne vulgaris and grade 3 to 4 according to the European Guidelines Group. **Exclusion details**	**Interventions** **Treatment intensity** Total 3 sessions, once every 2 weeks. FU at 4 and 8 wks after last session. Assumed endpoint is 4 wks FU. **Number of arms** 2 **Split face design** Yes **Intervention: arm 1** 5ALA 5%-RED LED-PDT **Intervention: arm 2** 5ALA 5%-IPL-PDT **Coded intervention: arm 1** 5ALA-RED-PDT **Coded intervention: arm 2** 5ALA-IPL-PDT	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information about allocation concealment provided **2. Deviation from intervention** Some concerns;not reported if investigators/participants were blinded; carry over effects unlikely **3. Missing outcome data (efficacy)** High;not reported if/how many participants discontinued **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered

Study details	Participants	Interventions	Outcomes and results	Comments
Municipal Science and Technology Commission. **Analysis method** **Intention to treat or completers analysis** completers	Pregnant and lactating females, or women planning to become pregnant during the study. History of cutaneous hypersensitisation, porphyria, or photodermatosis; any ongoing skin conditions (such as psoriasis, seborrheic dermatitis or allergic dermatitis) that could interfere with assessments; a severe systemic condition and unsafe for participants to participate. History of systemic retinoids within 6 months or history of systemic steroids and antibiotics within 1 month or history of any topical treatment of acne within 2 weeks. **Number included** **Number randomised: arm 1** 12 **Number randomised: arm 2** 12 **Number completed: arm 1** 12 **Number completed: arm 2** 12			**6. Overall bias** High
Study details **Reference** Zhang, J. Z., X.,He, Y.,Wu, X.,Huang, J.,Huang, H.,Lu, C.Photodynamic therapy for severe facial acne vulgaris with 5% 5-aminolevulinic acid vs	N=56 **Characteristics** **Sex** mixed **age (mean±SD)** 24±4.0999999999999996	**Interventions** **Treatment intensity** Total 4 sessions, once every 10 days. Fu at 4-wks and 12-wks after last session, assumed 4-wks as endpoint.	**Results** **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;no information provided **2. Deviation from intervention**

Study details	Participants	Interventions	Outcomes and results	Comments
10% 5-aminolevulinic acid: A split-face randomized controlled study. 2019. Journal of Cosmetic Dermatology. **Trial ID** Zhang 2019 **Country** China **Study type** RCT **Source of funding** National Natural Science Foundation of China (no conflicts of interest). **Analysis method** **Intention to treat or completers analysis** completers	**Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Pillsbury **Inclusion details** Chinese adult participants attending an outpatient department. Symmetrically distributed severe facial acne (Pillsbury III and IV) and Fitzpatrick skin type III and IV. **Exclusion details** Pregnant or lactating women. Exposure to systemic isotretinoin during the past 6 months; exposed to systemic antibiotics, contraceptives or photosensitive drugs during the past month; exposed to topical acne drugs 2 weeks prior to study. Participants with other facial diseases, a history of photosensitivity disorders or keloids. Participants with diabetes or severe heart, lung, liver or renal diseases. **Number included** **Number randomised: arm 1** 28 **Number randomised: arm 2** 28 **Number completed: arm 1** 23 **Number completed: arm 2** 23	**Number of arms** 2 **Split face design** Yes **Intervention: arm 1** 5ALA 5%-PDT **Intervention: arm 2** 5ALA 10% PDT **Coded intervention: arm 1** 5ALA-RED-PDT **Coded intervention: arm 2** 5ALA-RED-PDT		Low;double-blinded ("Neither patients nor the operator knew the treatment allocation"); carry over effects unlikely; it appears that no ITT analysis was done **3. Missing outcome data (efficacy)** High;18% discontinued - unclear why; no ITT **4. Outcome measurement (efficacy)** Some concerns;not reported if assessment of outcome was blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Zouboulis Ch, C. D., L.,Decroix, J.,Maciejewska-Udziela, B.,Cambazard, F.,Stuhlert, A.A multicentre, single-blind, randomized comparison of a fixed clindamycin phosphate/tretinoin gel formulation (Velac) applied once daily and a clindamycin lotion formulation (Dalacin T) applied twice daily in the topical treatment of acne vulgaris. 2000. British Journal of Dermatology **Trial ID** Zouboulis 2000 **Country** Europe **Study type** RCT **Source of funding** Yamanouchi Europe BV, The Netherlands. **Analysis method** **Intention to treat or completers analysis** completers	N=209 **Characteristics** **Sex** mixed **age group** =25 years **age (mean±SD)** 18.6±3.2 **age (median)** 18 **age (min/max)** 14/26 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Cook **Inclusion details** Participants aged between 14 and 26 years. Moderate to severe acne vulgaris; scoring =3 on the Cook acne scale. **Exclusion details** Use of tretinoin or antibiotic treatments for acne during the 4 weeks prior to study; use of irritants such as salicylic acid and benzoyl peroxide during the 2 weeks prior to study; required other medical interventions within 5 days of the study. Participants with skin disorders likely to compromise drug absorption, known or suspected	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** CLIND 1%/TRET 0.025% gel **Intervention: arm 2** CLIND 1% lotion **Coded intervention: arm 1** CLIND-topical + TRET-topical **Coded intervention: arm 2** CLIND-topical	**Results** **Treatment discontinuation for any reason** See supplement 8 **Treatment discontinuation due to side effects** See supplement 8 **Clinician rated improvement in acne** See supplement 8	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns;No information provided **2. Deviation from intervention** Low;patients were blinded; ITT used **3. Missing outcome data (efficacy)** Some concerns;Withdrawal imbalanced between groups,(5% vs 13%) - mostly due to patient request. **4. Outcome measurement (efficacy)** Some concerns;Investigator not blinded **5. Selective reporting** Some concerns;not reported if trial protocol was registered **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	hypersensitivity to lincomycin, clindamycin or vitamin A derivatives. Participants who had changed or started use of contraceptives or use of Diane® within 3 months of the study. Those who had participated in another clinical trial within 3 months of the study. **Number included** **Number randomised: arm 1** 104 **Number randomised: arm 2** 105 **Number completed: arm 1** 90 **Number completed: arm 2** 100			

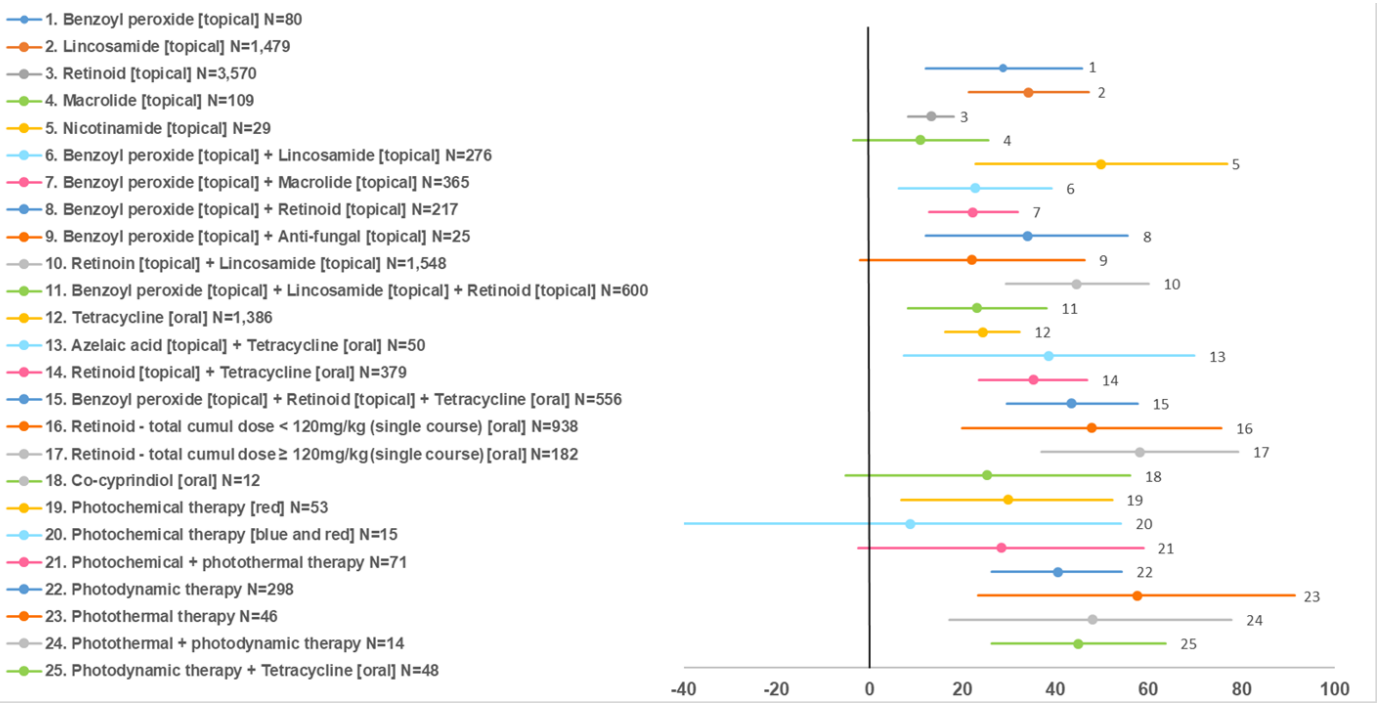
ADAP: adapalene; ALA-PDT: aminolevulinic acid photodymanic therapy; ALA-RED-PDT: aminolevulinic acid using red light photodymanic therapy; AZITH: azithromycin; BPO: benzoyl peroxide; CLIND: clindomycin; CPA: cyproterone acetate; DAPS: dapsone; DOXY: doxycycline; EE: ethinylestradiol; ERYTH: erythromycin; FU: follow up; ISO: isotretinoin; IPL: intense pulsed light; ITT: intention to treat analysis; LOCF: last observation carried forward; LYME: lymecycline; MAL DL: methyl aminolevulinate using daylight; MICO: miconazole nitrate; MINO: minocycline; MOT: motretinide; NAFL: fractional erbium glass laser; NOR: norfloxacin; PDL: pulsed dye laser; PLC: placebo; PDT: photodynamic; PT: photochemical; RCT: randomised controlled trial; SAR/SARE: sarecycline; SD: standard deviation; TAZ: tazarotene; TETRA: tetracycline; TRET: tretinoin

Appendix E – Network meta-analysis results

Network meta-analysis results for review question: For people with moderate to severe acne vulgaris what are the most effective treatment options?

Efficacy: % change in total acne lesion count from baseline

Figure 5. NMA treatment efficacy in people with moderate to severe acne: base-case forest plots, treatment class effects vs placebo



All treatment class effects versus placebo (N=4122). Results expressed as mean difference in % change from baseline; values on the right side of vertical axis indicate higher effect compared with placebo.

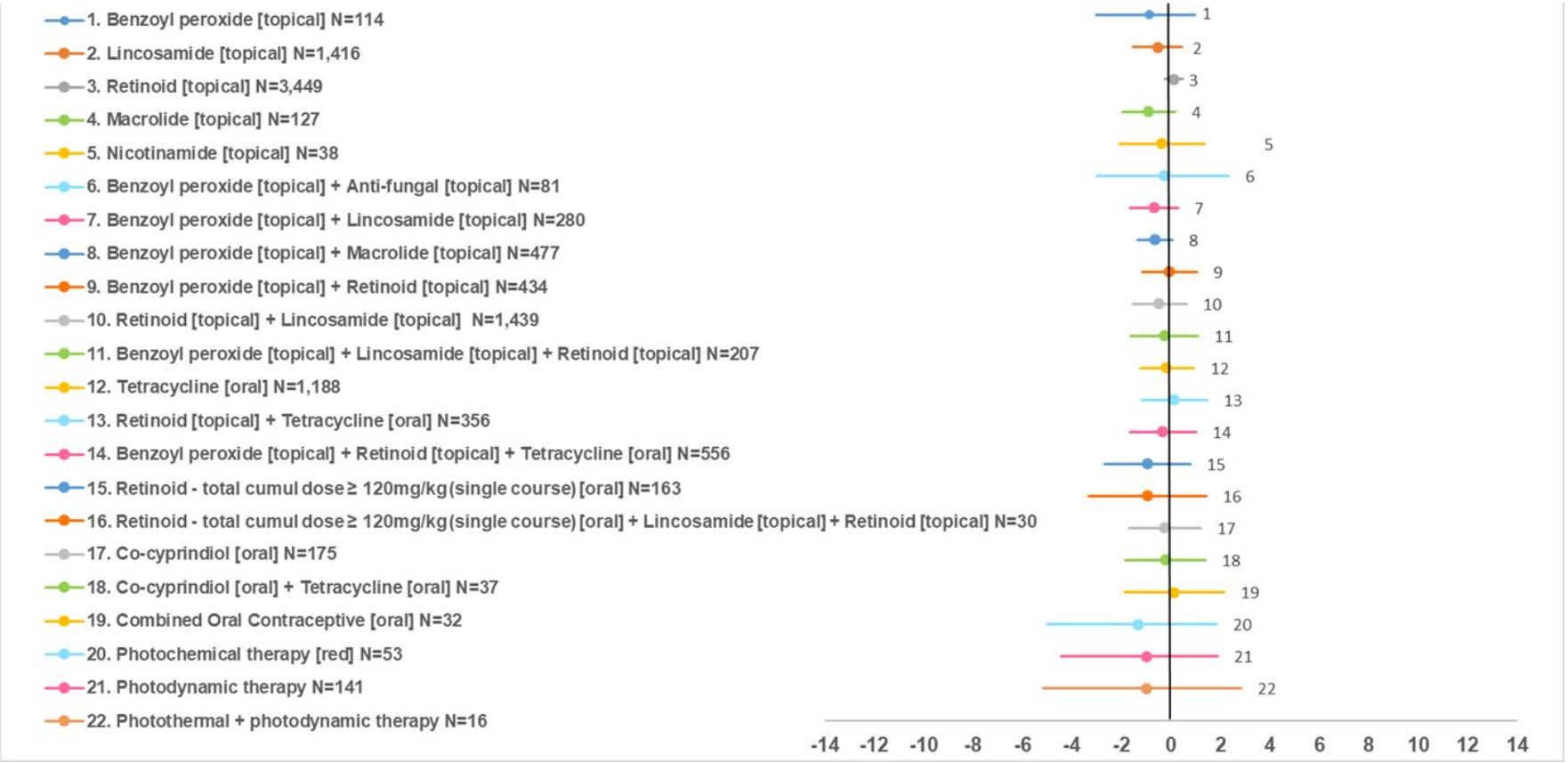
Table 8. NMA treatment efficacy in people with moderate to severe: base-case treatment class effects vs placebo & rankings

Class	N	Effect vs placebo (mean, 95% CrI)	Rank, females (mean, 95% CrI)	Rank, males (mean, 95% CrI)
Retinoid - total cumulative dose ≥ 120mg/kg (single course) [oral]	182	58.09 (36.99 to 79.29)	3.39 (1 to 11)	3.35 (1 to 10)
Photothermal therapy	46	57.60 (23.38 to 91.34)	4.29 (1 to 17)	4.21 (1 to 16)
Nicotinamide [topical]	29	49.75 (22.74 to 76.82)	6.43 (1 to 19)	6.31 (1 to 19)
Retinoid - total cumulative dose < 120mg/kg (single course) [oral]	938	47.72 (19.76 to 75.65)	7.10 (1 to 20)	6.96 (1 to 20)
Photothermal + photodynamic therapy	14	47.82 (17.10 to 77.78)	7.33 (1 to 22)	7.18 (1 to 21)
Lincosamide [topical] + Retinoid [topical]	1,548	44.43 (29.20 to 60.02)	7.66 (2 to 15)	7.53 (2 to 15)
Tetracycline [oral] + Photodynamic therapy	48	44.84 (26.19 to 63.58)	7.75 (2 to 17)	7.61 (2 to 17)
Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral]	556	43.53 (29.49 to 57.70)	8.15 (3 to 16)	8.01 (3 to 15)
Photodynamic therapy	298	40.45 (26.17 to 54.11)	9.47 (4 to 16)	9.29 (4 to 16)
No treatment	25	39.44 (2.64 to 75.70)	11.02 (2 to 25)	10.74 (2 to 24)
Azelaic acid [topical] + Tetracycline [oral]	50	38.55 (7.31 to 69.87)	11.48 (2 to 25)	11.20 (2 to 24)
Retinoid [topical] + Tetracycline [oral]	379	35.22 (23.55 to 46.75)	12.50 (7 to 19)	12.22 (6 to 18)
Benzoyl peroxide [topical] + Retinoid [topical]	217	33.97 (12.04 to 55.53)	13.14 (3 to 24)	12.81 (3 to 23)
Lincosamide [topical]	1,479	34.08 (21.26 to 47.02)	13.22 (6 to 21)	12.92 (6 to 20)
Photochemical therapy [red]	53	29.72 (6.81 to 52.10)	15.46 (5 to 25)	15.06 (5 to 24)
Benzoyl peroxide [topical]	80	28.75 (12.08 to 45.65)	15.62 (6 to 23)	15.20 (6 to 22)
Photochemical + photothermal therapy	71	28.21 (-2.54 to 58.82)	16.09 (4 to 26)	15.65 (4 to 25)
Co-cyprindiol [oral]	12	25.25 (-5.24 to 55.96)	17.12 (3 to 27)	Not relevant
Tetracycline [oral]	1,386	24.23 (16.24 to 32.28)	18.63 (14 to 23)	18.10 (13 to 22)
Benzoyl peroxide [topical] + Lincosamide [topical] + Retinoid [topical]	600	23.09 (8.21 to 37.97)	18.82 (10 to 25)	18.27 (10 to 24)
Benzoyl peroxide [topical] + Anti-fungal [topical]	25	21.98 (-2.11 to 46.13)	18.99 (6 to 26)	18.43 (6 to 25)
Benzoyl peroxide [topical] + Lincosamide [topical]	276	22.64 (6.24 to 39.14)	19.11 (10 to 25)	18.55 (10 to 24)
Benzoyl peroxide [topical] + Macrolide [topical]	365	22.14 (12.76 to 31.79)	19.53 (13 to 24)	18.96 (13 to 23)
Photochemical therapy [blue and red]	15	8.76 (-43.29 to 53.96)	21.88 (5 to 27)	21.17 (5 to 26)
Retinoid [topical]	3,570	13.15 (8.30 to 18.05)	23.60 (20 to 26)	22.82 (19 to 25)
Macrolide [topical]	109	10.91 (-3.66 to 25.39)	23.80 (17 to 27)	23.00 (17 to 26)
Placebo	4,122	Reference	26.43 (25 to 27)	25.48 (24 to 26)

Classes ordered by mean rank for females (rank=1 indicates highest efficacy)
Effects with 95% CrI crossing the no effect line and respective classes are shown in red. CrI: credible intervals

Acceptability: treatment discontinuation for any reason

Figure 6. NMA treatment discontinuation for any reason in people with moderate to severe acne: base-case forest plots, treatment class effects vs placebo for females



All treatment class effects versus placebo (N=4133). Results expressed as log-odds ratios; values on the left side of vertical axis indicate lower discontinuation for any reason compared with placebo. Results for males, estimated after exclusion of studies assessing hormonal treatments, were very similar.

Table 9. NMA treatment discontinuation for any reason in people with moderate to severe acne: base-case treatment class effects vs placebo for females & rankings

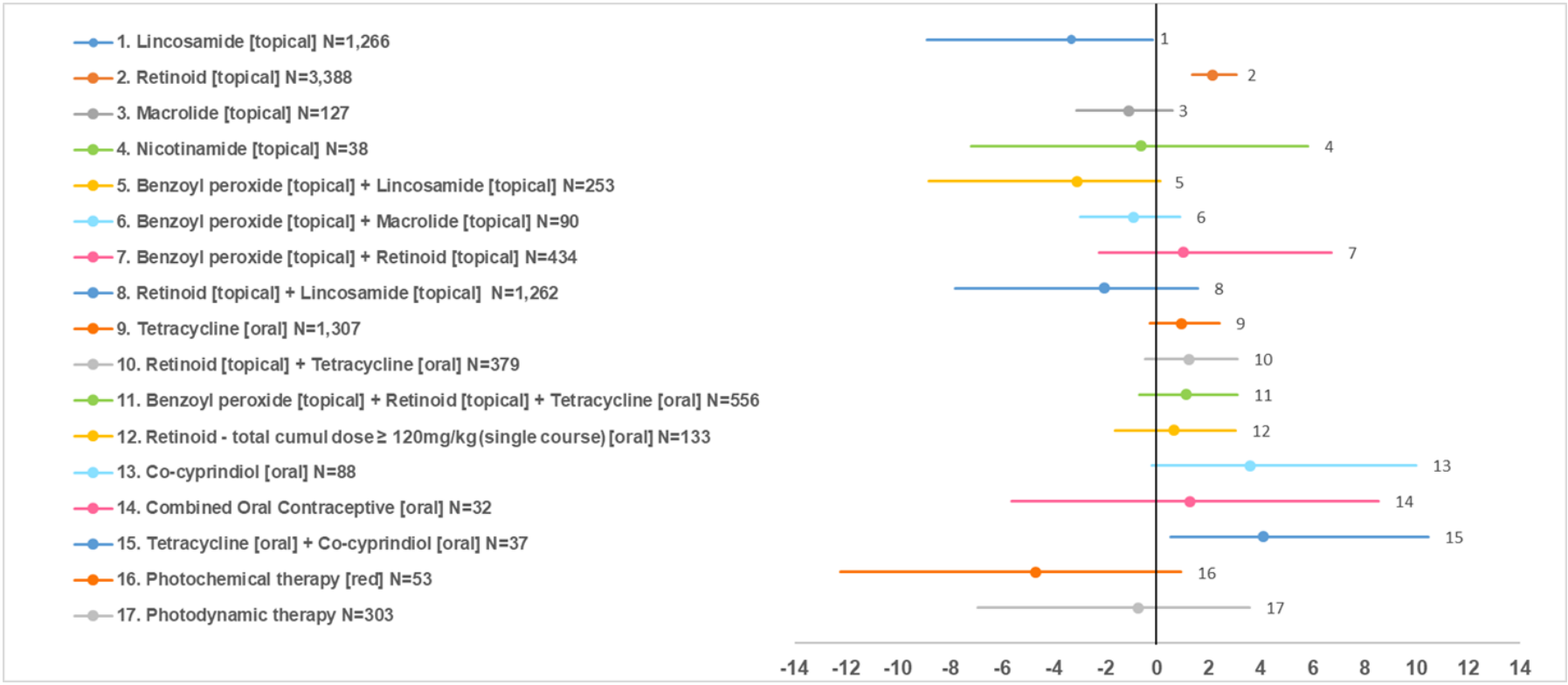
Class	N	logOR vs placebo (mean, 95% CrI)	Rank, females (mean, 95% CrI)	Rank, males (mean, 95% CrI)
Macrolide [topical]	127	-0.90 (-1.97 to 0.16)	7.67 (1 to 19)	7.28 (1 to 17)
Retinoid - total cumulative dose ≥ 120mg/kg (single course) [oral]	163	-0.95 (-2.67 to 0.78)	7.74 (1 to 21)	6.52 (1 to 18)
Photochemical therapy [red]	53	-1.34 (-5.01 to 1.83)	7.86 (1 to 23)	7.31 (1 to 20)
Retinoid - total cumulative dose ≥ 120mg/kg (single course) [oral] + Lincosamide [topical] +	30	-0.95 (-3.35 to 1.44)	8.73 (1 to 23)	7.35 (1 to 20)
Benzoyl peroxide [topical]	114	-0.88 (-3.05 to 0.98)	9.02 (1 to 22)	8.29 (1 to 19)
Benzoyl peroxide [topical] + Lincosamide [topical]	280	-0.69 (-1.65 to 0.27)	9.34 (2 to 20)	8.77 (2 to 18)
Benzoyl peroxide [topical] + Macrolide [topical]	477	-0.65 (-1.35 to 0.05)	9.52 (2 to 18)	9.03 (3 to 16)
Photodynamic therapy	141	-1.00 (-4.42 to 1.89)	9.57 (1 to 23)	8.88 (1 to 20)
Photothermal + photodynamic therapy	16	-1.00 (-5.16 to 2.83)	9.95 (1 to 23)	9.15 (1 to 20)
Lincosamide [topical]	1416	-0.55 (-1.53 to 0.45)	10.62 (3 to 20)	9.90 (3 to 18)
Lincosamide [topical] + Retinoid [topical]	1439	-0.48 (-1.56 to 0.64)	11.33 (2 to 22)	10.49 (2 to 19)
Nicotinamide [topical]	38	-0.38 (-2.09 to 1.34)	12.36 (1 to 23)	11.35 (1 to 20)
Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral]	556	-0.34 (-1.66 to 1.02)	12.63 (3 to 22)	10.59 (3 to 19)
Benzoyl peroxide [topical] + Anti-fungal [topical]	81	-0.26 (-2.98 to 2.33)	13.27 (1 to 23)	11.89 (1 to 20)
Co-cyprindiol [oral]	175	-0.25 (-1.70 to 1.20)	13.30 (3 to 22)	not relevant
Benzoyl peroxide [topical] + Lincosamide [topical] + Retinoid [topical]	207	-0.26 (-1.64 to 1.10)	13.38 (2 to 23)	12.23 (2 to 20)
Tetracycline [oral] + Co-cyprindiol [oral]	37	-0.23 (-1.84 to 1.39)	13.51 (2 to 23)	not relevant
Tetracycline [oral]	1188	-0.18 (-1.23 to 0.92)	14.22 (6 to 21)	11.90 (4 to 19)
Benzoyl peroxide [topical] + Retinoid [topical]	434	-0.08 (-1.15 to 1.04)	14.99 (4 to 23)	13.64 (4 to 20)
Combined Oral Contraceptive [oral]	32	0.12 (-1.91 to 2.15)	15.90 (2 to 23)	not relevant
Placebo	4133	Reference	16.36 (10 to 21)	14.95 (10 to 19)
Retinoid [topical] + Tetracycline [oral]	356	0.12 (-1.19 to 1.45)	17.02 (6 to 23)	14.37 (5 to 20)
Retinoid [topical]	3449	0.12 (-0.24 to 0.46)	17.71 (11 to 23)	16.11 (10 to 20)

Classes ordered by mean rank for females (rank=1 indicates lowest risk for discontinuation for any reason)
Effects with 95% CrI NOT crossing the no effect line and respective classes are shown in red.
logORs are for females; logORs for males, estimated after exclusion of hormonal treatments, were very similar
CrI: credible intervals; OR: odds ratio

Tolerability: treatment discontinuation due to side effects

Base-case analysis

Figure 7. NMA treatment discontinuation due to side effects in people with moderate to severe acne: base-case forest plots, treatment class effects vs placebo for females



All treatment class effects versus placebo (N=3920). Results expressed as log-odds ratios; values on the left side of vertical axis indicate lower discontinuation due to side effects compared with placebo. Results for males, estimated after exclusion of studies assessing hormonal treatments, were very similar.

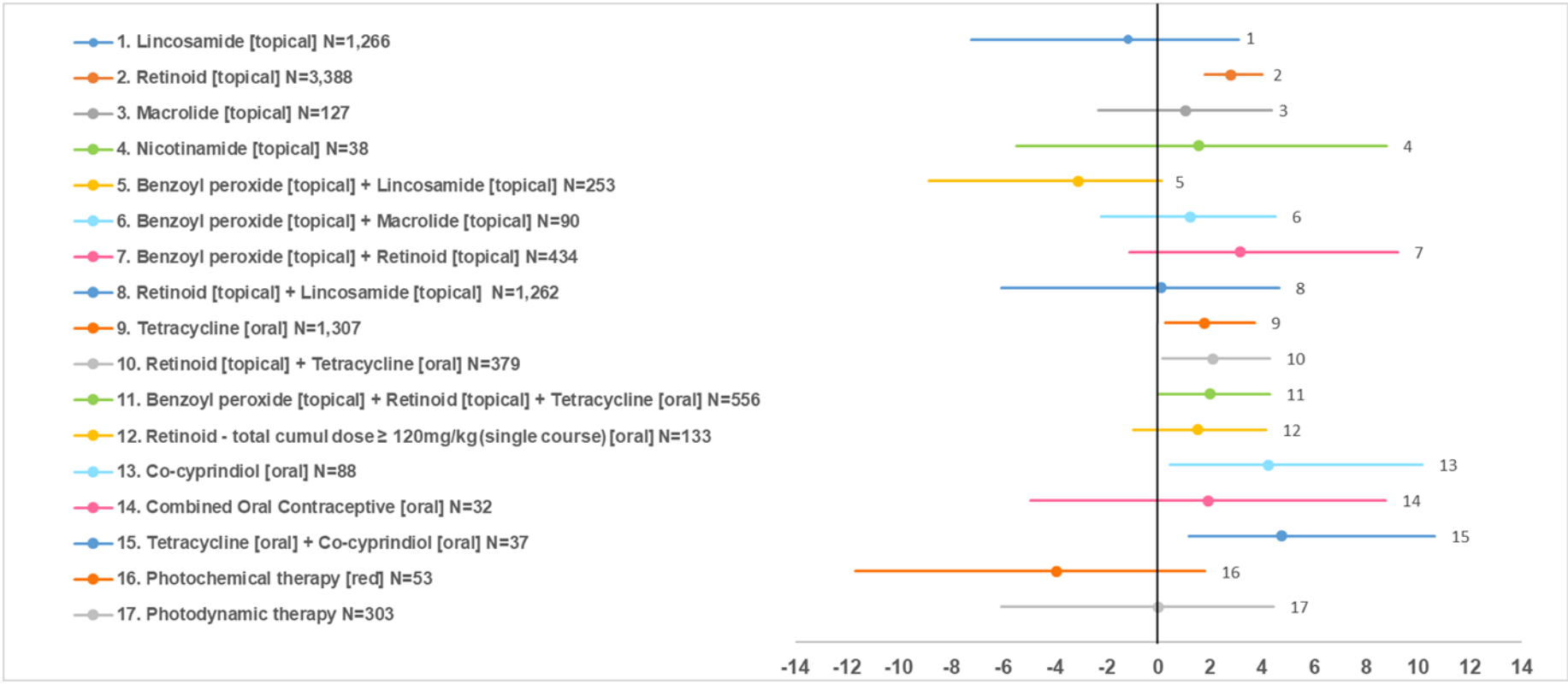
Table 10. NMA treatment discontinuation due to side effects in people with moderate to severe acne: base-case treatment class effects vs placebo for females & rankings

Class	N	logOR vs placebo (mean, 95% CrI)	Rank, females (mean, 95% CrI)	Rank, males (mean, 95% CrI)
Photochemical therapy [red]	53	-4.71 (-12.23 to 0.92)	2.72 (1 to 10)	2.60 (1 to 9)
Lincosamide [topical]	1266	-3.30 (-8.89 to -0.18)	2.95 (1 to 7)	2.82 (1 to 7)
Benzoyl peroxide [topical] + Lincosamide [topical]	253	-3.11 (-8.83 to 0.10)	3.68 (1 to 9)	3.58 (1 to 9)
Lincosamide [topical] + Retinoid [topical]	1262	-2.05 (-7.81 to 1.57)	5.63 (2 to 14)	5.34 (2 to 13)
Macrolide [topical]	127	-1.12 (-3.13 to 0.57)	6.14 (2 to 12)	5.95 (2 to 11)
Benzoyl peroxide [topical] + Macrolide [topical]	90	-0.91 (-2.99 to 0.87)	6.65 (2 to 13)	6.40 (2 to 12)
Photodynamic therapy	303	-0.75 (-6.92 to 3.58)	8.19 (2 to 17)	7.66 (2 to 15)
Nicotinamide [topical]	38	-0.63 (-7.19 to 5.82)	8.47 (2 to 18)	7.84 (2 to 15)
Placebo	3920	Reference	8.94 (6 to 13)	8.59 (6 to 12)
Retinoid - total cumulative dose ≥ 120mg/kg (single course) [oral]	133	0.65 (-1.63 to 3.01)	10.69 (5 to 16)	10.11 (4 to 15)
Benzoyl peroxide [topical] + Retinoid [topical]	434	1.00 (-2.25 to 6.72)	11.04 (3 to 18)	10.33 (3 to 15)
Combined Oral Contraceptive [oral]	32	1.27 (-5.64 to 8.53)	11.27 (1 to 18)	not relevant
Tetracycline [oral]	1307	0.92 (-0.30 to 2.41)	11.67 (8 to 15)	11.08 (8 to 14)
Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral]	556	1.12 (-0.69 to 3.09)	12.41 (7 to 17)	11.72 (7 to 15)
Retinoid [topical] + Tetracycline [oral]	379	1.24 (-0.46 to 3.11)	12.76 (8 to 17)	12.05 (8 to 15)
Retinoid [topical]	3388	2.14 (1.36 to 3.06)	15.06 (11 to 18)	13.91 (10 to 15)
Co-cyprindiol [oral]	88	3.59 (-0.22 to 10.00)	15.88 (9 to 18)	not relevant
Tetracycline [oral] + Co-cyprindiol [oral]	37	4.11 (0.50 to 10.48)	16.86 (12 to 18)	not relevant

Classes ordered by mean rank for females (rank=1 indicates lowest risk of discontinuation due to side effects)
Effects with 95% CrI NOT crossing the no effect line and respective classes are shown in red.
logORs are for females; logORs for males, estimated after exclusion of hormonal treatments, were very similar
CrI: credible intervals; OR: odds ratio

Bias-adjusted analysis

Figure 8. NMA treatment discontinuation due to side effects in people with moderate to severe acne: bias-adjusted forest plots, treatment class effects vs placebo for females



All treatment class effects versus placebo (N=3920). Results expressed as log-odds ratios; values on the left side of vertical axis indicate lower discontinuation due to side effects compared with placebo. Results for males, estimated after exclusion of studies assessing hormonal treatments, were very similar.

Table 11. NMA treatment discontinuation due to side effects in people with moderate to severe acne: bias-adjusted treatment class effects vs placebo for females & rankings

Class	N	logOR vs placebo (mean, 95% CrI)	Rank, females (mean, 95% CrI)	Rank, males (mean, 95% CrI)
Photochemical therapy [red]	53	-3.95 (-11.68 to 1.77)	2.40 (1 to 9)	2.29 (1 to 8)
Benzoyl peroxide [topical] + Lincosamide [topical]	253	-3.12 (-8.87 to 0.10)	2.54 (1 to 7)	2.40 (1 to 6)
Lincosamide [topical]	1266	-1.14 (-7.22 to 3.09)	4.44 (1 to 13)	4.21 (1 to 12)
Placebo	3920	Reference	5.69 (3 to 10)	5.34 (2 to 9)
Photodynamic therapy	303	-0.01 (-6.06 to 4.44)	7.25 (2 to 17)	6.88 (2 to 15)
Lincosamide [topical] + Retinoid [topical]	1262	0.10 (-6.06 to 4.67)	7.56 (2 to 17)	7.12 (2 to 14)
Macrolide [topical]	127	1.055 (-2.32 to 4.38)	8.76 (2 to 17)	8.14 (2 to 14)
Benzoyl peroxide [topical] + Macrolide [topical]	90	1.22 (-2.21 to 4.52)	9.28 (3 to 17)	8.68 (3 to 15)
Retinoid - total cumulative dose ≥ 120mg/kg (single course) [oral]	133	1.51 (-0.97 to 4.15)	9.73 (4 to 16)	9.13 (4 to 15)
Nicotinamide [topical]	38	1.54 (-5.49 to 8.79)	10.25 (2 to 18)	9.41 (2 to 15)
Combined Oral Contraceptive [oral]	32	1.92 (-4.92 to 8.77)	10.44 (1 to 18)	not relevant
Tetracycline [oral]	1307	1.78 (0.25 to 3.71)	10.58 (6 to 14)	9.95 (6 to 13)
Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral]	556	1.98 (-0.04 to 4.28)	11.48 (6 to 16)	10.74 (6 to 15)
Retinoid [topical] + Tetracycline [oral]	379	2.09 (0.14 to 4.29)	11.83 (6 to 17)	11.06 (6 to 15)
Benzoyl peroxide [topical] + Retinoid [topical]	434	3.14 (-1.11 to 9.24)	13.15 (4 to 18)	11.89 (4 to 15)
Retinoid [topical]	3388	2.77 (1.77 to 4.00)	13.89 (8 to 18)	12.77 (8 to 15)
Co-cyprindiol [oral]	88	4.24 (0.43 to 10.17)	15.31 (8 to 18)	not relevant
Tetracycline [oral] + Co-cyprindiol [oral]	37	4.77 (1.16 to 10.64)	16.44 (10 to 18)	not relevant

Classes ordered by mean rank for females (rank=1 indicates lowest risk of discontinuation due to side effects)
Effects with 95% CrI NOT crossing the no effect line and respective classes are shown in red.
logORs are for females; logORs for males, estimated after exclusion of hormonal treatments, were very similar
CrI: credible intervals; OR: odds ratio

Appendix F – GRADE tables

GRADE tables for review question: For people with moderate to severe acne vulgaris what are the most effective treatment options?

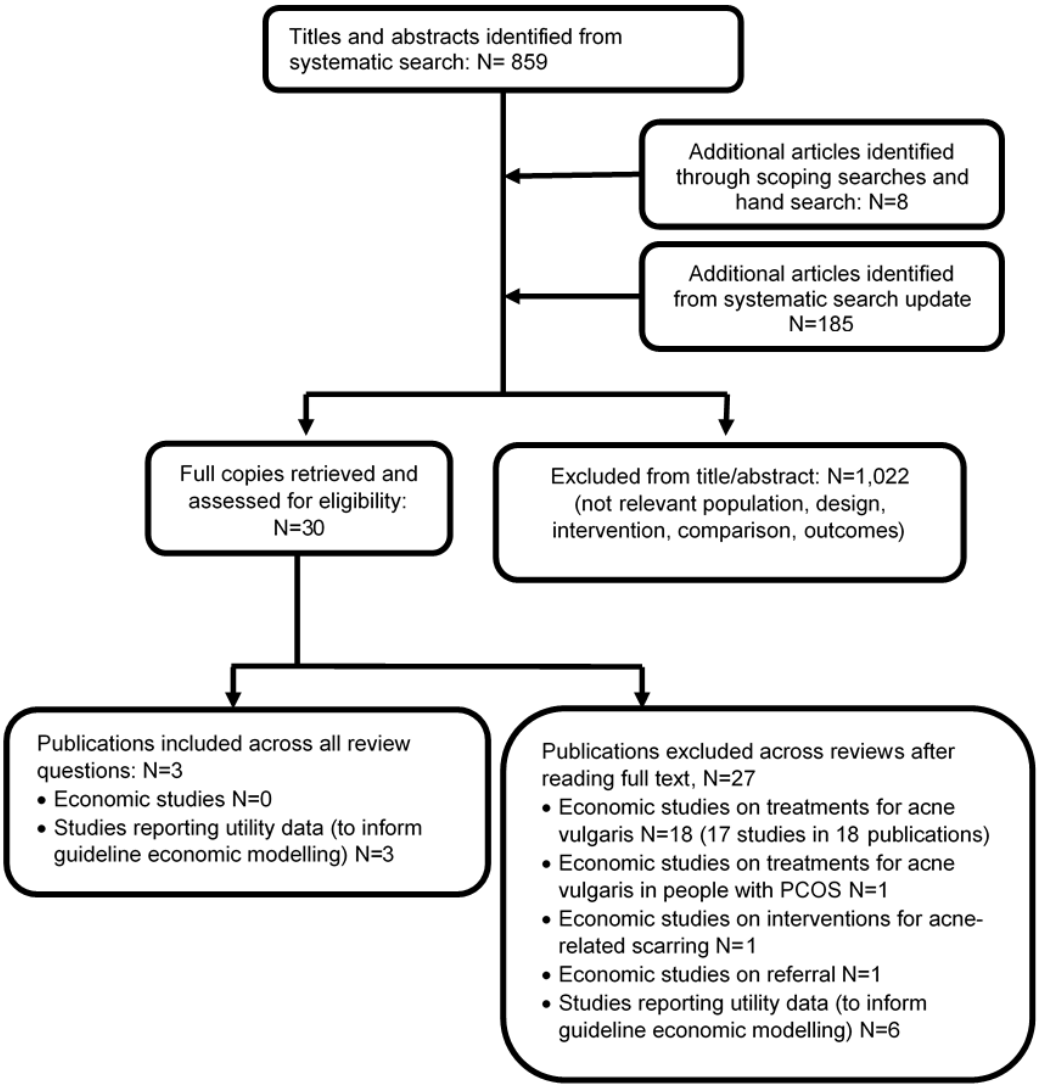
GRADE was not undertaken for this review question. Instead, threshold analysis was conducted as an alternative to GRADE, to test the robustness of treatment recommendations based on the NMA, to potential biases or sampling variation in the included evidence. Methods and results of threshold analysis are presented in appendix N.

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: For people with moderate to severe acne vulgaris what are the most effective treatment options?

A global health economics search was undertaken for all areas covered in the guideline. Figure 9 shows the flow diagram of the selection process for economic evaluations of interventions and strategies associated with the care of people with acne vulgaris and studies reporting acne vulgaris-related health state utility data.

Figure 9. Flow diagram of selection process for economic evaluations of interventions and strategies associated with the care of people with acne vulgaris and studies reporting acne vulgaris-related health state utility data



Appendix H – Economic evidence tables

Economic evidence tables for review question: For people with moderate to severe acne vulgaris what are the most effective treatment options?

No economic evidence was identified which was applicable to this review question.

1 Appendix I – Economic evidence profiles

2 Economic evidence profile for review question: For people with moderate to severe acne vulgaris what are the most effective 3 treatment options?

4 **Table 12: Economic evidence profile – females with moderate to severe acne**

Economic evidence profile: topical, oral and physical treatments for females with moderate to severe acne vulgaris							
Study & country	**Limitations**	**Applicability**	**Other comment**	**Incremental cost vs GP care (£)[1]**	**Incremental QALY vs GP care**	**NMB (£)[1]**	**Uncertainty[1]**
Guideline economic analysis UK	Minor limitations [2]	Partially applicable[3]	Outcome: QALY Step-wise approach: most cost-effective treatment is omitted at each step & prob of cost-effectiveness of next most cost-effective treatment is re-calculated Results for males were very similar	ADAP top £39 BPO top -£40 CLIND top -£17 BPO+CLIND top £31 BPO+ERYTH top £25 BPO+ADAP top £9 CLIND+TRET top -£20 BPO+CLIND+TRET top £40 LYME oral -£8 AZEL top + LYME oral -£13 ADAP top + LYME oral £29 BPO+ADAP top + LYME oral £25 Oral iso<120mg/kg £508 Oral iso≥120mg/kg £516 PDT £627 PCT red £409 PTT £604 PDT+LYME oral £577	ADAP top 0.013 BPO top 0.038 CLIND top 0.048 BPO+CLIND top 0.028 BPO+ERYTH top 0.027 BPO+ADAP top 0.049 CLIND+TRET top 0.072 BPO+CLIND+TRET top 0.028 LYME oral 0.029 AZEL top + LYME oral 0.060 ADAP top + LYME oral 0.050 BPO+ADAP top + LYME oral 0.068 Oral iso<120mg/kg 0.061 Oral iso≥120mg/kg 0.081 PDT 0.069 PCT red 0.047 PTT 0.110 PDT+LYME oral 0.72	PTT £16,597 CLIND+TRET top £16,460 BPO+ADAP top + LYME oral £16,352 AZEL top + LYME oral £16,232 Oral iso≥120mg/kg £16,122 CLIND top £15,988 BPO+ADAP top £15,978 ADAP top + LYME oral £15,971 PDT+LYME oral £15,876 BPO top £15,802 PDT £15,753 Oral iso<120mg/kg £15,715 LYME oral £15,603 PCT red £15,547 BPO+CLIND top £15,543 BPO+CLIND+TRET top £15,538 BPO+ERYTH top £15,515	Prob of cost effectiveness at WTP £20,000 /QALY (step-wise approach): PTT 0.43; CLIND + TRET top 0.30; BPO + ADAP top + LYME oral 0.25; AZEL top + LYME oral 0.34; oral iso ≥ 120mg/kg 0.27; CLIND top 0.14; BPO + ADAP top 0.26; ADAP top + LYME oral 0.20; PDT + LYME oral 0.28; BPO top 0.26; PDT 0.24; oral iso < 120mg/kg 0.39; LYME oral 0.20; PCT red 0.33; BPO + CLIND top 0.37; BPO + CLIND + TRET top 0.52; BPO + ERYTH top 0.97; ADAP top

Economic evidence profile: topical, oral and physical treatments for females with moderate to severe acne vulgaris							
						ADAP top £15,223 GP care £15,009	1.00; GP care 1.00
1. Costs expressed in 2019 GBP *2. Decision-analytic model (decision-tree); time horizon 1 year; relative effects based on guideline systematic review and NMA; baseline effects & other clinical input parameters derived from published literature and the committee's expert advice; resource use based on RCT data & other published literature supplemented by the committee's expert advice; national unit costs used; PSA conducted; CEAF presented* *3. UK study; NHS & PSS perspective; QALY estimates based on the committee's expert opinion due to lack of relevant data of adequate quality* *ADAP: adapalene; AZEL: azelaic acid; BPO: benzoyl peroxide; CLIND: clindamycin; ERYTH: erythromycin; iso: isotretinoin; LYME: lymecycline; PCT: photochemical therapy; PDT: photodynamic therapy; prob: probability; PTT: photothermal therapy; top: topical; TRET: tretinoin; WTP: willingness to pay*							

1

Appendix J – Economic analysis

Economic analysis for review question: For people with moderate to severe acne vulgaris what are the most effective treatment options?

Introduction – objective of economic modelling

The choice of treatment for people with moderate to severe acne was identified by the committee and the guideline health economist as an area with potentially major resource implications. The review of economic evidence identified no studies meeting inclusion criteria that could inform recommendations; however, there is a solid clinical evidence base that can inform primary economic modelling. An economic model was therefore developed to assess the relative cost effectiveness of treatments for people with moderate to severe acne in England.

Economic modelling methods

Population

The study population of the economic model comprised people with moderate to severe acne who present to primary care services, although they may be subsequently referred to a specialist dermatology setting.

Interventions assessed

The range of treatments assessed in the economic analysis was determined by the availability of relevant clinical data included in the guideline systematic review of topical, oral and physical treatments for people with moderate to severe acne. Network meta-analysis (NMA) was employed for synthesis of the available efficacy data. Details of the NMA are provided in appendix M.

Based on the advice of the committee, only treatment classes with evidence of effect versus placebo with at least 40 observations each across the RCTs included in the NMA of efficacy were considered in the economic analysis, as this was deemed as the minimum amount of evidence that could suggest that a treatment may be effective and potentially cost-effective. A treatment class demonstrated evidence of effect if the 95% credible intervals [CrI] of its effect versus placebo did not cross the line of no effect.

One intervention was selected as a representative from each treatment class; this was necessary only for costing purposes, as there was no adequate evidence to estimate individual treatment effects within each treatment class. The criteria for selecting interventions to represent each treatment class were the intervention availability and usage in the UK and other practicalities of use (e.g. a combination of topical treatments available in a single formulation was preferred to combinations that are only available as separate formulations); the evidence base for each intervention within class; the risk of side effects of individual interventions within a class; and, for pharmacological treatments, the drug acquisition cost (drugs with lower acquisition costs were preferred).

Based on the above criteria, the following treatment classes and interventions were considered in the economic analysis of treatments for people with moderate to severe acne:

- Topical retinoids: adapalene
- Benzoyl peroxide (topical treatment, own class)
- Topical lincosamides: topical clindamycin

- Benzoyl peroxide + topical retinoid (adapalene)
- Benzoyl peroxide + topical lincosamide (clindamycin)
- Benzoyl peroxide + topical macrolide (erythromycin)
- Topical retinoid + topical lincosamide: tretinoin + clindamycin
- Benzoyl peroxide + topical retinoid (tretinoin) + topical lincosamide (clindamycin)
- Oral tetracycline: lymecycline
- Topical retinoid (adapalene) + oral tetracycline (lymecycline)
- Azelaic acid (topical treatment, own class) + oral tetracycline (lymecycline)
- Benzoyl peroxide + topical retinoid (adapalene) + oral tetracycline (lymecycline)
- Oral isotretinoin - total cumulative dose ≥ 120mg/kg (single course)
- Oral isotretinoin - total cumulative dose < 120mg/kg (single course)
- Photodynamic therapy
- Photochemical therapy (red light)
- Photothermal therapy
- Photodynamic therapy + oral tetracycline (lymecycline)
- GP care, comprising GP consultations without provision of any pharmacological or physical treatment, reflecting the placebo arm of the network.

Model structure

A decision-analytic model in the form of a decision-tree was constructed using Microsoft Office Excel 2016. The model estimated the total costs and benefits associated with provision of effective treatment options for people with moderate to severe acne. The structure of the model, which aimed to simulate the course of acne and relevant clinical practice in the UK, was also driven by the availability of clinical data.

According to the model structure, hypothetical cohorts of people with moderate to severe acne were initiated on each of the treatment options assessed and followed for one year (52 weeks). People within each cohort might receive a full course of treatment, or they might discontinue treatment due to intolerable side effects or any other reason. Those who discontinued received 'average acne care', comprising a mixture of care that is anticipated to be currently received by people with acne in the NHS. Following treatment, people in each cohort experienced a percentage change in their total acne lesion count (between start and end of treatment), which, for every person in each cohort, corresponded to a level of perceived acne symptom improvement: 'excellent', 'good', 'moderate' or no improvement. By the end of one year, those who experienced excellent, good or moderate improvement might relapse and return to their initial state of moderate to severe acne, otherwise they remained at the same level of improvement. Those who experienced no improvement remained in the state of no improvement until the model endpoint.

Treatment effects (i.e. % change in total acne lesion count from baseline, % CFB) that informed the model were obtained, where possible, from intention to treat (ITT) analysis reported in relevant RCTs for each treatment, usually with last observation carried forward (LOCF). This means that, for every treatment option, the model utilised data on effects that were applicable to all people in the cohort initiating this particular treatment option, whether they completed a full course of treatment or not. Therefore, in each cohort, treatment efficacy (% CFB) and associated 'acne symptom status' (i.e. excellent, good, moderate or no improvement) at end of treatment was independent of 'treatment status' (i.e. completion of a full course of treatment or early discontinuation) and therefore these two parameters were modelled separately.

A full course of any drug treatment considered in the model other than oral isotretinoin and also a full course of a 'GP care' lasted 3 months (13 weeks). Acne symptom status at end of these treatment options was measured at this point. People who completed a full course of any of these treatments and who experienced excellent or good improvement received another 3 months (13 weeks) of their initial treatment as maintenance, i.e. between 3 and 6 months in the model. Those who completed a full course of treatment but experienced moderate improvement either continued their initial treatment as maintenance (33%), or moved to average acne care (66%) for the next 3 months (13 weeks, 3-6 months in the model). Those who completed a full course of treatment but experienced no improvement moved to average acne care between 3 and 6 months in the model (13 weeks). All people were assumed to retain their acne status achieved at the end of treatment (i.e. at 3 months) between 3 and 6 months in the model.

A full course of oral isotretinoin lasted 6 months (26 weeks). Acne symptom status at end of treatment with oral isotretinoin was measured at this point. People who completed a full course of oral isotretinoin did not receive further maintenance treatment.

A full course of physical treatment was assumed to last approximately 2 months (8 weeks). Acne symptom status at the end of physical treatment was measured at this point. People who completed a full course of physical treatment received average acne care between 2 and 6 months in the model, either as maintenance treatment (if initial treatment was successful) or as alternative treatment (if initial treatment was not successful). All people were assumed to retain their acne status achieved at the end of treatment (i.e. at 2 months) between 2 and 6 months in the model.

Treatment discontinuation was assumed to occur after 25% of the time of a full course of treatment (i.e. at 6.5 weeks if they were initiated on oral isotretinoin, at 3 weeks if they were initiated on any other pharmacological treatment option or GP care, and 2 weeks if they were initiated on physical treatments). From the point of treatment discontinuation and up to 6 months in the model, they were assumed to receive average acne care.

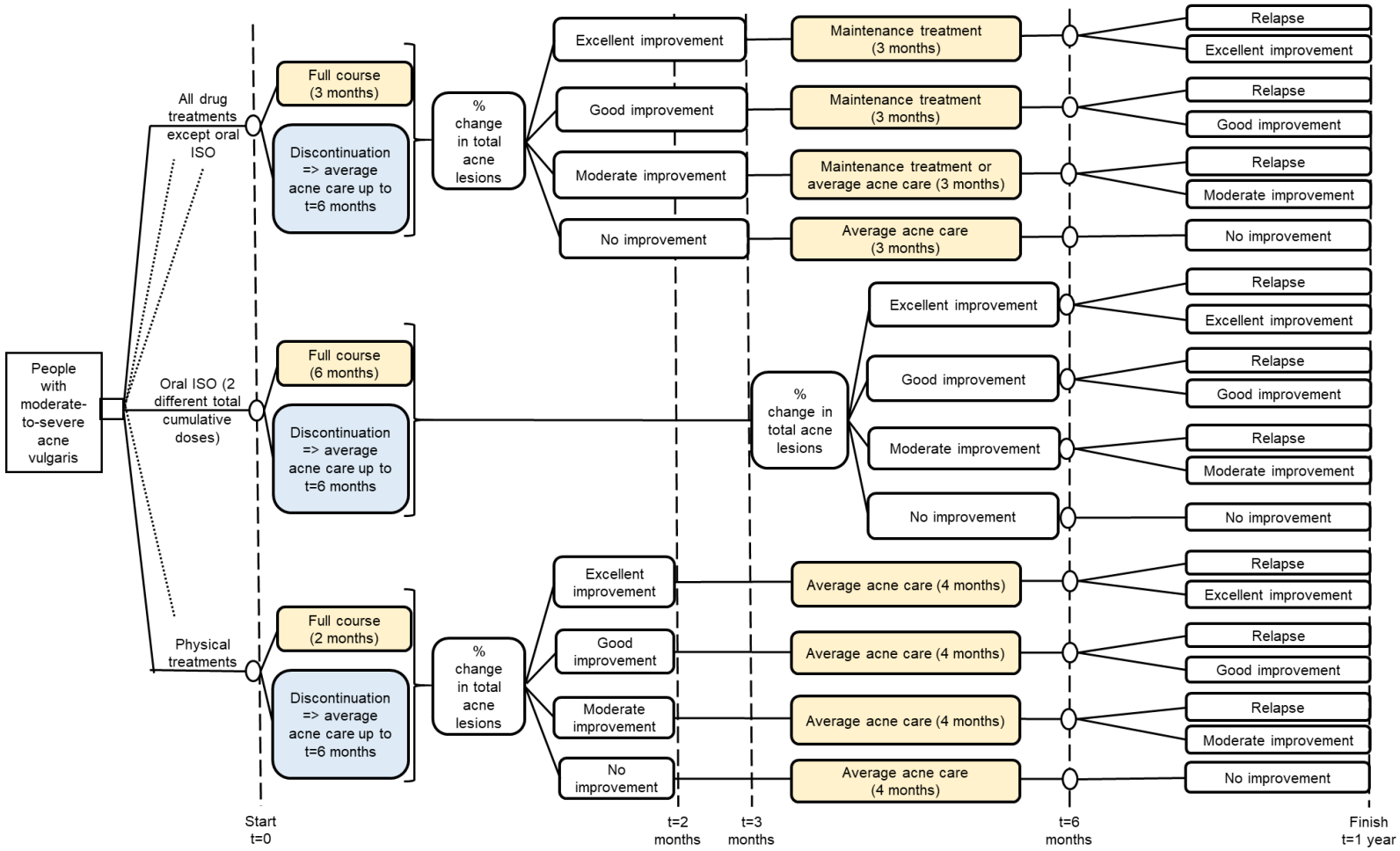
During the last 6 months (26 weeks) of the model, 90% of people who relapsed after excellent or good improvement, 90% of people with moderate improvement (regardless of whether they relapsed or not) and 90% of people with no improvement received average acne care. For people with excellent or good improvement who received average acne care only if they relapsed, average acne care costs were applied only over 3 months within this period, as relapse was assumed to occur on average in the middle of the 6-month period. For people with moderate or no improvement who received average acne care during this period, average acne care costs were applied over the whole period of the last 6 months in the model.

People who discontinued treatment due to intolerable side effects experienced a reduction in their health-related quality of life (HRQoL), assumed to last over the period they received treatment and up to the point of discontinuation, plus 2 weeks after treatment discontinuation.

The one-year time horizon of the analysis was considered to be long enough to capture longer-term costs and effects of treatment, beyond treatment endpoint, without significant extrapolation and assumptions around the course of moderate to severe acne.

The structure of the economic model for treatments for people with moderate to severe acne is shown in Figure 10.

Figure 10. Schematic diagram of the economic model structure: interventions for the treatment of people with moderate to severe acne



Costs and outcomes considered in the analysis

The economic analysis adopted the perspective of the NHS and personal social services (PSS), as recommended by NICE (NICE, 2014). Costs consisted of intervention costs (healthcare professional time including follow-up, drug acquisition, laboratory testing and procedures related to physical interventions, as relevant), and costs incurred by people with acne who discontinued treatment before completion of a course, those who did not respond adequately to treatment, and those who relapsed following treatment. The cost year was 2019.

The measure of outcome was the Quality Adjusted Life Year (QALY), which incorporated utilities associated with the levels of acne improvement following treatment, as well as utility decrements due to intolerable side effects of treatment (that led to early discontinuation). The likelihood of a person having excellent or good improvement at the end of the model (i.e. at 1 year after treatment initiation) was a secondary outcome.

Relative effects on efficacy, acceptability and tolerability and methods of evidence synthesis

Relative effects on efficacy (expressed as difference in % CFB of total lesion count between pairs of treatments), acceptability (discontinuation for any reason, expressed in the form of log-odds ratios [LORs] between pairs of treatments) and tolerability (discontinuation due to intolerable side effects, also expressed in the form of LORs between pairs of treatments) for all treatment classes considered in the economic modelling were derived from the respective NMAs of treatments for people with moderate to severe acne that were undertaken for this guideline. Details on the methods and results of the NMAs, which were conducted in WinBUGS 1.4.3 (Lunn 2000; Spiegelhalter 2003) for discontinuation data and OpenBUGS 3.2.3 (www.openbugs.net) for efficacy data are provided in appendix M. For the economic analysis the first 100,000 iterations undertaken in WinBUGS were discarded and another 300,000 were run, thinned by 30, so as to obtain 10,000 iterations that populated the economic model.

Separate analyses were conducted for females and males, as sex-specific data on discontinuation for any reason and due to side effects were available from the respective NMAs.

Relative effects were combined with respective ‘baseline’ absolute effect data for each outcome, in order to estimate the absolute effects (absolute % CFB of total lesion count and absolute risks of discontinuation for any reason and due to side effects) of each treatment class in people with moderate to severe acne. Topical retinoids (adapalene) was the treatment selected to serve as baseline, as explained in the next section.

For some treatment classes considered in the economic analysis, relative effects on discontinuation (for any reason and/or due to side effects) were not available. In such cases, the class ‘borrowed’ the relative effect of another class of a similar type and with an anticipated similar effect.

The results of the network meta-analysis that were used to populate the economic model for people with moderate to severe acne are provided in Table 13.

Table 13. Results of the guideline NMA utilised in the economic analysis: efficacy, discontinuation for any reason and discontinuation due to side effects of all treatments versus topical retinoids (adapalene) in people with moderate to severe acne

Treatment class and intervention	Relative effects versus topical retinoids (adapalene) [mean, 95% CrI]		
	Efficacy (difference in % CFB)	Discontinuation for any reason (LOR)	Discontinuation due to side effects (LOR)
GP care	-13.11 (-18.05 to -8.28)	Females: -0.12 (-0.46 to 0.24) Males: -0.12 (-0.45 to 0.24)	Females: -2.14 (-3.05 to -1.35) Males: -2.13 (-3.03 to -1.37)
Benzoyl peroxide	15.69 (-1.69 to 33.17)	Females: -1.01 (-3.25 to 0.86) Males: -1.01 (-3.23 to 0.87)	Borrowed from topical retinoid
Topical lincosamides: topical clindamycin	21.07 (7.23 to 34.82)	Females: -0.66 (-1.70 to 0.42) Males: -0.66 (-1.70 to 0.40)	Females: -5.48 (-11.23 to -2.19) Males: -5.58 (-11.65 to -2.19)
Benzoyl peroxide + topical retinoid (adapalene)	21.02 (-1.18 to 42.88)	Females: -0.20 (-1.34 to 0.98) Males: -0.21 (-1.33 to 0.97)	Females: -1.14 (-4.53 to 4.40) Males: -1.07 (-4.49 to 4.82)
Benzoyl peroxide + topical lincosamide (clindamycin)	9.55 (-7.62 to 26.61)	Females: -0.80 (-1.82 to 0.21) Males: -0.80 (-1.81 to 0.23)	Females: -5.26 (-11.03 to -1.90) Males: -5.26 (-10.99 to -1.90)
Benzoyl peroxide + topical macrolide (erythromycin)	9.05 (-1.43 to 19.89)	Females: -0.76 (-1.55 to 0.04) Males: -0.76 (-1.52 to 0.03)	Females: -3.06 (-5.34 to -1.09) Males: -3.05 (-5.31 to -1.07)
Topical retinoid + topical lincosamide: tretinoin + clindamycin	31.45 (15.09 to 48.17)	Females: -0.60 (-1.73 to 0.57) Males: -0.60 (-1.71 to 0.55)	Females: -4.24 (-10.04 to -0.41) Males: -4.34 (-10.49 to -0.46)
Benzoyl peroxide + topical retinoid (tretinoin) + topical lincosamide (clindamycin)	10.01 (-4.19 to 24.05)	Females: -0.38 (-1.69 to 0.93) Males: -0.36 (-1.68 to 0.95)	Borrowed from topical retinoid + topical lincosamide
Oral tetracycline: lymecycline	11.18 (1.75 to 20.57)	Females: -0.31 (-1.40 to 0.82) Males: -0.43 (-1.62 to 0.82)	Females: -1.23 (-2.78 to 0.48) Males: -1.23 (-2.75 to 0.45)
Topical retinoid (adapalene) + oral tetracycline (lymecycline)	22.25 (9.46 to 34.67)	Females: -0.01 (-1.35 to 1.33) Males: -0.14 (-1.55 to 1.27)	Females: -0.91 (-2.86 to 1.20) Males: -0.91 (-2.81 to 1.15)
Azelaic acid + oral tetracycline (lymecycline)	25.67 (-5.98 to 56.52)	Borrowed from topical retinoid + oral tetracycline	
Benzoyl peroxide + topical retinoid (adapalene) + oral	30.46 (15.56 to 45.29)	Females: -0.47 (-1.83 to 0.89)	Females: -1.03 (-3.03 to 1.14)

Treatment class and intervention	Relative effects versus topical retinoids (adapalene) [mean, 95% CrI]		
	Efficacy (difference in % CFB)	Discontinuation for any reason (LOR)	Discontinuation due to side effects (LOR)
tetracycline (lymecycline)		Males: -0.60 (-2.02 to 0.84)	Males: -1.02 (-3.04 to 1.12)
Oral isotretinoin - total cumul dose ≥120mg/kg (single course)	44.95 (23.27 to 66.74)	Females: -1.10 (-2.83 to 0.69) Males: -1.22 (-2.97 to 0.60)	Females: -1.49 (-3.94 to 1.09) Males: -1.49 (-4.01 to 1.00)
Oral isotretinoin - total cumul dose <120mg/kg (single course)	34.90 (6.86 to 62.88)	Borrowed from oral isotretinoin – total cumul dose ≥120mg/kg	
Photodynamic therapy	27.59 (12.28 to 42.30)	Females: -1.14 (-4.56 to 1.75) Males: -1.19 (-4.79 to 1.73)	Females: -2.89 (-8.87 to 1.57) Males: -2.99 (-8.98 to 1.46)
Photochemical therapy (red light)	16.97 (-6.29 to 39.34)	Females: -1.48 (-5.08 to 1.78) Males: -1.53 (-5.29 to 1.65)	Females: -6.83 (-14.67 to -1.10) Males: -6.93 (-14.69 to -1.12)
Photothermal therapy	44.71 (10.05 to 79.46)	Borrowed from photochemical therapy (red light)	
Photodynamic therapy + oral tetracycline (lymecycline)	31.71 (12.30 to 51.03)	Borrowed from oral tetracycline (lymecycline)	
Topical retinoid: adapalene	Reference	Reference	

CFB: change from baseline; CrI: credible intervals; cumul: cumulative; LOR: log-odds ratio

Baseline parameters in people with moderate to severe acne

'Baseline' (b) absolute effect data for each outcome (i.e. efficacy, discontinuation for any reason and discontinuation due to side effects) need to be combined with respective relative effects obtained from the guideline NMAs in order to estimate absolute effects for every treatment (t) considered in the economic analysis:

$$\text{Absolute effect}_{[t]} = \text{absolute effect}_{[b]} + \text{relative effect}_{[t\text{-}b]}$$

Any treatment included in the NMA can serve as baseline treatment, including placebo (reflecting GP care in the model). The selection of a treatment to serve as baseline depends on the availability of good quality data on its absolute treatment effects. Absolute treatment effects depend on epidemiological and prognostic factors and need to be representative of the study population under conditions of routine care (i.e. of people with moderate to severe acne receiving care in England).

Ideally, baseline absolute treatment effects should be obtained from routinely collected UK data, such as those derived from large naturalistic studies, national surveys or administrative databases, which reflect routine care (rather than trial conditions). If UK data are not available, non-UK data from similar settings regarding the epidemiology of acne and routine clinical practice may be used. Alternatively, if no suitable data are available, absolute effects from one or more RCTs of good quality, with participants and settings that are representative of the model population, could be used (Dias 2011).

Baseline efficacy

Baseline data on efficacy (% CFB) were derived from large RCTs included in the respective NMA for people with moderate to severe acne, as no relevant observational data were possible to identify. Adapalene 0.1% (topical retinoid) was selected as the baseline treatment, because good quality data from large trials were available, and for consistency purposes with the available baseline discontinuation data, as reported below. Adapalene 0.1% is the most commonly used topical retinoid for acne in England. Weighted RCT data on efficacy were derived from adapalene 0.1% trial arms with treatment duration of 12 to <24 weeks (which is the optimal treatment duration for adapalene), from studies conducted in Europe, North America or Australia that reported ITT data and were included in the guideline NMA. These countries were selected to reflect similar settings and epidemiological data to those in the UK. Following review of the available efficacy data, adapalene arm data from 2 RCTs were synthesised in order to estimate baseline efficacy for people with moderate to severe acne, using the data and approach shown in Table 14, and assuming a log-normal distribution for (100 + % CFB) based on review of % CFB data from a study reporting data from 4,081 people with moderate to severe facial acne that participated in 7 clinical trials of oral contraceptives or topical treatments conducted in Europe (Gerlinger 2008).

Table 14: Baseline efficacy (% change in total lesion count from baseline, CFB) for topical retinoids, estimated from data derived from adapalene 0.1% trial arms with treatment duration of 12 to <24 weeks, included in the NMA of efficacy of treatments for people with moderate to severe acne

Study ID	Country	N randomised	% CFB
Eichenfield 2010 (Study 1)	North America/Europe	533	Median -39.00% (estimated SD 49.68)
Eichenfield 2010 (Study 2)	North America	535	Median -34.00% (estimated SD 39.58)
Pooled % CFB*	**% CFB: mean -36.03%; log (100 + % CFB): 4.16**		

Study ID	Country	N randomised	% CFB
	SE of log-normal distribution of (100 + % CFB): 0.02		

CFB: change from baseline; SD: standard deviation; SE; standard error of the mean
SDs were not reported in the studies; they were imputed using the same methods used for the imputation of SDs in the NMA of efficacy (appendix M).
Available data were synthesised following the observation that (100 + % CFB) has a log-normal distribution, based on review of % CFB data from a study reporting data from 4,081 people with moderate to severe facial acne that participated in 7 clinical trials of oral contraceptives or topical treatments conducted in Europe (Gerlinger 2008).
The mean of $\ln(100+P)$ *can be obtained from the median of the percent change from baseline from:*

$$mean_{\ln(100+P),1} = \ln\left(100 + median_P\right)$$

where the subscript 1 denotes the baseline treatment.

Using properties of the log-Normal distribution, the standard error of $mean_{\ln(100+P),1}$ *is:*

$$se(mean_{\ln(100+P),1}) = \sqrt{\frac{1}{n}\ln\left(\frac{1}{2}\left(1+\sqrt{1+\left(\frac{2sd_P}{e^{mean_{(100+P)}}}\right)^2}\right)\right)}$$

- *The mean of* $\ln(100+P)$ *was then pooled across the 2 RCTs using a fixed effect single arm meta-analysis.*

Subsequently, for each treatment k the mean of $\ln(100+P)$ is:

$$mean_{\ln(100+P),k} = \ln\left(\exp\left(mean_{\ln(100+P),1}\right) + d_k\right)$$

where d_k is the estimated mean change in the percentage change from baseline for treatment k relative to treatment 1 (topical retinoid), obtained from the NMA on the efficacy outcome.

Baseline risk of discontinuation

Baseline data on the absolute risk of discontinuation for any reason and due to intolerable side effects were derived from an observational study of 250 people with acne in Turkey, who were prescribed topical treatments (Dikicier 2019). This was the only identified observational study that provided data on people with acne discontinuing treatment for any reason and due to side effects. Of the 250 participants in the study, 75 were prescribed topical retinoids. Of them, 30 (40% of the sample) discontinued treatment for any reason, and 15 (20% of the sample) discontinued treatment due to intolerable side effects.

The study sample had mild to moderate acne. It is possible that people with moderate to severe acne treated with topical retinoids have different risks of discontinuation. To estimate the absolute risk of discontinuation in people with moderate to severe acne, we first estimated the ratio of discontinuation for any reason and due to side effects in people with moderate to severe acne to those with mild to moderate acne and applied that onto the observational discontinuation risks derived from people with mild to moderate acne reported in Dikicier (2019). To estimate the ratio of discontinuation for any reason and due to side effects in people with moderate to severe acne to those with mild to moderate acne, we used weighted RCT data on the absolute risk of discontinuation in people with moderate to severe acne and people with mild to moderate acne in adapalene 0.1% arms with treatment duration of 12 to <24 weeks, included in the respective guideline NMAs. Only data from studies conducted in Europe, North America and/or Australia were considered, to reflect similar settings and epidemiological data to those in the UK. The following formula was used:

$$ADR_{M2S} = ADR_{M2M} * \frac{ADR\ (RCT,M2S)}{ADR\ (RCT,M2M)}$$

where ADR_{M2S} is the absolute risk of discontinuation for people with moderate to severe acne used in the economic analysis; ADR_{M2M} is the absolute risk of discontinuation for people with mild to moderate acne, as derived from Dikicier 2019; ADR (RCT, M2S) is the weighted absolute risk of discontinuation in the adapalene 0.1% arms of RCTs included in the respective NMA for people with moderate to severe acne; and ADR (RCT, M2M) is the absolute risk of discontinuation in the adapalene 0.1% arms of RCTs included in the respective NMA for people with mild to moderate acne. The RCT arm data utilised for this purpose and the resulting estimates of the baseline risk of discontinuation for any reason and due to side effects for topical retinoids are shown in Table 15.

Table 15: Baseline discontinuation risks (for any reason and due to side effects) of topical retinoids, estimated from data derived from adapalene 0.1% trial arms with treatment duration of 12 to <24 weeks, included in the NMAs of discontinuation for people with moderate to severe acne and people with mild to moderate acne

Study ID	Country	Observations	Discontinuation due to	
			Any reason	Side effects
Moderate to severe acne				
Eichenfield 2010 (Study 1)	US	533	62 (11.6%)	3 (0.6%)
Eichenfield 2010 (Study 2)	US	535	60 (11.2%)	3 (0.6%)
Ioannides 2002	Greece	40	4 (10.0%)	3 (7.5%)
Pariser 2005	US	70	5 (7.1%)	2 (2.9%)
Weighted risk of discontinuation for adapalene 0.1%			**11.1%**	**0.9%**
Mild to moderate acne				
Cunliffe 1997	Europe	134	14 (10.4%)	0 (0.0%)
Gollnick 2009	North America /Europe	418	49 (11.7%)	1 (0.2%)
Grosshans 1998	Europe	52	7 (13.5%)	1 (1.9%)
Guerra-Tapia 2012	Spain	85	27 (31.8%)	3 (3.5%)
Thiboutout 2006	North America	261	21 (8.0%)	2 (0.8%)
Thiboutout 2007	US	148	17 (11.5%)	1 (0.7%)
Langner 2008	Europe	65	7 (10.8%)	2 (3.1%)
Leyden 2001	US	82	7 (8.5%)	1 (1.2%)
Lucky 2001	US	119	13 (10.9%)	2 (1.7%)
Thielitz 2015	Germany	19	8 (42.1%)	2 (10.5%)
Weighted risk of discontinuation for adapalene 0.1%			**12.3%**	**1.1%**
Discontinuation for any reason M2S acne to M2M acne ratio: 0.90 Discontinuation due to side effects M2S to M2M ratio: 0.86				
Absolute risk of discontinuation for topical retinoids – mild to severe acne (Dikicier 2019)**:** **For any reason: 40%** **Due to side effects: 20%**				
Estimated absolute risk of discontinuation for topical retinoids – moderate to severe acne: **For any reason: 36.2%** **Due to side effects: 17.2%**				

Other clinical input parameters

Relationship between treatment efficacy (% CFB) and level of perceived acne symptom improvement and distribution of individuals' outcomes around the mean % CFB in the economic model

The relationship between a person's % CFB and their perceived acne symptom improvement was determined using an analysis of data from 4,081 people with moderate to severe facial acne that participated in 7 clinical trials of oral contraceptives or topical agents conducted in Europe (Gerlinger 2008). The measure of efficacy in the trials was the % CFB of total acne lesion counts (objective, clinician-rated assessment). At the end of treatment, participants rated the change in the severity of their acne using the categories of "excellent improvement", "good improvement", "moderate improvement", "no improvement" as well as "aggravation" (subjective, participant-rated assessment). The authors then compared the % CFB of total acne lesion counts with participants' self-ratings, and applied nonparametric discriminant statistical analysis to determine the range of % CBF (upper and lower thresholds) that corresponded to each level of improvement. They found that a 71.26% to 100% reduction in acne lesions corresponded to "excellent improvement"; a 53.14% to 71.26% reduction in acne lesions corresponded to "good improvement; a 28.20% to 53.14% reduction in acne lesions corresponded to "moderate improvement"; and a less than 28.20% reduction or any % increase in acne lesions corresponded to "no improvement / aggravation".

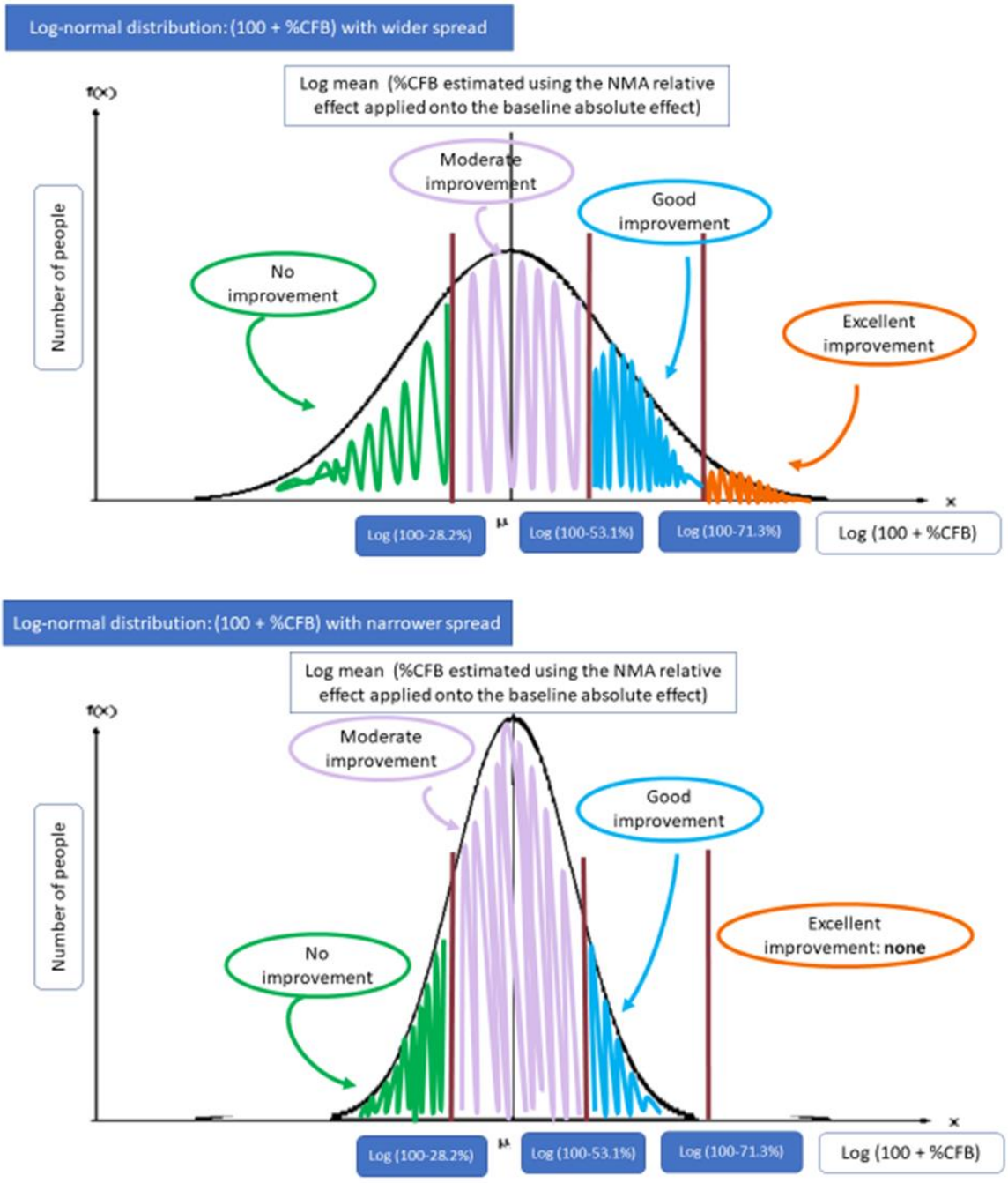
To estimate the proportion of people with excellent, good, moderate and no improvement in each cohort examined in the economic analysis, we needed to determine the distribution of people's outcomes in each cohort around the mean % CFB at end of treatment, i.e. the spread of the distribution. The mean % CFB and the spread of the distribution determine the proportions of people with each level of improvement. A narrow spread means that people are distributed closer to the mean of the distribution. The impact of the spread of the distribution on allocating people in a cohort to different levels of perceived improvement is shown in Figure 11, which shows the allocation of people using a wider and a narrower spread around the same mean % CFB.

The spread around the mean % CFB was also determined using data from Gerlinger (2008), due to lack of more relevant data. According to this study, the median % CFB across cohorts was -62.3% with an interquartile range (IQR) of -79.49% to -40%; the (100 + % CFB) appeared to have a log-normal distribution. Using these data, the standard deviation (spread) around the mean was estimated as follows:

(100 + % CFB) had a median of 37.7 and IQR of 20.51 to 60. It's log-normal distribution has therefore a mean of 3.02 and a standard error (SE) that equals (4.09-3.02)/(2*0.6745) = 0.80.

This spread (SE) around the log-normal mean of (100 + % CFB) was assumed to apply to all treatment cohorts at treatment endpoint and allowed estimation of the proportion of people with excellent, good, moderate and no improvement in every cohort, using the mean value of % CFB estimated for each treatment after applying its relative efficacy versus the baseline treatment (obtained from the NMA on efficacy) onto the absolute baseline effect.

Figure 11. Examples of the distribution of people in a cohort receiving treatment for acne, according to their level of perceived symptom severity, using the same mean % change from baseline (CFB) but different standard error (spread).



Risk of relapse according to the level of perceived acne symptom improvement

The risk of relapse following response to treatment was assumed to depend on the level of perceived acne symptom improvement. Based on the committee's expert opinion, the risk of relapse in people with moderate to severe acne one year after treatment initiation was 10%, 40% and 60% in people who experienced excellent, good and moderate improvement, respectively, following treatment. People who relapsed were assumed to return to the acne symptom status they had at treatment initiation, i.e. moderate to severe acne. People who

experienced no improvement post-treatment were assumed to retain this acne symptom status until the end of modelling period.

Assumptions on the risk of relapse were made because relevant research is rather limited and characterised by high heterogeneity in study design, populations, types of acute and maintenance treatment received, and follow-up times. In reality, some people will experience only partial relapse (i.e. their symptoms will worsen but they will not return to their initial acne symptom status) and some others may further improve, for example from moderate to excellent improvement. However, to incorporate such events further assumptions would be required that would introduce additional uncertainty into the model. This simplification of events associated with relapse or with retaining post-treatment status until the end of the model is acknowledged as a limitation of the analysis.

Utility data and estimation of quality adjusted life years (QALYs)

In order to express outcomes in the form of QALYs, the health states of the economic model (initial level of acne, excellent improvement, good improvement, no improvement, relapse) need to be linked to appropriate utility scores. Utility scores represent the HRQoL associated with specific health states on a scale from 0 (death) to 1 (perfect health); they are estimated using preference-based measures that capture people's preferences on the HRQoL experienced in the health states under consideration.

The systematic review of utility data on acne-related heath states identified 3 studies that reported utility data corresponding to acne-related health states that met inclusion criteria (Chen 2008; Klassen 2000; Al Robaee 2009). There were 3 studies that were excluded after obtaining full text, and these are reported in appendix K, together with reasons for exclusion.

Chen (2008) reported utility scores derived from a convenience sample of 266 students (age range 14-18 years, 59% female, 65% of Asian origin) from public high schools in the US, who were graded with a score of ≥1 on the Investigator's Static Global Assessment (ISGA) scale for acne. The students provided valuations for hypothetical health states related to acne (100% clearance, 50% clearance, 100% clearance but with scarring), using the time trade-off technique (TTO). The utility value for each person's current acne health state was calculated using their valuation for a state of 'never having acne'; this utility value (for current state) subsequently served as an anchor state for the 3 hypothetical scenarios.

Klassen (2000) reported EQ-5D utility scores derived from 60 people aged ≥ 16 years with acne (mean 22 years, range 16-39; 38.7% females) identified through general practitioner referral letters to a tertiary dermatology centre in England. Participants in the study were prescribed either a course of isotretinoin (71%) or were given a variety of antibiotic, hormonal, physical, and topical treatments. The UK EQ-5D tariff, formed using the time trade-off (TTO) technique, was used (Dolan 1997). The authors reported utility scores before treatment, at 4 months post-treatment and at 12 months post-treatment. The mean Dermatology Life Quality Index (DLQI) score of the population was 9.2 before treatment, suggesting a moderate mean effect on people's quality of life, and fell at 3.5 at 4 months post-treatment and 2.2 at 12 months post-treatment, suggesting, at both time points, a small mean effect on people's quality of life.

Al Robaee (2009) reported mean SF-36 dimension scores from 454 people with acne (237 males, 217 females) visiting an outpatient clinic in Saudi Arabia. Participants were categorised by level of acne symptom severity into those having mild acne, moderate acne, severe acne and very severe acne; however, the method for determining the level of acne severity was not reported. EQ-5D scores were mapped from the SF-36 dimension scores for each level of acne symptom severity using the algorithm reported in Ara (2008).

An overview of the study characteristics, the methods used to define health states, and the health-state utility values reported by each of the three studies is provided in Table 16.

Table 16: Summary of available health-state utility data for people with acne

Study	Definition of health states	Utility measure, valuation method, population valuing	Health states, number of respondents & corresponding utility scores		
Chen 2008	Vignettes (hypothetical states) plus current state of acne from a convenience sample of 266 students (age range 14-18 years, 59% female, 65% of Asian origin) from public high schools in the US, who were graded with a score of ≥1 on the ISGA scale for acne. Note: utility value for current acne state was calculated using valuations for a state of 'never having acne' and served as an anchor state for the remaining 3 scenarios.	No measure used (vignettes and current state used) TTO students with acne in the US	Health state 100% clearance 50% clearance 100% clearance but with scarring Acne – current state	N	Mean (SD) 0.978 (0.073) 0.967 (0.089) 0.965 (0.091) 0.961 (0.092)
Klassen 2000	EQ-5D ratings from 60 people aged ≥ 16 years with acne (mean 22 years, range 16-39; 38.7% females) identified through general practitioner referral letters to a tertiary dermatology centre in England. Participants were prescribed either a course of isotretinoin (71%) or given a variety of antibiotic, hormonal, physical, and topical treatments. Mean (SD) DLQI score: before treatment 9.2 (5.8); 4 months post-treatment 3.5 (3.6); 12 months post-treatment 2.2 (3.3). DLQI SCORES – EFFECT ON RESPONDENTS' LIFE: 0 - 1 no effect at all; 2 - 5 small effect; 6 - 10 moderate effect; 11 - 20 very large effect; 21 - 30 extremely large effect	EQ-5D TTO UK adult general population	Health state Acne before treatment Acne 4 months post-treatment Acne 12 months post-treatment	N 56 56 54	Mean (SD) 0.82 (0.16) 0.89 (0.17) 0.93 (0.15)
Al Robaee 2009	SF-36 ratings obtained from 454 people with acne (237 males, 217 females) visiting an outpatient clinic in Saudi Arabia; method for determining level of acne severity not reported.	EQ-5D mapped from reported mean SF-36 dimension scores using the algorithm by Ara (2008) TTO UK adult general population	Health state Mild Moderate Severe Very severe	N 252 153 35 14	Mean 0.68 0.69 0.58 0.75

Study	Definition of health states	Utility measure, valuation method, population valuing	Health states, number of respondents & corresponding utility scores

DLQI: dermatology life quality index; ISGA: investigator's static global assessment; N: number; SD: standard deviation; TTO: time trade-off

According to NICE guidance on the selection of utility values for use in cost-utility analysis (NICE, 2013), the measurement of changes in HRQoL should be reported directly from people with the condition examined, or, if this is not possible, by their carers, and the valuation of health states should be based on public preferences elicited using a choice-based method, such as the time trade-off (TTO) or standard gamble (SG), in a representative sample of the UK population. NICE recommends the EQ-5D utility system (Dolan 1997) as the preferred measure of HRQoL in adults for use in cost-utility analysis of healthcare interventions.

The study by Chen (2008) was characterised by methodological limitations (as the current acne state, and not the death state, served as the lowest anchor state) and was not further considered. The committee noted that the population in Klassen (2000) had a mean DLQI baseline score of 9.2, corresponding to the upper level of 'moderate effects' in people's lives; nevertheless, they advised that this symptom level corresponds to mild to moderate acne. The study reported a utility value of 0.82 for pre-treatment acne, based on EQ-5D ratings. Thus, the committee expressed the opinion that the utility value of 0.82 characterised mild to moderate acne.

Al Robaee (2009) reported a difference of 0.10 between the utility of mild to moderate acne (0.68) and moderate to severe acne (0.58). The study reported SF-36 ratings from people with acne in Saudi Arabia, converted to EQ-5D using a published mapping algorithm. The committee questioned the face validity of some of the estimated utility values (for example, the utility of severe acne was higher than all milder states) and highlighted that SF-36 ratings came from a population in Saudi Arabia with potentially different characteristics than those of people with acne in England. Nevertheless, use of a published mapping algorithm (Ara 2008) translated these ratings to utility values using the UK SF-6D algorithm (Brazier 2002). The committee did not trust the absolute utility values estimated using this approach, but found the difference in utility of 0.10 between moderate to severe acne and mild to moderate acne reasonable. By combining this difference of 0.10 with the EQ-5D-based baseline utility of 0.82 reported in Klassen (2000), the committee estimated a utility value of 0.72 for moderate to severe acne.

According to UK population norms for EQ-5D, the utility value in the general adult population aged <25 years in the UK is 0.94 (Kind 1999). The committee agreed that this age group was consistent with the mean age of the study population in the economic analysis and assumed that this utility value (0.94) corresponded to excellent improvement following acne treatment. For the estimation of utility values for good and moderate improvement, the utility values of 0.72 (corresponding to moderate to severe acne and also assumed to correspond to no improvement) and 0.94 (mean utility of general population assumed to correspond to excellent improvement) were used as the lowest and highest limit of acne-related utilities, respectively, and a linear relationship between utility and the level of perceived improvement was assumed. This resulted in estimated utility values of 0.79 and 0.87 corresponding to moderate and good improvement, respectively.

People who discontinued treatment due to side effects were assumed to experience deterioration in their HRQoL lasting while they were receiving their initiated treatment (i.e. during 25% of time of full course) plus 2 weeks after treatment discontinuation. A reduction in utility equal to the difference in utility between consecutive improvement levels was assumed over this period (i.e. 0.07).

Table 17 shows all utility values that were used in the economic analysis of treatments for people with moderate to severe acne.

Table 17. Relationship between efficacy (% CFB), perceived acne symptom improvement and utility values in people with moderate to severe acne

% CFB – related health state	Perceived improvement	Utility value
71.26% - 100% reduction in acne lesions	excellent	0.94
53.14% - 71.26% reduction in acne lesions	good	0.87
28.20% - 53.14% reduction in acne lesions	moderate	0.79
<28.20% reduction or any % increase	none	0.72
Moderate to severe acne (baseline)	NA	0.72
Reduction in utility due to intolerable side effects	NA	-0.07

CFB: change from baseline; NA: non-applicable

Changes in utility were assumed to occur linearly over the time period of the change. When running the probabilistic analysis, values were restricted so that utility values of milder states were not allowed to be lower than those of more severe health states.

Intervention resource use and costs

Intervention costs were estimated by combining resource use associated with each treatment, as described in relevant RCTs, modified to reflect optimal routine practice in the UK, with appropriate unit costs. Estimation of intervention costs took into account (as relevant for each treatment) the drug dosage & optimal duration of treatment, informed by optimal clinical practice and evidence from trials included in the guideline NMA; health professional time (GP and/or specialist care) considering the number of contacts over the course of treatment, including any follow-up care; any required laboratory testing; and operational procedures, including the number of sessions of physical treatments and any follow-up contacts. Unit costs were obtained from national sources (Curtis 2019; Department of Health and Social Care 2020; NHS Business Services Authority 2020; NHS Improvement 2020) and other published literature (Akhtar 2014).

People who discontinued treatment early were assumed to have incurred the following costs until discontinuation and before they moved on to average acne care:

- People discontinuing pharmacological treatments other than oral isotretinoin incurred the cost of 1 GP visit plus a month's drug supply.
- People discontinuing oral isotretinoin incurred the cost of 1 GP visit for referral, 1 specialist consultant-led dermatology first visit, 1 specialist dermatology follow-up visit (at the average cost of consultant-led and non-consultant led), a 2-month drug supply (in 2 separate prescriptions), 2 pregnancy urine tests (females only), 1 full blood count test, 1 urea & electrolytes test, 2 liver function tests and 2 serum lipid tests.
- People discontinuing physical treatments (light therapy) incurred the cost of 1 GP visit for referral, 1 specialist consultant-led dermatology first visit, and 1 session of physical treatment.
- People discontinuing physical treatment combined with an oral antibiotic incurred the cost of 1 GP visit for referral, 1 specialist consultant-led dermatology first visit, a month's drug supply, and 1 session of physical treatment
- People discontinuing GP care incurred the cost of 1 GP visit.

In addition, people who discontinued treatment due to intolerable side effects incurred a further cost of a visit to a health professional: the cost of 1 GP visit was incurred by people who initiated GP care or pharmacological treatment other than oral isotretinoin; the cost of 1 specialist dermatologist visit was incurred by people who initiated oral isotretinoin or physical treatments alone or combined with an oral antibiotic.

Details on the resource use and total costs of treatments for people with moderate to severe acne that were assessed in the economic analysis are provided in Table 18.

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Table 18: Intervention costs of treatments for people with moderate to severe acne considered in the economic analysis (2019 prices)

Treatment class and modelled intervention	Resource use details[1]	Intervention cost[2]
Topical retinoid: adapalene	Daily dosage: 1.5 g/day Acute treatment: 2 GP visits + 3 x 45g tubes Maintenance treatment: 1 GP visit + 3 x 45g tubes Resource use in discontinuers: 1 GP visit + 1 x 45g tube	Acute: £127.29 Maintenance: £88.29 Total: £215.58 Discontinuer: £55.43
Benzoyl peroxide (topical)	Daily dosage: 1.5 g/day Acute treatment: 2 GP visits + 3 x 50g tubes prescribed (2.7 needed) Maintenance treatment: 1 GP visit + 3 x 50g tubes prescribed (2.7 needed) Resource use in discontinuers: 1 GP visit + 1 x 50g tube prescribed (0.9 needed)	Acute: £90.39 Maintenance: £51.39 Total: £141.78 Discontinuer: £43.13
Topical lincosamides: topical clindamycin	Daily dosage: 1.5 g/day Acute treatment: 2 GP visits + 5 x 30g tubes prescribed (4.5 needed) Maintenance treatment: 1 GP visit + 4 x 30g tubes prescribed (4.5 needed) Resource use in discontinuers: 1 GP visit + 2 x 30g tubes prescribed (1.5 needed)	Acute: £121.30 Maintenance: £73.64 Total: £194.94 Discontinuer: £56.32
Benzoyl peroxide + topical retinoid (adapalene)	Daily dosage: 1.5 g/day Acute treatment: 2 GP visits + 3 x 45g tubes Maintenance treatment: 1 GP visit + 3 x 45g tubes Resource use in discontinuers: 1 GP visit + 1 x 45g tube	Acute: £136.59 Maintenance: £97.59 Total: £234.18 Discontinuer: £58.53
Benzoyl peroxide + topical lincosamide (clindamycin)	Daily dosage: 1.5 g/day Acute treatment: 2 GP visits + 5 x 30g tubes prescribed (4.5 needed) Maintenance treatment: 1 GP visit + 4 x 30g tubes prescribed (4.5 needed) Resource use in discontinuers: 1 GP visit + 2 x 30g tubes prescribed (1.5 needed)	Acute: £143.70 Maintenance: £91.56 Total: £235.26 Discontinuer: £65.28
Benzoyl peroxide + topical macrolide (erythromycin)	Daily dosage: benzoyl peroxide: 1.5 g/day; erythromycin: 1.5 ml/day Acute treatment: 2 GP visits + 3 x 50g tubes of benzoyl peroxide prescribed (2.7 needed) + 5 x 30ml bottles of erythromycin prescribed (4.5 needed) Maintenance treatment: 1 GP visit + 3 x 50g tubes of benzoyl peroxide prescribed (2.7 needed) + 4 x 30ml bottles of erythromycin prescribed (4.5 needed) Resource use in discontinuers: 1 GP visit + 1 x 50g tube of benzoyl peroxide prescribed (0.9 needed) + 2 x 30ml bottles of erythromycin prescribed (1.5 needed)	Acute: £136.64 Maintenance: £88.39 Total: £225.03 Discontinuer: £61.63

Treatment class and modelled intervention	Resource use details[1]	Intervention cost[2]
Topical retinoid + topical lincosamide: tretinoin + clindamycin	Daily dosage: 1.5 g/day Acute treatment: 2 GP visits + 5 x 30g tubes prescribed (4.5 needed) Maintenance treatment: 1 GP visit + 4 x 30g tubes prescribed (4.5 needed) Resource use in discontinuers: 1 GP visit + 2 x 30g tubes prescribed (1.5 needed)	Acute: £137.70 Maintenance: £86.76 Total: £224.46 Discontinuer: £62.88
Benzoyl peroxide + topical retinoid (tretinoin) + topical lincosamide (clindamycin)	Daily dosage: benzoyl peroxide: 1.5 g/day; clindamycin / tretinoin: 1.5 g/day Acute treatment: 2 GP visits + 3 x 50g tubes of benzoyl peroxide prescribed (2.7 needed) + 5 x 30g tubes of clindamycin / tretinoin prescribed (4.5 needed) Maintenance treatment: 1 GP visit + 3 x 50g tubes of benzoyl peroxide prescribed (2.7 needed) + 4 x 30g tubes of clindamycin / tretinoin prescribed (4.5 needed) Resource use in discontinuers: 1 GP visit + 1 x 50g tube of benzoyl peroxide prescribed (0.9 needed) + 2 x 30g tubes of clindamycin / tretinoin prescribed (1.5 needed)	Acute: £150.09 Maintenance: £99.15 Total: £249.24 Discontinuer: £67.01
Oral tetracycline: lymecycline	Daily dosage: 408 mg/day Acute treatment: 2 GP visits + 4 packs of 28 capsules prescribed (3.25 needed) Maintenance treatment: 1 GP visit + 3 packs of 28 capsules prescribed (3.25 needed) Resource use in discontinuers: 1 GP visit + 1 pack of 28 capsules prescribed	Acute: £108.64 Maintenance: £61.98 Total: £170.62 Discontinuer: £46.66
Topical retinoid (adapalene) + oral tetracycline (lymecycline)	Daily dosage: adapalene: 1.5 g/day; lymecycline 408 mg/day Acute treatment: 2 GP visits + 3 x 45g tubes of adapalene + 4 packs of 28 capsules of lymecycline prescribed (3.25 needed) Maintenance treatment: 1 GP visit + 3 x 45g tubes of adapalene + 3 packs of 28 capsules of lymecycline prescribed (3.25 needed) Resource use in discontinuers: 1 GP visit + 1 x 45g tube of adapalene + 1 pack of 28 capsules of lymecycline	Acute: £157.93 Maintenance: £111.27 Total: £269.20 Discontinuer: £63.09
Azelaic acid (topical treatment, own class) + oral tetracycline (lymecycline)	Daily dosage: azelaic acid: 1.5 g/day; lymecycline 408 mg/day Acute treatment: 2 GP visits + 5 x 30g tubes of azelaic acid prescribed (4.5 needed) prescribed + 4 packs of 28 capsules of lymecycline prescribed (3.25 needed) Maintenance treatment: 1 GP visit + 4 x 30g tubes of azelaic acid prescribed (4.5 needed) + 91 capsules of lymecycline + 3 packs of 28 capsules of lymecycline prescribed (3.25 needed) Resource use in discontinuers: 1 GP visit + 2 x 30g tubes of azelaic acid prescribed	Acute: £131.09 Maintenance: £79.94 Total: £211.03 Discontinuer: £55.64

Treatment class and modelled intervention	Resource use details[1]	Intervention cost[2]
	(1.5 needed) + 1 pack of 28 capsules of lymecycline	
Benzoyl peroxide + topical retinoid (adapalene) + oral tetracycline (lymecycline)	Daily dosage: benzoyl peroxide and adapalene: 1.5 g/day; lymecycline 408 mg/day Acute treatment: 2 GP visits + 3 x 45g tubes of benzoyl peroxide and adapalene + 4 packs of 28 capsules of lymecycline prescribed (3.25 needed) Maintenance treatment: 1 GP visit + 3 x 45g tubes of benzoyl peroxide and adapalene + 3 packs of 28 capsules of lymecycline prescribed (3.25 needed) Resource use in discontinuers: 1 GP visit + 1 x 45g tube of benzoyl peroxide and adapalene + 1 pack of 28 capsules of lymecycline	Acute: £167.23 Maintenance: £120.57 Total: £287.80 Discontinuer: £66.19
Oral isotretinoin - total cumulative dose ≥ 120mg/kg (single course)	Daily dosage: 0.7 mg/kg/day; total cumulative dose over 6 months 127 mg/kg. Assuming mean weight of 70 kg, then daily dose is ≈ 50 mg/day Over 6 months: 12 packs of (30 x 20mg) capsules + 6 packs of (30 x 10mg) capsules 1 GP visit for referral to specialist dermatology outpatient clinic Females: 7 dermatology outpatient visits (1 consultant-led first + 6 follow-up mixed consultant-/non-consultant-led) Males: 4 dermatology outpatient visits (1 consultant-led first + 3 follow-up mixed consultant-/non-consultant-led) Females only: Pregnancy urine test at initiation and every month (x 7 in total) Full blood count, urea & electrolytes: at initiation (2 tests in total) Liver function, serum lipids (cholesterol and triglycerides) at initiation; month 1; month 4; month 6 (2 tests x 4 times in total) Resource use in discontinuers: 1 GP visit for referral, 4 packs of (30 x 20mg) capsules + 2 packs of (30 x 10mg) capsules, 1 specialist consultant-led dermatology first visit + 1 specialist dermatology mixed consultant-/non-consultant-led follow-up visit, 2 pregnancy urine tests (females only), 1 full blood count test, 1 urea & electrolytes test, 2 liver function tests, 2 serum lipid tests.	Total: £902.20 [females] £581.70 [males] Discontinuers: £309.90 [females] £307.90 [males]
Oral isotretinoin - total cumulative dose < 120mg/kg (single course)	Daily dosage: 0.6 mg/kg/day; total cumulative dose over 6 months 109 mg/kg. Assuming mean weight of 70 kg, then daily dose is ≈ 40 mg/day Over 6 months: 12 packs of (30 x 20mg capsules) 1 GP visit for referral to specialist dermatology outpatient clinic Females: 7 dermatology outpatient visits (1 consultant-led first + 6 follow-up mixed consultant-/non-consultant-led)	Total: £869.32 [females] £548.82 [males] Discontinuer: £298.94 [females]

Treatment class and modelled intervention	Resource use details[1]	Intervention cost[2]
	Males: 4 dermatology outpatient visits (1 consultant-led first + 3 follow-up mixed consultant-/non-consultant-led) Females only: Pregnancy urine test at initiation and every month (x 7 in total) Full blood count, urea & electrolytes: at initiation (2 tests in total) Liver function, serum lipids (cholesterol and triglycerides) at initiation; month 1; month 4; month 6 (2 tests x 4 times in total) Resource use in discontinuers: 1 GP visit for referral, 4 packs of (30 x 20mg) capsules, 1 specialist consultant-led dermatology first visit + 1 specialist dermatology mixed consultant-/non-consultant-led follow-up visit, 2 pregnancy urine tests (females only), 1 full blood count test, 1 urea & electrolytes test, 2 liver function tests, 2 serum lipid tests.	£296.94 [males]
Photodynamic therapy	1 GP visit for referral to specialist dermatology outpatient clinic 1 dermatology consultant-led outpatient first visit 3 photodynamic therapy sessions 1 dermatology outpatient follow-up visit (at an average cost of consultant-/non-consultant-led follow-up visit) Resource use in discontinuers: 1 GP visit + 1 specialist consultant-led dermatology first visit + 1 photodynamic therapy session	Total: £850.82 Discontinuer: £354.77
Photochemical therapy (red light)	1 GP visit for referral to specialist dermatology outpatient clinic 1 dermatology consultant-led outpatient first visit 3 photochemical therapy sessions 1 dermatology outpatient follow-up visit (at an average cost of consultant/non-consultant-led follow-up visit) Resource use in discontinuers: 1 GP visit + 1 specialist consultant-led dermatology first visit + 1 photochemical therapy session	Total: £546.14 Discontinuer: £253.21
Photothermal therapy	1 GP visit for referral to specialist dermatology outpatient clinic 1 dermatology consultant-led outpatient first visit 3 photothermal therapy sessions 1 dermatology outpatient follow-up visit (at an average cost of consultant-/non-consultant-led follow-up visit)	Total: £850.82 Discontinuer: £354.77

Treatment class and modelled intervention	Resource use details[1]	Intervention cost[2]
	Resource use in discontinuers: 1 GP visit + 1 specialist consultant-led dermatology first visit + 1 photothermal therapy session Unit cost assumed to be equal to that of photodynamic therapy	
Photodynamic therapy + oral tetracycline (lymecycline)	Daily dosage: 408 mg/day Acute treatment: 2 GP visits + 4 packs of 28 capsules prescribed (3.25 needed) 1 dermatology consultant-led outpatient first visit 3 photodynamic therapy sessions 1 dermatology outpatient follow-up visit (at an average cost of consultant-/non-consultant-led follow-up visit) Maintenance treatment: 1 GP visit + 3 packs of 28 capsules prescribed (3.25 needed) Resource use in discontinuers: 1 GP visit + 1 pack of 28 capsules prescribed + 1 specialist consultant-led dermatology first visit + 1 photodynamic therapy session	Acute: £920.46 Maintenance: £61.98 Total: £982.44 Discontinuer: £362.43
GP care	Acute treatment: 2 GP visits Maintenance treatment: 1 GP visit Resource use in discontinuers: 1 GP visit	Acute: £78.00 Maintenance: £39.00 Total: £117.00 Discontinuer: £39

1 For all pharmacological treatment options other than oral isotretinoin the duration of 'acute' treatment is 3 months and the duration of maintenance treatment, received by those responding to acute treatment, is another 3 months. Duration of treatment with oral isotretinoin is 6 months; no maintenance treatment assumed.

2 Unit costs
Drug acquisition costs (NHS Business Services Authority 2020 except oral isotretinoin for which dispensation by a hospital pharmacy was assumed and acquisition cost was derived from Department of Health and Social Care, 2020)
Adapalene 0.1% cream or gel, 45g: £16.43
Adapalene 0.1% and benzoyl peroxide 2.5% gel, 45g: £19.53
Azelaic acid 20% cream, 30 g: £4.49
Benzoyl peroxide 4% cream, 50g: £4.13
Benzoyl peroxide 3% or 5% and clindamycin 1% gel, 30g: £13.14
Clindamycin 1% gel, 30g: £8.66
Clindamycin 1% and tretinoin 0.025% gel, 30g: £11.94
Erythromycin 40mg/ml and zinc acetate 12mg/ml lotion, 30ml: £9.25
Isotretinoin 10mg, 30 capsules: £5.48; 20mg, 30 capsules: £3.86
Lymecycline 408mg, 28 capsules: £7.66

Treatment class and modelled intervention	Resource use details[1]	Intervention cost[2]
Healthcare contact unit costs *GP: £39 per patient contact lasting 9.22 minutes, including direct care staff and qualification costs (Curtis 2019)* *Dermatology consultant-led outpatient first visit: £120 (NHS Improvement 2020; service code 330)* *Dermatology consultant-led outpatient follow-up visit: £112 (NHS Improvement 2020; service code 330)* *Dermatology non-consultant-led outpatient follow-up visit: £97 (NHS Improvement 2020; service code 330)* *Procedure costs (NHS Improvement 2020)* *Photodynamic therapy: £196 (weighted average national cost of day and outpatient cases; currency code JC46Z)* *Photochemical therapy: £94 (weighted average national cost of day and outpatient cases; currency code JC47Z)* *Laboratory testing* *Pregnancy urine test: £1 (assumption)* *All other testing: £2.90 (Akhtar 2014, uplifted to reflect 2019 price)*		

Cost of average acne care

People discontinuing one of the modelled treatments, people relapsing following improvement in acne care symptoms, and people with no or moderate improvement following treatment were assumed to receive average acne care, comprising a mixture of care that is anticipated to be currently received by people with acne in the NHS. The mean cost of average acne care for people with acne was estimated based on an analysis of primary care consultations and prescription data of 318,515 people with acne, aged ≥ 8 years, over a 10-year period (2004-2013) in the UK (Francis 2017). The analysis included data obtained from people with a new ('index') acne consultation. A person was considered to have a new acne consultation if no primary care consultations and/or prescriptions for acne were recorded for this person in the year prior to their index consultation. Therefore, some people might have had previous consultations for acne more than 12 months before their index consultation. People with a new acne consultation were included in the analysis if follow-up data of at least one year following the new acne consultation were available. The study reported prescription data (types of drugs prescribed) at the index consultation, for the period during the subsequent 90 days after the index consultation, and during the year following the index consultation, including the first 90 days but excluding the index consultation.

The study found that, of people presenting with a new episode of acne, only one-third were seen in the subsequent 12 months. In total, 167,573 people were identified as having a new acne consultation with 12-month follow-up data being available. Of these, 44,809 (26.74%) did not receive a prescription for acne treatment during their index consultation, while 39,314 (23.46%) did not receive a prescription for acne treatment both at the index consultation and in the following 90 days. Most of the issued prescriptions amounted to 2-3 months' treatment.

In order to calculate an annual acne-related cost, estimates of the proportions of people receiving each type of treatment over one year and the duration of treatment were required; these were made using the following assumptions:

- People who were not prescribed an acne treatment at the index consultation and in the next 90 days were assumed to receive no prescription for acne treatment within the year after the index consultation. People not prescribed any acne-related medication over the first 90 days within index consultation were deemed to be non-representative of the economic model's study population, as they were assumed not to require prescribed treatment. Therefore, these people were excluded from the estimation of acne care costs.
- At the index consultation people were prescribed treatment lasting for 3 months. This is supported by the study finding that "most of the issued prescriptions amounted to 2-3 months' worth of treatment."
- Prescription data on the year after the index consultation were assumed to refer to a treatment duration of 6 months, as this is the optimal treatment duration (initial & maintenance treatment, where relevant) for most pharmacological treatments. Therefore, the cost of 6 months of treatment was attached to each type of prescription over this period. However, it is acknowledged that some people might have been treated for a longer and others for a shorter period than 6 months. Moreover, some people might have only been continuing medication from their index consultation over this follow-up period, and therefore their 'follow-up' medication might have lasted only for 3 months.

The final annual care cost comprised the sum of the weighted average cost of the index consultation and prescribing (assuming a 3-month treatment duration) and the weighted average cost of the consultations and prescribing over the year following the index consultation (assuming a 6-month treatment duration). This was estimated for the population of interest only, that is, after excluding people who did not receive a prescription for acne treatment both at the index consultation and in the following 90 days. Costs of all treatments included in average acne care were readily available from calculation of intervention costs for

the analysis; the only exception was co-cyprindiol, the cost of which was estimated specifically for this exercise.

The estimated cost from this exercise captures only primary acne care (with the exception of isotretinoin, which has been assumed to be prescribed in a dermatology specialist setting). However, some people with moderate to severe acne will receive specialist care. It was assumed that 20% of people receive specialist care and incur the cost of 6 specialist dermatology visits (1 consultant-led first visit and 5 follow-up visits at an average consultant/non-consultant-led cost) over one year. This cost was added to the estimated mean primary care cost of average acne care. The 20% figure was based on assumption after taking into account evidence that 8.5% of people with acne (which includes people with all levels of severity, from mild to severe) are referred to a dermatologist over 2 years (Purdy 2003). This percentage is likely to be higher in people with moderate to severe acne.

Based on the above, the mean annual average acne care cost for people with moderate to severe acne was estimated at £430 for females and £429 for males, with the difference in costs reflecting extra specialist visits and pregnancy urine tests for females receiving treatment with isotretinoin (price year 2019). Details on the GP consultation and prescription data and treatment costs that were synthesised in order to obtain this figure are provided in Table 19.

Because the estimated cost was based to a large degree on the committee's expert opinion and further assumptions, a sensitivity analysis was conducted, in which the estimated cost figure was varied by ±50% to explore its impact on the results of the economic analysis.

Table 19. Acne-related prescriptions and estimated average acne care annual cost incurred by people with moderate to severe acne

Prescribed ARM[1]	Index consultation			Following year			Index consultation		Following year	
	N	Population of interest		N	Population of interest		Cost	Weighted cost	Cost	Weighted cost
		n	%		n	%				
No AMR at index or next 90 days	*39,314*			*39,314*						
No ARM	44,809	*5,495**	4.28%	78,567	*39,253**	30.60%	£78.00	£3.34	£117.00	£35.81
Oral antibiotic alone	41,791	41,791	32.58%	32,750	32,750	25.53%	£108.64	£35.40	£170.62	£43.57
Topical antibiotic (+combined) alone	39,529	39,529	30.82%	16,806	16,806	13.10%	£134.23	£41.37	£218.22	£28.59
Topical non-antibiotic alone	20,875	20,875	16.28%	6,458	6,458	5.04%	£118.09	£19.22	£197.18	£9.93
Oral antibiotic + topical non-antibiotic	9,168	9,168	7.15%	12,009	12,009	9.36%	£152.08	£10.87	£256.01	£23.97
Oral antibiotic + topical antibiotic	4,671	4,671	3.64%	11,215	11,215	8.74%	£151.94	£3.96	£248.56	£14.92
Co-cyprindiol alone	4,014	4,014	3.13%	3,987	3,987	3.11%	£88.78	£2.78	£138.56	£4.31
Co-cyprindiol + any topical agent	793	793	0.62%	2,265	2,265	1.77%	£137.34	£0.85	£235.69	£4.16
Oral isotretinoin alone[2]	15	15	0.01%	47	47	0.04%	£451.10F £290.80M	£0.05F £0.03M	£902.20F £581.70M	£0.33F £0.21M
Oral isotretinoin + other ARM[2]	2	2	0.00%	98	98	0.08%	£494.46F £334.21M	£0.01F £0.01M	£988.92F £668.42M	£0.76M £0.51M
Other combination	1906	1,906	1.49%	3,371	3,371	2.63%	£132.69	£1.97	£220.77	£5.80
Total[2]	167,573	128,259	100%	167,573	128,259	100%		**£121.61F £121.59M**		**£179.64F £179.28M**
Specialist care for people with moderate to severe acne[3]						20%			£642.50	**£128.50**
Total annual average acne care cost for people with moderate to severe acne[2]										**£429.75F £429.37M**

** calculated after subtracting 39,314 people without a ARM prescription at the index consultation and at next 90 days, from the 44,809 people who received no ARM prescription at index consultation and the 78,567 people who received no ARM prescription within the year following the index consultation, respectively. The latter might have been prescribed an ARM at the index consultation.*
1 prescription data on ARM from Francis (2017)
2 Costs of isotretinoin are different for females (F) and males (M) due to extra specialist visits and pregnancy urine tests required for females. This difference is reflected in slightly different total costs for females (F) and males (M).
3 20% figure based on assumption, after taking into account evidence that 8.5% of people with acne (which includes people with all levels of severity, from mild to

Prescribed ARM[1]	Index consultation			Following year			Index consultation		Following year	
	N	Population of interest		N	Population of interest		Cost	Weighted cost	Cost	Weighted cost
		n	%		n	%				

severe) are referred to a dermatologist over 2 years (Purdy 2003); 6 specialist dermatology visits assumed (1 consultant-led first visit and 5 follow-up visits at an average consultant/non-consultant-led cost)
Costs of all treatments based on calculation of intervention costs (Table 18). For cost of co-cyprindiol, the following data and assumptions were used: Co-cyprindiol 63 tablets: £10.78 (NHS Business Services Authority); 3 GP visits, and 21 tablets needed every 3 months; 3-month cost: £88.78; 6-month cost: £138.56
ARM: acne-related medication

Discounting

Discounting of costs and outcomes was not needed as the time horizon of the analysis was one year.

Handling uncertainty

Model input parameters were synthesised in a probabilistic analysis. This means that the input parameters were assigned probabilistic distributions (rather than being expressed as point estimates); this approach allowed more comprehensive consideration of the uncertainty characterising the input parameters and captured the non-linearity characterising the economic model structure. Subsequently, 10,000 iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. Results (mean costs and QALYs for each treatment) were calculated by averaging across the 10,000 iterations. This exercise provides more accurate estimates than those derived from a deterministic analysis (which utilises the mean value of each input parameter ignoring any uncertainty around the mean), by capturing the non-linearity characterising the economic model structure (Briggs 2006).

The distributions of the difference in efficacy (% CFB) as well as of the log-odds ratios of relative effects on discontinuation for any reason and due to side effects of all treatments versus topical retinoids were obtained from the respective NMAs, defined directly from values recorded in each of the 10,000 iterations used after thinning the 300,000 iterations performed in WinBUGS or OpenBUGS, as relevant.

Regarding baseline efficacy (% CFB), a log-normal distribution was assumed for (100 + % CFB), based on published literature.

The distribution of baseline discontinuation was determined by data used for its estimation: baseline discontinuation data for people with mild to moderate depression were assigned a beta distribution. The ratio of discontinuation of people with moderate to severe acne to people with mild to moderate acne was assigned a log-normal distribution.

The variability (spread) around the log (100 + % CFB) across all treatments and the thresholds were not assigned a distribution. Beta distribution was assigned to the risk of relapse, utility values, the proportion of full course duration during which average acne care is received following treatment discontinuation, the proportion of people with moderate improvement after drug treatment other than oral isotretinoin who switch to average acne care between 3-6 months, and the proportion of people who receive average acne care following relapse or moderate or no improvement between 6-12 months. The average acne care cost was assigned a gamma distribution.

Uncertainty in intervention costs was taken into account by assigning probability distributions to the number of health professional contacts (GP visits and specialist outpatient contacts) and physical treatment sessions when estimating full course treatment costs. Number of contacts and physical treatment sessions were not assigned a distributions in people discontinuing treatment early, with the exception of the additional contacts attributed to discontinuation due intolerable side effects. Respective unit costs were assigned a normal distribution. Drug acquisition costs were not assigned a probability distribution, as these are not characterised by uncertainty.

Table 20 reports the mean values of all input parameters utilised in the economic model and provides details on the types of distributions assigned to each input parameter and the methods employed to define their range.

A number of deterministic one-way sensitivity analyses were also employed to explore the impact of alternative hypotheses on the results. The following scenarios were explored:

- The baseline % CFB for topical retinoids was varied by ± 50%.
- The baseline risk of discontinuation for any reason was varied by ± 50%.
- The spread (SE) around the log (100 +% CFB) was varied by ± 50%.
- The risk of relapse, following any improvement level, was varied by ± 50%.
- The average acne care cost was changed by ± 50%.
- The mean number of sessions of physical treatments was increased to 4.
- People who improved after completion of any physical treatment did not receive average acne care between 2-6 months.
- The unit cost of a session of photothermal therapy was assumed to equal the unit cost of a session of photochemical therapy (rather than that of a session of photodynamic therapy) or to increase by 100%.

A bias-adjusted NMA on the efficacy outcome suggested no evidence of bias; the only NMA outcome with evidence of bias in people with moderate to severe acne was discontinuation due to side effects (analysis suggested presence of bias relating to outcome measurement). As this outcome was secondary, with a small impact on the economic model structure and results, no bias-adjusted economic analysis was conducted.

Table 20: Input parameters (deterministic values and probability distributions) that informed the economic model of treatments for people with moderate to severe acne

Input parameter	Mean deterministic value	Probability distribution	Source of data – comments
Difference in efficacy (% change of total lesion count from baseline) versus topical retinoids			
		95% CrI	Guideline NMA; distribution based on 10,000 iterations
GP care (placebo)	-13.11	-18.05 to -8.28	
BPO	15.69	-1.69 to 33.17	
Topical lincosamides	21.07	7.23 to 34.82	
BPO + retinoid (topical)	21.02	-1.18 to 42.88	
BPO + lincosamide (topical)	9.55	-7.62 to 26.61	
BPO + macrolide (topical)	9.05	-1.43 to 19.89	
Retinoid + lincosamide (topical)	31.45	15.09 to 48.17	
BPO + retinoid + lincosamide (topical)	10.01	-4.19 to 24.05	
Oral tetracyclines	11.18	1.75 to 20.57	
Topical retinoid + oral tetracycline	22.25	9.46 to 34.67	
Azelaic acid + oral tetracycline	25.67	-5.98 to 56.52	
BPO + retinoid (topical) + tetracycline (oral)	30.46	15.56 to 45.29	
Oral isotretinoin - total cumul dose ≥120mg/kg	44.95	23.27 to 66.74	
Oral isotretinoin - total cumul dose <120mg/kg	34.90	6.86 to 62.88	
Photodynamic therapy	27.59	12.28 to 42.30	
Photochemical therapy (red light)	16.97	-6.29 to 39.34	
Photothermal therapy	44.71	10.05 to 79.46	
Photodynamic therapy + oral tetracycline	31.71	12.30 to 51.03	
Log-odds ratios of discontinuation for any reason versus topical retinoids - females			
		95% CrI	Guideline NMA; distribution based on 10,000 iterations
GP care (placebo)	-0.12	-0.46 to 0.24	
BPO	-1.01	-3.25 to 0.86	
Topical lincosamides	-0.66	-1.70 to 0.42	
BPO + retinoid (topical)	-0.20	-1.34 to 0.98	

Input parameter	Mean deterministic value	Probability distribution	Source of data – comments
BPO + lincosamide (topical)	-0.80	-1.82 to 0.21	
BPO + macrolide (topical)	-0.76	-1.55 to 0.04	
Retinoid + lincosamide (topical)	-0.60	-1.73 to 0.57	
BPO + retinoid + lincosamide (topical)	-0.38	-1.69 to 0.93	
Oral tetracyclines	-0.31	-1.40 to 0.82	
Topical retinoid + oral tetracycline	-0.01	-1.35 to 1.33	
BPO + retinoid (topical) + tetracycline (oral)	-0.47	-1.83 to 0.89	
Oral isotretinoin - total cumul dose ≥120mg/kg	-1.10	-2.83 to 0.69	
Photodynamic therapy	-1.14	-4.56 to 1.75	
Photochemical therapy (red light)	-1.48	-5.08 to 1.78	
Log-odds ratios of discontinuation for any reason versus topical retinoids - males			
		95% CrI	Guideline NMA; distribution based on 10,000 iterations
GP care (placebo)	-0.12	-0.45 to 0.24	
BPO	-1.01	-3.23 to 0.87	
Topical lincosamides	-0.66	-1.70 to 0.40	
BPO + retinoid (topical)	-0.21	-1.33 to 0.97	
BPO + lincosamide (topical)	-0.80	-1.81 to 0.23	
BPO + macrolide (topical)	-0.76	-1.52 to 0.03	
Retinoid + lincosamide (topical)	-0.60	-1.71 to 0.55	
BPO + retinoid + lincosamide (topical)	-0.36	-1.68 to 0.95	
Oral tetracyclines	-0.43	-1.62 to 0.82	
Topical retinoid + oral tetracycline	-0.14	-1.55 to 1.27	
BPO + retinoid (topical) + tetracycline (oral)	-0.60	-2.02 to 0.84	
Oral isotretinoin - total cumul dose ≥120mg/kg	-1.22	-2.97 to 0.60	
Photodynamic therapy	-1.19	-4.79 to 1.73	
Photochemical therapy (red light)	-1.53	-5.29 to 1.65	
Log-odds ratios of discontinuation due to side effects versus topical retinoid - females			
		95% CrI	Guideline NMA; distribution based on 10,000 iterations

Input parameter	Mean deterministic value	Probability distribution	Source of data – comments
GP care (placebo)	-2.14	-3.05 to -1.35	
Topical lincosamides	-5.48	-11.23 to -2.19	
BPO + retinoid (topical)	-1.14	-4.53 to 4.40	
BPO + lincosamide (topical)	-5.26	-11.03 to -1.90	
BPO + macrolide (topical)	-3.06	-5.34 to -1.09	
Retinoid + lincosamide (topical)	-4.24	-10.04 to -0.41	
Oral tetracyclines	-1.23	-2.78 to 0.48	
Topical retinoid + oral tetracycline	-0.91	-2.86 to 1.20	
BPO + retinoid (topical) + tetracycline (oral)	-1.03	-3.03 to 1.14	
Oral isotretinoin - total cumul dose ≥120mg/kg	-1.49	-3.94 to 1.09	
Photodynamic therapy	-2.89	-8.87 to 1.57	
Photochemical therapy (red light)	-6.83	-14.67 to -1.10	
Log-odds ratios of discontinuation due to side effects versus topical retinoid – males			
		95% CrI	Guideline NMA; distribution based on 10,000 iterations
GP care (placebo)	-2.13	-3.03 to -1.37	
Topical lincosamides	-5.58	-11.65 to -2.19	
BPO + retinoid (topical)	-1.07	-4.49 to 4.82	
BPO + lincosamide (topical)	-5.26	-10.99 to -1.90	
BPO + macrolide (topical)	-3.05	-5.31 to -1.07	
Retinoid + lincosamide (topical)	-4.34	-10.49 to -0.46	
Oral tetracyclines	-1.23	-2.75 to 0.45	
Topical retinoid + oral tetracycline	-0.91	-2.81 to 1.15	
BPO + retinoid (topical) + tetracycline (oral)	-1.02	-3.04 to 1.12	
Oral isotretinoin - total cumul dose ≥120mg/kg	-1.49	-4.01 to 1.00	
Photodynamic therapy	-2.99	-8.98 to 1.46	
Photochemical therapy (red light)	-6.93	-14.69 to -1.12	
Baseline parameters – topical retinoids			
		log-normal (100+% CFB)	Weighted data from 2 RCTs (Eichenfield 2010, Studies 1 and

Input parameter	Mean deterministic value	Probability distribution	Source of data – comments
% CFB (total lesion count)	-36.03	mean: 4.16; SE: 0.02	2)
Discontinuation for any reason	0.36	determined by data reported below	Discontinuation data on people with mild to moderate acne from Dikicier 2019, adjusted for people with moderate to severe acne using RCT discontinuation data from adapalene RCT arms (see Table 15).
Discontinuation due to side effects	0.17		
For mild to moderate acne:			
Discontinuation for any reason	0.40	Beta: α=30; β=45	Dikicier 2019
Discontinuation due to side effects	0.20	Beta: α=15; β=15	
Moderate to severe to mild to moderate acne:			
Ratio of discontinuation for any reason	0.90	Log-norm: SE=0.3 of mean	See Table 15; distribution based on assumption
Ratio of discontinuation due to side effects	0.86	Log-norm: SE=0.3 of mean	
Variability (spread) of log (100+ % CFB) applied to all treatments	0.796	No distribution	Based on analysis of data obtained from 4,081 people with moderate to severe facial acne that participated in 7 clinical trials of oral contraceptives or topical agents conducted in Europe (Gerlinger 2008).
Perceived improvement thresholds (%CBF)			
Excellent / good	-71.26	No distribution	Gerlinger 2008
Good / moderate	-53.14	No distribution	
Moderate / no	-28.20	No distribution	
Amount of AAC received after discontinuation, relapse, moderate or no improvement		Beta distribution	
Proportion of full course duration during which AAC is received after discontinuation	0.75	α=75; β=25	Committee's expert opinion
Proportion of people with moderate improvement switching to AAC at 3-6 months	0.67	α=67; β=33	
Proportion of people with relapse, moderate or no improvement receiving AAC at 6-12 months	0.90	α=90; β=10	

Input parameter	Mean deterministic value	Probability distribution	Source of data – comments
Risk of relapse - end of year 1, following:		Beta distribution	Assumption based on committee's expert opinion
Excellent improvement	0.10	α=10; β=90	
Good improvement	0.40	α=40; β=60	
Moderate improvement	0.60	α=60; β=40	
Utility values		Beta distribution	Synthesis of available evidence (Al Robaee 2009 using a mapping algorithm from Ara 2008; Kind 1999; Klassen 2000) supplemented by committee's expert opinion and further assumptions and assuming a linear relationship between utility and level of perceived improvement.
Excellent improvement	0.94	α=94; β=6	
Good improvement	0.87	α=87; β=13	
Moderate improvement	0.79	α=79; β=21	
No improvement and moderate to severe acne	0.72	α=72; β=28	
Utility decrement - intolerable side effects	0.07	α=7; β=93	
Intervention costs – resource use			
Number of GP contacts			
0-3 months (acute treatment)	2	0.80: 2, 0.20: 1	Probabilities assigned to numbers of sessions; number of visits based on the committee's expert opinion; distribution based on assumption. Details on intervention costs are provided in Table 18.
3-6 months (maintenance treatment)	1	0.60: 1, 0.20: 2, 0.20: 0	
Management of intolerable side effects	1	0.80: 1, 0.20: 0	
Referral to specialist care [oral isotretinoin & physical treatments]	1	No distribution	
Number of dermatology specialist contacts			
0-6 months, oral isotretinoin – women	7	0.70: 7, 0.20: 6, 0.10: 5	
0-6 months, oral isotretinoin – men	4	0.70: 4, 0.30: 3	
Initiation of physical treatments	1	No distribution	
Follow-up of physical treatments	1	No distribution	
Management of intolerable side effects	1	0.90: 1, 0.20: 2	
Number of sessions (physical treatments)	3	0.80: 3, 0.20: 2	
Number of laboratory tests (oral isotretinoin)			

Input parameter	Mean deterministic value	Probability distribution	Source of data – comments
Pregnancy urine test (females only)	7	No distribution	
FBT, U&E	1	No distribution	British National Formulary, July 2020
LFT, serum lipids	4	No distribution	
Intervention costs - unit costs			
GP	£39	Normal, SE=0.10 of mean	Curtis 2019; distribution based on assumption
Dermatology outpatient cons-led first visit	£120	Normal, SE=0.10 of mean	NHS Improvement 2020; service code 330
Dermatology outpatient cons-led FU visit	£112	Normal, SE=0.10 of mean	NHS Improvement 2020; service code 330
Dermatology outpatient non-cons-led FU visit	£97	Normal, SE=0.10 of mean	NHS Improvement 2020; service code 330
Photodynamic therapy	£196	Normal, SE=0.10 of mean	NHS Improvement 2020; weighted day/outpatient; code JC46Z
Photochemical therapy	£94	Normal, SE=0.10 of mean	NHS Improvement 2020; weighted day/outpatient; code JC47Z
Photothermal therapy	£196	Normal, SE=0.30 of mean	Assumed to equal the unit cost of photodynamic therapy
Pregnancy urine test	£1	Normal, SE=0.10 of mean	Assumption
FBC, LFT, serum lipids U&E - each	£3	Normal, SE=0.10 of mean	Akhtar 2014; uplifted to reflect 2019 price
Drug acquisition costs	See Table 18	No distribution	NHS Business Services Authority 2020; Department of Health and Social Care, 2020 All distributions based on assumptions
Annual average acne care cost (moderate to severe acne)	£430 (females) £429 (males)	Gamma: SE=0.30 of mean	Based on GP consultation and prescription data from people with acne (Francis 2017) and further assumptions on dermatology specialist care (Purdy 2003), combined with relevant intervention costs (Table 18).

AAC: average acne care; BPO: benzoyl peroxide; CFB: change from baseline; cons: consultant; CrI: credible intervals; cumul: cumulative; FBC: full blood count; FU: follow-up; LFT: liver function test; SE: standard error; U&E: urea and electrolytes

Presentation of the results

For each treatment option, the Net Monetary Benefit (NMB) was estimated for each iteration and averaged across the 10,000 iterations, determined by the formula

$$NMB = E \bullet \lambda - C$$

where E and C are the effects (QALYs) and total costs, respectively, of each treatment option, and λ represents the willingness-to-pay per unit of effectiveness, set at the NICE lower cost-effectiveness threshold of £20,000/QALY (NICE, 2014). The treatment with the highest NMB is the most cost-effective option (Fenwick 2001).

Incremental mean costs and effects (QALYs) of each treatment option versus GP care are also presented in the form of cost effectiveness planes.

The mean ranking by cost-effectiveness is reported for each treatment (out of 10,000 iterations), where a rank of 1 suggests that a treatment is the most cost-effective amongst all evaluated treatment options. The probability of the treatment with the highest NMB being the most cost-effective option is also provided, calculated as the proportion of the 10,000 iterations in which the treatment had the highest NMB amongst all treatment options considered in the analysis. The probability of cost-effectiveness has been estimated in a step-wise approach, according to which the most cost-effective treatment is omitted at each step, and the probability of cost-effectiveness of the next most cost-effective treatment amongst the remaining treatment options is re-calculated. The probabilities estimated following this approach reflect the uncertainty around the cost-effectiveness not only of the most cost-effective treatment, but also of the second, third, fourth, etc. most cost-effective treatment, after more cost-effective treatment options have been omitted from analysis. Finally, the cost-effectiveness acceptability frontier (CEAF) has been plotted, showing the treatment with the highest mean NMB over different cost-effectiveness thresholds (λ), and the probability that this treatment is the most cost-effective among those assessed (Fenwick 2001).

Validation of the economic model

The economic model (including the conceptual model and the identification and selection of input parameters) was developed by the health economist in collaboration with a health economics sub-group formed by members of the committee. As part of the model validation, all inputs and model formulae were systematically checked; the model was tested for logical consistency by setting input parameters to null and extreme values and examining whether results changed in the expected direction. The base-case results and results of sensitivity analyses were discussed with the committee to confirm their plausibility. In addition, the economic model (excel spreadsheet) and the model methods and results reporting in this appendix were checked for their validity and accuracy by a health economist that was external to the guideline development team.

Economic modelling results

The economic analysis included treatments that are suitable to both females and males. However, separate analyses were conducted for each sex for two reasons:

1. sex-specific data for each treatment class on discontinuation for any reason and due to side effects were available from the respective NMAs
2. the intervention cost of oral isotretinoin differs between sexes, due to the need for increased monitoring and pregnancy tests for females, and this may impact on its cost-effectiveness relative to other treatment options.

The results of the base-case economic analysis are provided in Table 21 and Table 22, for females and males, respectively. The tables provide the number of observations on each treatment class in the NMA of efficacy that informed the economic analysis, the mean QALYs and mean intervention and total costs of each treatment option, the likelihood of a person having good or excellent improvement one year after initiation of each treatment, the mean NMB and ranking of each treatment, and its probability of being cost-effective in a step-wise approach at a threshold of £20,000/QALY. For each sex, treatments have been ordered from the most to the least cost-effective.

For females, the order of treatments from the most to the least cost-effective was photothermal therapy, clindamycin + tretinoin (topical), benzoyl peroxide + adapalene (topical) combined with lymecycline (oral), azelaic acid (topical) combined with lymecycline (oral), oral isotretinoin of total cumulative dose ≥ 120mg/kg, clindamycin (topical), benzoyl peroxide + adapalene (topical), adapalene (topical) combined with lymecycline (oral), photodynamic therapy combined with lymecycline (oral), benzoyl peroxide (topical), photodynamic therapy, oral isotretinoin of total cumulative dose < 120mg/kg, lymecycline (oral), photochemical therapy [red], benzoyl peroxide + clindamycin (topical), benzoyl peroxide + clindamycin + tretinoin (topical), benzoyl peroxide + erythromycin (topical), adapalene (topical), GP care. The probability of photothermal therapy being the most cost-effective treatment option was 0.42 at the lower NICE cost-effectiveness threshold of £20,000/QALY.

For males, the order of treatments from the most to the least cost-effective was photothermal therapy, clindamycin + tretinoin (topical), oral isotretinoin of total cumulative dose ≥ 120mg/kg, benzoyl peroxide + adapalene (topical) combined with lymecycline (oral), azelaic acid (topical) combined with lymecycline (oral), clindamycin (topical), benzoyl peroxide + adapalene (topical), adapalene (topical) combined with lymecycline (oral), oral isotretinoin of total cumulative dose < 120mg/kg, photodynamic therapy combined with lymecycline (oral), benzoyl peroxide (topical), photodynamic therapy, lymecycline (oral), photochemical therapy [red], benzoyl peroxide + clindamycin (topical), benzoyl peroxide + clindamycin + tretinoin (topical), benzoyl peroxide + erythromycin (topical), adapalene (topical), GP care. The probability of photothermal therapy being the most cost-effective treatment option was 0.41 at the lower NICE cost-effectiveness threshold of £20,000/QALY.

Oral isotretinoin showed a higher relative cost-effectiveness in males compared with females, due to its lower intervention cost resulting from less intensive monitoring being required in males receiving oral isotretinoin compared with females (and no need for pregnancy tests).

Figure 12 and

Figure **13** provide the cost effectiveness plane of the analysis for females and males, respectively. Each treatment class is placed on the plane according to its incremental total costs and QALYs compared with GP care, which has been placed at the origin.

The CEAF of the analysis for females and males is shown in

Figure **14** and

Figure **15**, respectively. In both sexes, benzoyl peroxide (topical) is the most cost-effective option at very low cost-effectiveness thresholds (up to £1000/QALY). Then, and up to a cost-effectiveness threshold of about £16,000/QALY, clindamycin and tretinoin (topical) appears to be the most cost-effective option. For higher cost-effectiveness thresholds, photothermal therapy appears to be the most cost-effective treatment options for both sexes.

Results were overall robust to the scenarios explored through deterministic sensitivity analysis. A ± 50% change in the risk of relapse had no impact in the ranking of treatments from the most to the least cost-effective, while a ± 50% change in the average acne care cost and a ± 50% change in the baseline risk of discontinuation had a negligible impact in this ranking. Changes in baseline efficacy and the spread around the log (100 + % CFB) had a more notable, albeit only moderate, impact on the results. Increasing the number of sessions of physical therapies reduced the relative cost-effectiveness of photodynamic therapy and of photochemical therapy [red] but had no impact on the cost-effectiveness of photothermal therapy. Assuming that people received no average acne care in 2-6 months following completion of physical treatment increased, as expected, the relative cost-effectiveness of physical treatments. Increasing the unit cost of a photothermal therapy session by 100% brought it from the top rank to the 5th place in the cost-effectiveness ranking. It is noted that some of the scenarios involving changes in efficacy and the spread of the log (100 + % CFB) were affected by ceiling effects, when some treatments (or some people receiving treatment) reached 100% improvement and could not possibly improve further. Results of the deterministic sensitivity analysis for females are shown in Table 23. Results for males, in terms of the impact on different assumptions on the base-case results and rankings, were similar.

Table 21: Base-case results of economic modelling: treatments for females with moderate to severe acne

Treatment	N	NMB / person	Likelihood of excellent / good improvement at 1 year	Mean per person			Prob* best	Mean rank
				QALY	Intervention cost	Total cost	At a threshold of £20,000/QALY	
Photothermal therapy	46	£16,599	0.70	0.876	£723	£921	0.42	4.77
Clindamycin + tretinoin (topical)	1,548	£16,460	0.55	0.838	£160	£299	0.30	3.65
Benzoyl peroxide + adapalene (topical) + lymecycline (oral)	556	£16,351	0.53	0.835	£196	£344	0.24	4.23
Azelaic acid (topical) + lymecycline (oral)	50	£16,231	0.49	0.827	£132	£306	0.34	6.52
Oral isotretinoin - total cumulative dose ≥ 120mg/kg	182	£16,122	0.72	0.848	£755	£832	0.27	6.95
Clindamycin (topical)	1,479	£15,986	0.43	0.814	£134	£303	0.14	7.58
Benzoyl peroxide + adapalene (topical)	217	£15,975	0.43	0.815	£146	£329	0.26	8.12
Adapalene (topical) + lymecycline (oral)	379	£15,969	0.44	0.816	£162	£349	0.20	7.48
Photodynamic therapy + lymecycline (oral)	48	£15,871	0.55	0.839	£748	£902	0.28	9.59
Benzoyl peroxide (topical)	80	£15,798	0.38	0.804	£97	£280	0.26	9.53
Photodynamic therapy	298	£15,755	0.50	0.835	£705	£945	0.25	10.68
Oral isotretinoin - total cumulative dose < 120mg/kg	938	£15,715	0.60	0.827	£726	£827	0.39	11.22
Lymecycline (oral)	1,386	£15,600	0.33	0.796	£106	£313	0.20	12.22
Photochemical therapy [red]	53	£15,547	0.40	0.814	£473	£727	0.33	13.02
Benzoyl peroxide + clindamycin (topical)	276	£15,539	0.33	0.795	£157	£352	0.37	12.98
Benzoyl peroxide + clindamycin + tretinoin (topical)	600	£15,534	0.33	0.795	£155	£360	0.52	12.85
Benzoyl peroxide + erythromycin (topical)	365	£15,511	0.32	0.793	£148	£346	0.97	13.29
Adapalene (topical)	3,570	£15,219	0.26	0.779	£120	£359	1.00	16.79
GP care	4,122	£15,006	0.19	0.766	£68	£319	1.00	18.53

** estimated in a step-wise approach, according to which the most cost-effective intervention is omitted at each step, and the probability of cost-effectiveness of the next most cost-effective intervention amongst the remaining treatment options is re-calculated*

Table 22: Base-case results of economic modelling: treatments for males with moderate to severe acne

Treatment	N	NMB / person	Likelihood of excellent / good improvement at 1 year	Mean per person			Prob* best	Mean rank
				QALY	Intervention cost	Total cost	At a threshold of £20,000/QALY	
Photothermal therapy	46	£16,599	0.70	0.876	£724	£923	0.41	4.91
Clindamycin + tretinoin (topical)	1,548	£16,459	0.55	0.838	£161	£300	0.26	3.90
Oral isotretinoin - total cumulative dose ≥ 120mg/kg	182	£16,373	0.72	0.848	£507	£582	0.26	4.99
Benzoyl peroxide + adapalene (topical) + lymecycline (oral)	556	£16,350	0.53	0.835	£200	£346	0.30	4.58
Azelaic acid (topical) + lymecycline (oral)	50	£16,231	0.49	0.827	£135	£307	0.35	6.77
Clindamycin (topical)	1,479	£15,986	0.43	0.815	£134	£305	0.12	7.86
Benzoyl peroxide + adapalene (topical)	217	£15,975	0.43	0.815	£146	£331	0.23	8.39
Adapalene (topical) + lymecycline (oral)	379	£15,969	0.44	0.816	£165	£351	0.17	7.78
Oral isotretinoin - total cumulative dose < 120mg/kg	938	£15,967	0.60	0.827	£478	£576	0.37	9.07
Photodynamic therapy + lymecycline (oral)	48	£15,861	0.55	0.839	£760	£912	0.34	9.94
Benzoyl peroxide (topical)	80	£15,797	0.38	0.804	£97	£282	0.36	9.79
Photodynamic therapy	298	£15,753	0.50	0.835	£706	£948	0.36	10.96
Lymecycline (oral)	1,386	£15,602	0.33	0.796	£108	£313	0.20	12.44
Photochemical therapy [red]	53	£15,547	0.40	0.814	£473	£729	0.33	13.26
Benzoyl peroxide + clindamycin (topical)	276	£15,539	0.33	0.795	£157	£353	0.37	13.20
Benzoyl peroxide + clindamycin + tretinoin (topical)	600	£15,535	0.33	0.795	£155	£362	0.52	13.08
Benzoyl peroxide + erythromycin (topical)	365	£15,513	0.32	0.793	£148	£348	0.97	13.52
Adapalene (topical)	3,570	£15,221	0.26	0.779	£120	£361	1.00	16.94
GP care	4,122	£15,009	0.19	0.767	£68	£321	1.00	18.64

** estimated in a step-wise approach, according to which the most cost-effective intervention is omitted at each step, and the probability of cost-effectiveness of the next most cost-effective intervention amongst the remaining treatment options is re-calculated*

Figure 12. Cost-effectiveness plane of treatments for females with moderate to severe acne

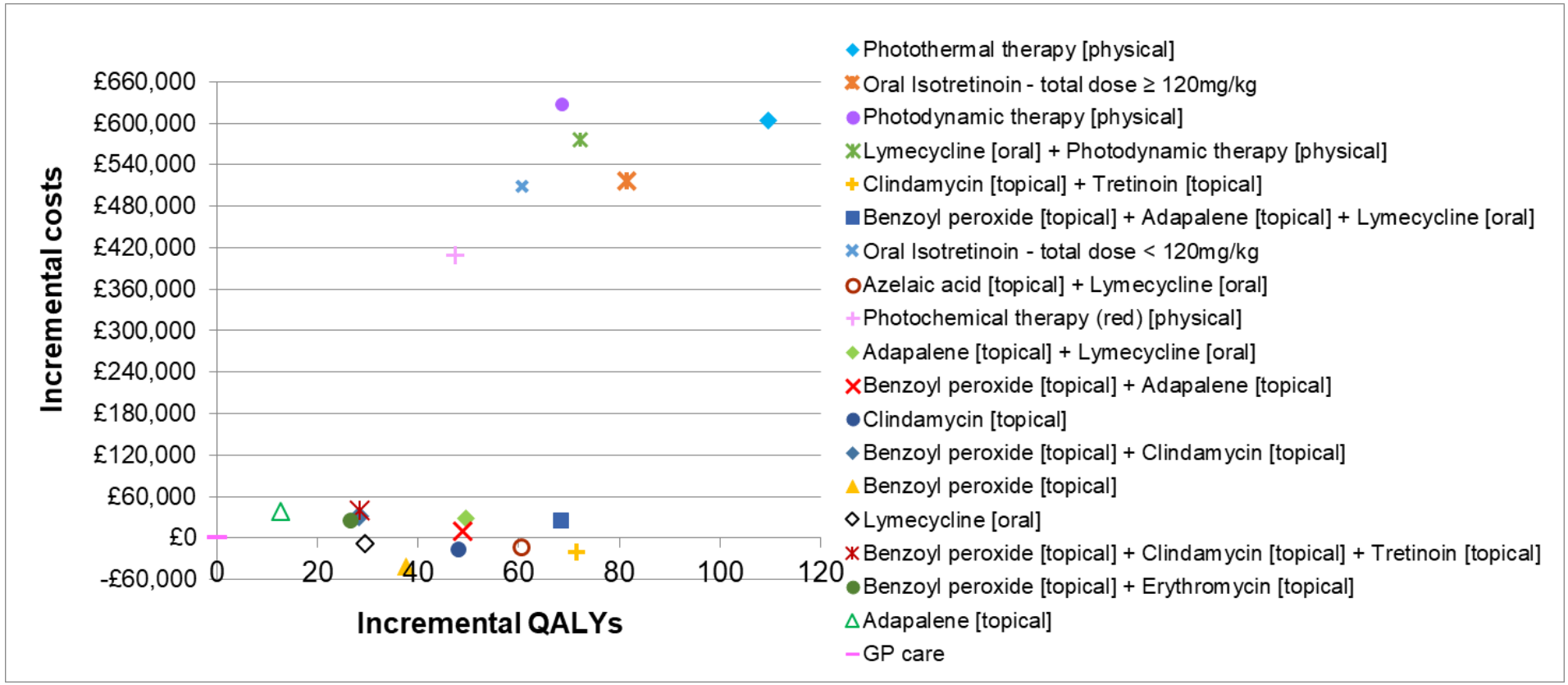

Figure 13. Cost-effectiveness plane of treatments for males with moderate to severe acne

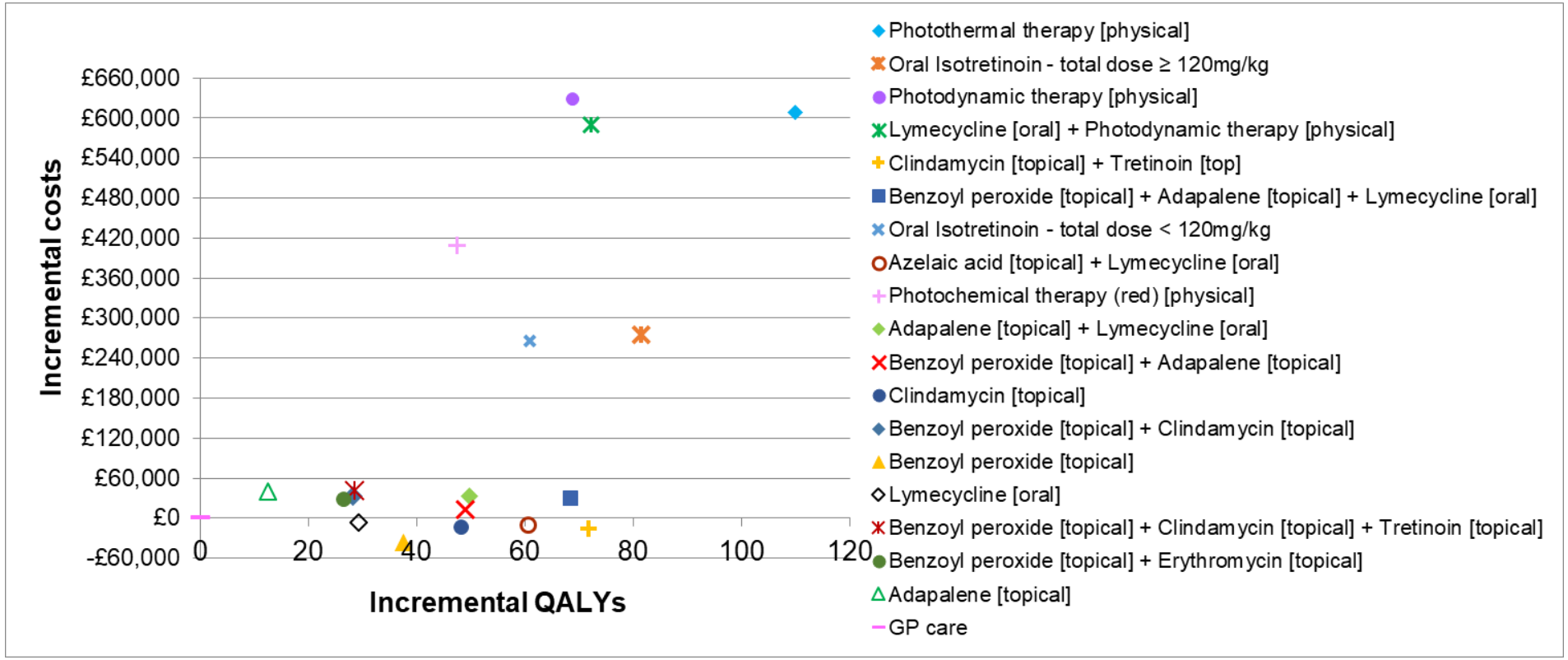

Figure 14. Cost-effectiveness acceptability frontier of treatments for females with moderate to severe acne

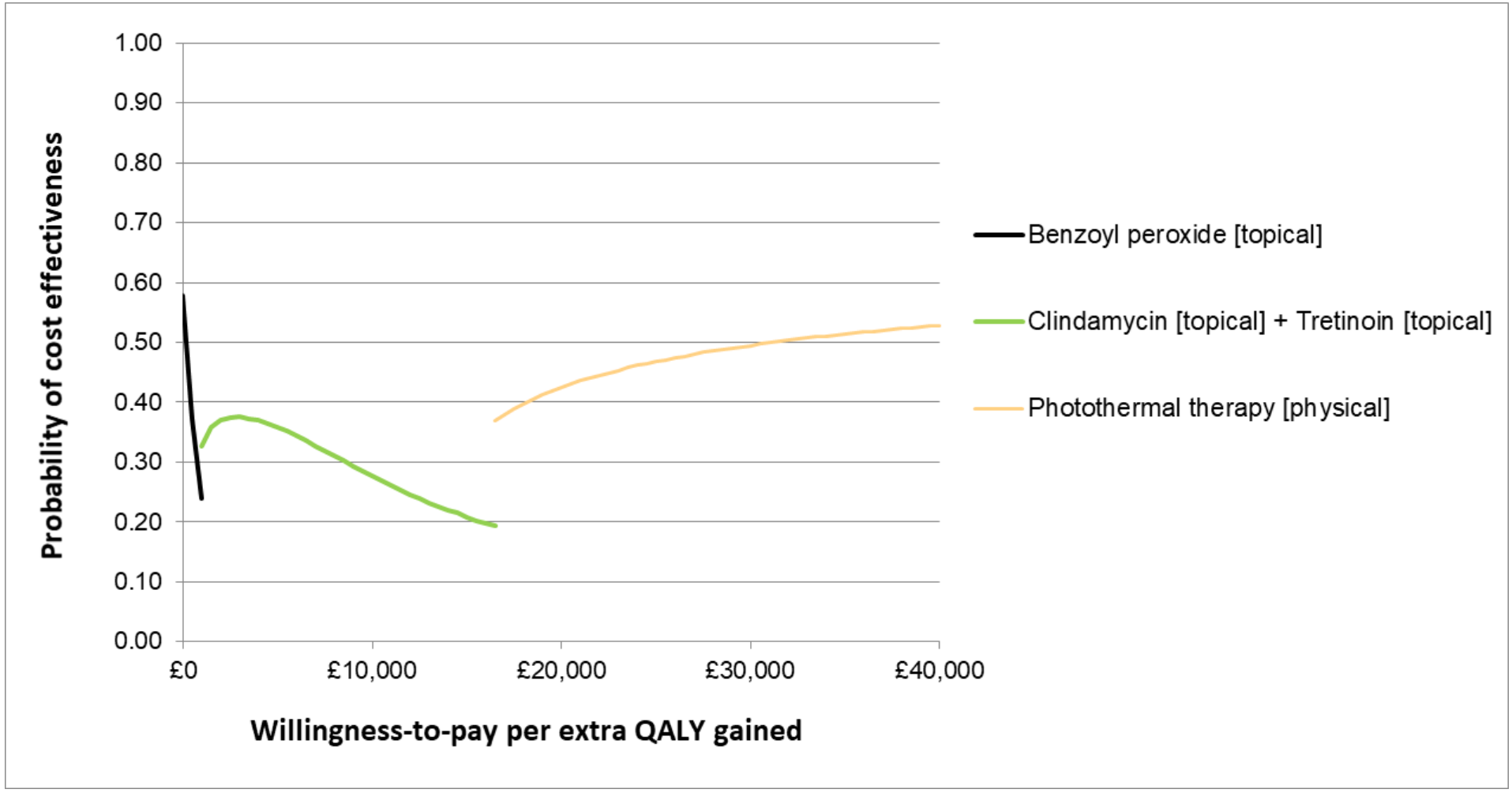

Figure 15. Cost-effectiveness acceptability frontier of treatments for males with moderate to severe acne

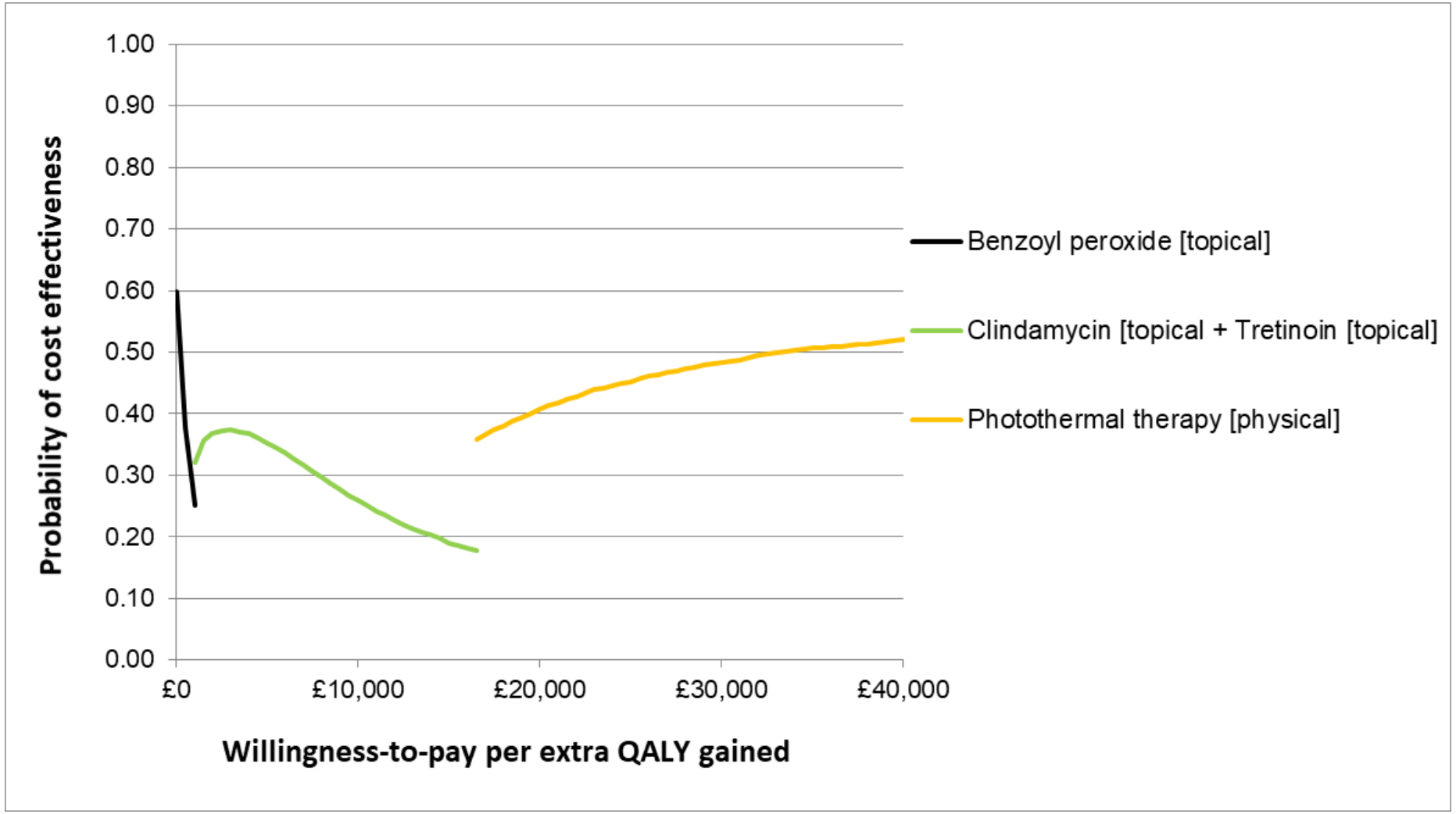

Table 23. Results of deterministic sensitivity analysis - females

Base-case deterministic analysis		Topical retinoid baseline % CFB: 50% reduction		Topical retinoid baseline % CFB: 50% increase	
Treatment	**NMB**	**Treatment**	**NMB**	**Treatment**	**NMB**
Photothermal therapy	£16,667	Clindamycin + tretinoin (topical)	£15,660	Clindamycin + tretinoin (topical)	£17,481
Clindamycin + tretinoin (topical)	£16,444	Photothermal therapy	£15,608	Photothermal therapy	£17,393
BPO + adapalene (topical) + lymecycline (oral)	£16,339	BPO + adapalene (topical) + lymecycline (oral)	£15,577	BPO + adapalene (topical) + lymecycline (oral)	£17,365
Azelaic acid (topical) + lymecycline (oral)	£16,154	Azelaic acid (topical) + lymecycline (oral)	£15,466	Azelaic acid (topical) + lymecycline (oral)	£17,131
Oral Isotretinoin - total dose ≥ 120mg/kg	£16,141	Clindamycin (topical)	£15,361	Adapalene (topical) + lymecycline (oral)	£16,888
Clindamycin (topical)	£15,981	Adapalene (topical) + lymecycline (oral)	£15,338	Clindamycin [topical]	£16,884
Adapalene (topical) + lymecycline (oral)	£15,970	BPO + adapalene (topical)	£15,327	Photodynamic therapy + lymecycline (oral)	£16,855
BPO + adapalene (topical)	£15,943	Oral Isotretinoin - total dose ≥ 120mg/kg	£15,268	BPO + adapalene (topical)	£16,842
Photodynamic therapy + lymecycline (oral)	£15,814	BPO (topical)	£15,229	Photodynamic therapy	£16,731
BPO (topical)	£15,778	Lymecycline (oral)	£15,124	Oral isotretinoin - total dose ≥ 120mg/kg	£16,731
Photodynamic therapy	£15,681	BPO + clindamycin + tretinoin (topical)	£15,064	BPO (topical)	£16,593
Oral Isotretinoin - total dose < 120mg/kg	£15,660	BPO + clindamycin (topical)	£15,062	Oral isotretinoin - total dose < 120mg/kg	£16,556
Lymecycline (oral)	£15,616	BPO + erythromycin (topical)	£15,058	Lymecycline (oral)	£16,350
BPO + clindamycin + tretinoin (topical)	£15,540	Photodynamic therapy + lymecycline (oral)	£15,022	Photochemical therapy [red]	£16,343
BPO + clindamycin (topical)	£15,534	Oral Isotretinoin - total dose < 120mg/kg	£14,934	BPO + clindamycin + tretinoin (topical)	£16,250
BPO + erythromycin (topical)	£15,524	Photodynamic therapy	£14,927	BPO + clindamycin (topical)	£16,238
Photochemical therapy [red]	£15,472	Photochemical therapy [red]	£14,883	BPO + erythromycin (topical)	£16,221
Adapalene (topical)	£15,245	Adapalene (topical)	£14,866	Adapalene (topical)	£15,808
GP care	£15,035	GP care	£14,749	GP care	£15,455
Topical retinoid discontinuation risk for any reason: 50% reduction		**Topical retinoid discontinuation risk for any reason: 50% increase**		**Spread (SE) around the log (100 +% CFB): 50% reduction**	
Treatment	**NMB**	**Treatment**	**NMB**	**Treatment**	**NMB**
Photothermal therapy	£16,637	Photothermal therapy	£16,667	Photothermal therapy	£17,128
Clindamycin + tretinoin (topical)	£16,447	Clindamycin + tretinoin (topical)	£16,444	Clindamycin + tretinoin (topical)	£16,698
BPO + adapalene (topical) + lymecycline (oral)	£16,342	BPO + adapalene (topical) + lymecycline (oral)	£16,339	BPO + adapalene (topical) + lymecycline (oral)	£16,565
Azelaic acid (topical) + lymecycline (oral)	£16,166	Azelaic acid (topical) + lymecycline (oral)	£16,154	Oral Isotretinoin - total dose ≥ 120mg/kg	£16,520
Oral Isotretinoin - total dose ≥ 120mg/kg	£16,111	Oral Isotretinoin - total dose ≥ 120mg/kg	£16,141	Azelaic acid (topical) + lymecycline (oral)	£16,267
Clindamycin (topical)	£15,985	Clindamycin (topical)	£15,981	Photodynamic therapy + lymecycline (oral)	£16,076
Adapalene (topical) + lymecycline (oral)	£15,975	Adapalene (topical) + lymecycline (oral)	£15,970	Adapalene (topical) + lymecycline (oral)	£16,002

Base-case deterministic analysis		Topical retinoid baseline % CFB: 50% reduction		Topical retinoid baseline % CFB: 50% increase	
Treatment	**NMB**	**Treatment**	**NMB**	**Treatment**	**NMB**
BPO + adapalene (topical)	£15,950	BPO + adapalene (topical)	£15,943	Clindamycin (topical)	£15,989
BPO (topical)	£15,803	Photodynamic therapy + lymecycline (oral)	£15,814	BPO + adapalene (topical)	£15,948
Photodynamic therapy + lymecycline (oral)	£15,753	BPO (topical)	£15,778	Oral Isotretinoin - total dose < 120mg/kg	£15,943
Photodynamic therapy	£15,644	Photodynamic therapy	£15,681	Photodynamic therapy	£15,849
Oral Isotretinoin - total dose < 120mg/kg	£15,632	Oral Isotretinoin - total dose < 120mg/kg	£15,660	BPO (topical)	£15,678
Lymecycline (oral)	£15,628	Lymecycline (oral)	£15,616	Lymecycline (oral)	£15,437
BPO + clindamycin + tretinoin (topical)	£15,540	BPO + clindamycin + tretinoin (topical)	£15,540	Photochemical therapy [red]	£15,393
BPO + clindamycin (topical)	£15,535	BPO + clindamycin (topical)	£15,534	BPO + clindamycin + tretinoin (topical)	£15,342
BPO + erythromycin (topical)	£15,527	BPO + erythromycin (topical)	£15,524	BPO + clindamycin (topical)	£15,329
Photochemical therapy [red]	£15,456	Photochemical therapy [red]	£15,472	BPO + erythromycin (topical)	£15,312
Adapalene (topical)	£15,264	Adapalene (topical)	£15,245	Adapalene (topical)	£14,923
GP care	£15,049	GP care	£15,035	GP care	£14,623
Spread (SE) around the log (100 +% CFB): 50% increase		**Risk of relapse: 50% reduction**		**Risk of relapse: 50% increase**	
Treatment	**NMB**	**Treatment**	**NMB**	**Treatment**	**NMB**
Photothermal therapy	£16,335	Photothermal therapy	£16,746	Photothermal therapy	£16,587
Clindamycin + tretinoin (topical)	£16,296	Clindamycin + tretinoin (topical)	£16,528	Clindamycin + tretinoin (topical)	£16,360
BPO + adapalene (topical) + lymecycline (oral)	£16,208	BPO + adapalene (topical) + lymecycline (oral)	£16,423	BPO + adapalene (topical) + lymecycline (oral)	£16,256
Azelaic acid (topical) + lymecycline (oral)	£16,087	Azelaic acid (topical) + lymecycline (oral)	£16,236	Azelaic acid (topical) + lymecycline (oral)	£16,073
Clindamycin (topical)	£15,972	Oral Isotretinoin - total dose ≥ 120mg/kg	£16,221	Oral Isotretinoin - total dose ≥ 120mg/kg	£16,062
Adapalene (topical) + lymecycline (oral)	£15,949	Clindamycin (topical)	£16,060	Clindamycin (topical)	£15,901
BPO + adapalene (topical)	£15,936	Adapalene (topical) + lymecycline (oral)	£16,051	Adapalene (topical) + lymecycline (oral)	£15,890
Oral Isotretinoin - total dose ≥ 120mg/kg	£15,870	BPO + adapalene (topical)	£16,022	BPO + adapalene (topical)	£15,863
BPO (topical)	£15,831	Photodynamic therapy + lymecycline (oral)	£15,898	Photodynamic therapy + lymecycline (oral)	£15,730
Lymecycline (oral)	£15,715	BPO (topical)	£15,854	BPO (topical)	£15,702
Photodynamic therapy + lymecycline (oral)	£15,661	Photodynamic therapy	£15,764	Photodynamic therapy	£15,599
BPO + clindamycin + tretinoin (topical)	£15,650	Oral Isotretinoin - total dose < 120mg/kg	£15,744	Oral Isotretinoin - total dose < 120mg/kg	£15,576
BPO + clindamycin (topical)	£15,648	Lymecycline (oral)	£15,689	Lymecycline (oral)	£15,543
BPO + erythromycin (topical)	£15,643	BPO + clindamycin + tretinoin (topical)	£15,611	BPO + clindamycin + tretinoin (topical)	£15,468
Photodynamic therapy	£15,583	BPO + clindamycin (topical)	£15,605	BPO + clindamycin (topical)	£15,463
Photochemical therapy [red]	£15,512	BPO + erythromycin (topical)	£15,595	BPO + erythromycin (topical)	£15,453

Base-case deterministic analysis	
Treatment	**NMB**
Oral Isotretinoin - total dose < 120mg/kg	£15,495
Adapalene (topical)	£15,432
GP care	£15,294

Topical retinoid baseline % CFB: 50% reduction	
Treatment	**NMB**
Photochemical therapy [red]	£15,549
Adapalene (topical)	£15,309
GP care	£15,090

Topical retinoid baseline % CFB: 50% increase	
Treatment	**NMB**
Photochemical therapy [red]	£15,395
Adapalene (topical)	£15,180
GP care	£14,981

Average acne care cost: 50% reduction	
Treatment	**NMB**
Photothermal therapy	£16,763
Clindamycin + tretinoin (topical)	£16,515
BPO + adapalene (topical) + lymecycline (oral)	£16,414
Azelaic acid (topical) + lymecycline (oral)	£16,245
Oral Isotretinoin - total dose ≥ 120mg/kg	£16,173
Clindamycin (topical)	£16,068
Adapalene (topical) + lymecycline (oral)	£16,066
BPO + adapalene (topical)	£16,037
Photodynamic therapy + lymecycline (oral)	£15,889
BPO (topical)	£15,870
Photodynamic therapy	£15,802
Lymecycline (oral)	£15,722
Oral Isotretinoin - total dose < 120mg/kg	£15,706
BPO + clindamycin + tretinoin (topical)	£15,646
BPO + clindamycin (topical)	£15,635
BPO + erythromycin (topical)	£15,627
Photochemical therapy [red]	£15,603
Adapalene (topical)	£15,366
GP care	£15,165

Average acne care cost: 50% increase	
Treatment	**NMB**
Photothermal therapy	£16,570
Clindamycin + tretinoin (topical)	£16,373
BPO + adapalene (topical) + lymecycline (oral)	£16,265
Oral Isotretinoin - total dose ≥ 120mg/kg	£16,109
Azelaic acid (topical) + lymecycline (oral)	£16,064
Clindamycin (topical)	£15,893
Adapalene (topical) + lymecycline (oral)	£15,875
BPO + adapalene (topical)	£15,848
Photodynamic therapy + lymecycline (oral)	£15,738
BPO (topical)	£15,687
Oral Isotretinoin - total dose < 120mg/kg	£15,614
Photodynamic therapy	£15,560
Lymecycline (oral)	£15,510
BPO + clindamycin + tretinoin (topical)	£15,434
BPO + clindamycin (topical)	£15,433
BPO + erythromycin (topical)	£15,422
Photochemical therapy [red]	£15,340
Adapalene (topical)	£15,123
GP care	£14,905

Mean number of physical therapy sessions increased to 4	
Treatment	**NMB**
Photothermal therapy	£16,493
Clindamycin + tretinoin (topical)	£16,444
BPO + adapalene (topical) + lymecycline (oral)	£16,339
Azelaic acid (topical) + lymecycline (oral)	£16,154
Oral Isotretinoin - total dose ≥ 120mg/kg	£16,141
Clindamycin (topical)	£15,981
Adapalene (topical) + lymecycline (oral)	£15,970
BPO + adapalene (topical)	£15,943
BPO (topical)	£15,778
Photodynamic therapy + lymecycline (oral)	£15,675
Oral Isotretinoin - total dose < 120mg/kg	£15,660
Lymecycline (oral)	£15,616
BPO + clindamycin + tretinoin (topical)	£15,540
BPO + clindamycin (topical)	£15,534
BPO + erythromycin (topical)	£15,524
Photodynamic therapy	£15,516
Photochemical therapy [red]	£15,388
Adapalene (topical)	£15,245
GP care	£15,035

No average acne care following completion of physical treatment	
Treatment	**NMB**
Photothermal therapy	£16,792
Clindamycin + tretinoin (topical)	£16,444
BPO + adapalene (topical) + lymecycline (oral)	£16,339

Unit cost of photothermal therapy assumed to equal that of photochemical therapy	
Treatment	**NMB**
Photothermal therapy	£16,948
Clindamycin + tretinoin (topical)	£16,444
BPO + adapalene (topical) + lymecycline (oral)	£16,339

Unit cost of photothermal therapy: 100% increase	
Treatment	**NMB**
Clindamycin + tretinoin (topical)	£16,444
BPO + adapalene (topical) + lymecycline (oral)	£16,339
Azelaic acid (topical) + lymecycline (oral)	£16,154

Base-case deterministic analysis		Topical retinoid baseline % CFB: 50% reduction		Topical retinoid baseline % CFB: 50% increase	
Treatment	**NMB**	**Treatment**	**NMB**	**Treatment**	**NMB**
Azelaic acid (topical) + lymecycline (oral)	£16,154	Azelaic acid (topical) + lymecycline (oral)	£16,154	Oral Isotretinoin - total dose ≥ 120mg/kg	£16,141
Oral Isotretinoin - total dose ≥ 120mg/kg	£16,141	Oral Isotretinoin - total dose ≥ 120mg/kg	£16,141	Photothermal therapy	£16,124
Clindamycin (topical)	£15,981	Clindamycin (topical)	£15,981	Clindamycin (topical)	£15,981
Adapalene (topical) + lymecycline (oral)	£15,970	Adapalene (topical) + lymecycline (oral)	£15,970	Adapalene (topical) + lymecycline (oral)	£15,970
BPO + adapalene (topical)	£15,943	BPO + adapalene (topical)	£15,943	BPO + adapalene (topical)	£15,943
Photodynamic therapy + lymecycline (oral)	£15,814	Photodynamic therapy + lymecycline (oral)	£15,814	Photodynamic therapy + lymecycline (oral)	£15,814
Photodynamic therapy	£15,782	BPO (topical)	£15,778	BPO (topical)	£15,778
BPO (topical)	£15,778	Photodynamic therapy	£15,681	Photodynamic therapy	£15,681
Oral Isotretinoin - total dose < 120mg/kg	£15,660	Oral Isotretinoin - total dose < 120mg/kg	£15,660	Oral Isotretinoin - total dose < 120mg/kg	£15,660
Lymecycline (oral)	£15,616	Lymecycline (oral)	£15,616	Lymecycline (oral)	£15,616
Photochemical therapy [red]	£15,564	BPO + clindamycin + tretinoin (topical)	£15,540	BPO + clindamycin + tretinoin (topical)	£15,540
BPO + clindamycin + tretinoin (topical)	£15,540	BPO + clindamycin (topical)	£15,534	BPO + clindamycin (topical)	£15,534
BPO + clindamycin (topical)	£15,534	BPO + erythromycin (topical)	£15,524	BPO + erythromycin (topical)	£15,524
BPO + erythromycin (topical)	£15,524	Photochemical therapy [red]	£15,472	Photochemical therapy [red]	£15,472
Adapalene (topical)	£15,245	Adapalene (topical)	£15,245	Adapalene (topical)	£15,245
GP care	£15,035	GP care	£15,035	GP care	£15,035

BPO: benzoyl peroxide

Discussion – conclusions, strengths and limitations of economic analysis

The guideline economic analysis assessed the cost effectiveness of a range of topical, oral and physical treatments for people with moderate to severe acne. The interventions assessed were determined by the availability of efficacy data obtained from the NMAs that were conducted to inform this guideline.

In the base-case analysis, for females, the order of treatments from the most to the least cost-effective was photothermal therapy, clindamycin + tretinoin (topical), benzoyl peroxide + adapalene (topical) combined with lymecycline (oral), azelaic acid (topical) combined with lymecycline (oral), oral isotretinoin of total cumulative dose ≥ 120mg/kg, clindamycin (topical), benzoyl peroxide + adapalene (topical), adapalene (topical) combined with lymecycline (oral), photodynamic therapy combined with lymecycline (oral), benzoyl peroxide (topical), photodynamic therapy, oral isotretinoin of total cumulative dose < 120mg/kg, lymecycline (oral), photochemical therapy [red], benzoyl peroxide + clindamycin (topical), benzoyl peroxide + clindamycin + tretinoin (topical), benzoyl peroxide + erythromycin (topical), adapalene (topical), GP care. The probability of photothermal therapy being the most cost-effective treatment option was 0.42 at the lower NICE cost-effectiveness threshold of £20,000/QALY.

For males, the order of treatments from the most to the least cost-effective was photothermal therapy, clindamycin + tretinoin (topical), oral isotretinoin of total cumulative dose ≥ 120mg/kg, benzoyl peroxide + adapalene (topical) combined with lymecycline (oral), azelaic acid (topical) combined with lymecycline (oral), clindamycin (topical), benzoyl peroxide + adapalene (topical), adapalene (topical) combined with lymecycline (oral), oral isotretinoin of total cumulative dose < 120mg/kg, photodynamic therapy combined with lymecycline (oral), benzoyl peroxide (topical), photodynamic therapy, lymecycline (oral), photochemical therapy [red], benzoyl peroxide + clindamycin (topical), benzoyl peroxide + clindamycin + tretinoin (topical), benzoyl peroxide + erythromycin (topical), adapalene (topical), GP care. The probability of photothermal therapy being the most cost-effective treatment option was 0.41 at the lower NICE cost-effectiveness threshold of £20,000/QALY.

The probabilities of cost-effectiveness estimated in a step-wise approach for the 2nd best treatment (topical clindamycin and tretinoin) and up to the 15th best treatment (topical benzoyl peroxide + clindamycin) in ranking did not exceed 0.39, although increasingly fewer treatment options were included in the step-wise analysis, indicating high uncertainty in the results.

Oral isotretinoin showed a higher relative cost-effectiveness in males compared with females, due to its lower intervention cost resulting from less intensive monitoring being required in males receiving oral isotretinoin compared with females (and no need for pregnancy tests).

Results of the economic analysis were overall robust to changes in input parameters tested in deterministic sensitivity analysis.

The analysis utilised clinical effectiveness parameters derived from NMAs on three outcomes: efficacy, discontinuation for any reason, and discontinuation due to side effects. This methodology enabled evidence synthesis from both direct and indirect comparisons between interventions, and allowed simultaneous inference on all treatments examined in pairwise trial comparisons while respecting randomisation (Caldwell 2005; Lu 2004). The quality and limitations of RCTs considered in the NMAs have unavoidably impacted on the quality of the economic model clinical input parameters. For example, economic results may be have been affected by reporting and publication bias.

Effects for some interventions were informed by limited evidence; more specifically, photothermal therapy, photochemical therapy (red), photodynamic therapy combined with

oral lymecycline, azelaic acid combined with oral lymecycline and benzoyl peroxide (topical) had fewer than 100 observations each, across the RCTs included in the NMA of efficacy.

Discontinuation data were not available for a number of treatments; in such cases, other treatments served as proxies, based on the committee's expert opinion. More specifically, the following proxies were used to inform discontinuation where relevant data were not available:

- topical adapalene was used as a proxy for benzoyl peroxide (for discontinuation due to side effects only)
- combined topical clindamycin with tretinoin was used as a proxy for combined topical clindamycin with tretinoin and benzoyl perixide (discontinuation due to side effects only)
- combined topical adapalene with oral lymecycline was used as a proxy for azelaic acid combined with oral lymecycline (for both discontinuation for any reason and due to side effects)
- oral isotretinoin with total cumultative dose ≥120mg/kg was used as a proxy for oral isotretinoin with total cumulative dose <120mg/kg (for both discontinuation for any reason and due to side effects)
- photochemical therapy [red] was used as a proxy for photothermal therapy (for both discontinuation for any reason and due to side effects)
- oral lymecycline was used as a proxy for combined photodynamic therapy and oral lymecycline etracycline (for both discontinuation for any reason and due to side effects).

This lack of discontinuation data for some treatments and use of other treatements in the analysis as proxies for discontinuation is acknowledged as a limitation of the economic analysis. Nevertheless, it is noted that the impact of discontinuation data on the results of the economic model was relatively small as it affected only costs associated with discontinuation and not outcomes; this is because efficacy data used in the economic analysis were taken from intention-to-treat rather than completer analysis, where possible, and therefore they reflected effects on both those completing treatment and those discontinuing treatment early.

Global inconsistency checks and further inconsistency checks through node-splitting indicated that there was inconsistency between direct and indirect evidence considered in the NMA on efficacy. Moreover, heterogeneity across all NMAs was found to be high. It is also noted that the relative effects of most interventions versus placebo were large and characterised, in many cases, by considerably wide 95% credible intervals. These findings need to be taken into account when interpreting the results of the NMAs but also the cost effectiveness results.

The baseline risk of efficacy was derived from 2 large RCTs (N=1,068) of adapalene 0.1% in people with moderate to severe acne, as no relevant observational data were possible to identify. The baseline risk of discontinuation for any reason and due to intolerable side effects were derived from an observational study of 250 people with mild to moderate acne in Turkey, who were prescribed topical treatments, as this was the only identified observational study that provided such data; these data were adjusted for people with moderate to severe acne using RCT adapalene discontinuation data on people with mild to moderate acne and people with moderate to severe acne. Baseline data were tested in deterministic sensitivity analysis.

The time horizon of the analysis was one year, which was considered adequate to capture longer terms and costs associated with a course of treatment for acne without significant extrapolation over the course of acne.

Utility data used in the economic model were estimated based primarily on the committee's expert opinion, as a systematic review of studies reporting utility data for acne-related health states yielded a very small number of studies of overall low quality that either provided no data on acne-specific health states or lacked face validity. Nevertheless, the number of

people with excellent or good improvement one year after treatment initiation was also estimated, to assist consideration of the relative cost-effectiveness of treatments beyond the QALY.

Intervention costs were estimated based on relevant information provided in the studies included in the NMA supplemented by the committee's expert opinion, in order to reflect routine NHS practice. Unit costs were taken from national sources.

The unit cost of a photothermal therapy session was based on the assumption that it equalled that of a photodynamic therapy sessions, due to lack of relevant data. The relative cost-effectiveness of photothermal therapy was rather sensitive to this parameter; considering that the efficacy of photothermal therapy was based on a small evidence base, the conclusion on its cost-effectiveness is rather uncertain.

Acne-related care costs were based on an analysis of primary care consultations and prescription data of 318,515 people with acne over a 10-year period in the UK, combined with the committee's expert opinion on resource use associated with prescribed treatments. These data were not specific to people with moderate to severe acne and covered only primary care. Resource use and costs associated with specialist care received by people with moderate to severe acne were estimated by the committee and added onto the primary care cost estimate, in order to estimate the total annual healthcare cost incurred by people with moderate to severe acne.

All types of treatment for people with moderate to severe acne may lead to the development of side effects. Ideally, the economic model should incorporate costs and decrements in HRQoL associated with the risk of development of side effects. However, relevant data on side-effect rates for each treatment considered in the economic model, from large observational studies, were not readily available. Therefore, the impact of side effects on HRQoL and their associated management costs were not considered in the economic model. On the other hand, the analysis incorporated the impact of intolerable side effects on HRQoL and costs; however, the costs associated with management of intolerable side effects may have been underestimated, in particular for oral isotretinoin, as people discontinuing oral isotretinoin due to intolerable side effects may have experienced mood changes or depression, which may involve further GP monitoring or psychiatric review, and not just an additional specialist dermatologist visit. Antimicrobial resistance resulting from use of topical or oral antibiotics and associated costs were also not considered in the analysis. These omissions in the model structure are acknowledged as limitations of the analysis.

Overall conclusion from the guideline economic analysis

The guideline economic analysis suggests that all assessed topical, oral and physical treatments are more cost-effective for people with moderate to severe acne compared with GP care. Photothermal therapy, topical combinations such as topical retinoid with lincosamide or topical retinoid with benzoyl peroxide, topical treatments combined with oral antibiotics such as topical retinoid with or without benzoyl peroxide combined with an oral tetracycline and azelaic acid combined with an oral tetracycline, oral isotretinoin of total cumulative dose ≥ 120mg/kg, and topical lincosamides are likely to comprise the most cost-effective treatment options for this population. Topical combinations of benzoyl peroxide with lincosamide, lincosamide and retinoid, and macrolide, as well as topical retinoids alone, appear to be less cost-effective, although more cost-effective than GP care alone. In-between, there is another group of treatments (photodynamic therapy alone or combined with an oral tetracycline, benzoyl peroxide, oral isotretinoin of total cumulative dose < 120mg/kg, oral tetracyclines and photochemical therapy [red]) that occupied middle cost effectiveness rankings in the guideline economic analysis.

The guideline economic analysis was based on the best quality data derived from the guideline NMA. However, the NMAs were overall characterised by inconsistency between direct and indirect evidence, high between-study heterogeneity, as well as large effects and

considerably wide 95% credible intervals for some treatments, and this should be taken into account when interpreting the results of the analysis.

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Appendix K – Excluded studies

Excluded studies for review question: For people with moderate to severe acne vulgaris what are the most effective treatment options?

Clinical studies

The excluded studies list below relates to all evidence reviews that used the same search output and these are studies that are excluded from all of the following reviews: mild-to-moderate NMA, moderate-to-severe NMA, mild-to-moderate pairwise and moderate-to-severe pairwise reports, as well as from refractory acne, maintenance of acne and polycystic ovary syndrome reports.

Table 24: Excluded clinical studies and reasons for their exclusion

Reference	Reason for exclusion
Abbasi, M. A. K., A., Aziz ur, Rehman, Saleem, H.,Jahangir, S. M.,Siddiqui, S. Z.,Ahmad, V. U.Preparation of new formulations of anti-acne creams and their efficacy. 2010. African Journal of Pharmacy and Pharmacology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Abdel Hay, R. H., R.,Abdel Hady, M.,Saleh, N.Clinical and dermoscopic evaluation of combined (salicylic acid 20% and azelaic acid 20%) versus trichloroacetic acid 25% chemical peel in acne: an RCT. 2019. Journal of Dermatological Treatment	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Abdel Meguid, A. M. A. E. A. A., D.,Omar, H.Trichloroacetic acid versus salicylic acid in the treatment of acne vulgaris in dark-skinned patients. 2015. Dermatologic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatmentsanalysis
Abdel-Naser, M. B. Z., C. C . Clindamycin phosphate/tretinoin gel formulation in the treatment of acne vulgaris. 2008. Expert Opinion on Pharmacotherapy	No relevant article type - expert opinion on pharmacotherapy
Abels, C. Glycolic acid: the effect is also now proven in acne. 2011a. Haut	Not in English language
Abramovits, W. G., A. Differin (adapalene) Gel, 0.3%. 2007. SKINmed	No relevant study design - not RCT
Abramovits, W. O., M., Gupta, A. K.Veltin gel (clindamycin phosphate 1.2% and tretinoin 0.025%). 2011. SKINmed	No relevant article type - non-systematic review
Adalatkhah, H. P., F., Sadeghi-Bazargani, H. Flutamide versus a cyproterone acetate-ethinyl estradiol combination in moderate acne: a pilot randomized clinical trial. 2011. Clinical, Cosmetic and	Moderate acne - no information on lesion counts at baseline and

Reference	Reason for exclusion
Investigational Dermatology CCID	study is not relevant for PCOS, maintenance or refractory treatments
Adams, J. T., P. Topical fusidic acid versus peroral doxycycline in the treatment of patients with acne vulgaris of the face. 1991. Current Therapeutic Research - Clinical and Experimental	No relevant intervention - suboptimal dose of doxycycline
Adams, R. M. B., K. H. An antiandrogen delta 1 chlormadinone acetate in acne: lack of effect topically. 1970a. Acta Dermato-Venereologica	Duplicate record
Adams, U. M. B., K. H. An antiandrogen delta 1 chlormadinone acetate in acne: lack of effect topically. 1970b. Acta Dermatologica	No relevant study population -insuficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Afzali, B. M. Y., E., Yaghoobi, R., Bagherani, N.,Dabbagh, M. A. Comparison of the efficacy of 5% topical spironolactone gel and placebo in the treatment of mild and moderate acne vulgaris: A randomized controlled trial. 2012. Journal of Dermatological Treatment	No relevant intervention - intervention & class not available in the UK
Agarwal, U. S. B., R. K., Bhola, K. Oral isotretinoin in different dose regimens for acne vulgaris: A randomized comparative trial. 2011. Indian Journal of Dermatology, Venereology and Leprology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Agren, U. M. A., M., Maenpaa-Liukko, K., Rantala, M. L.,Rautiainen, H.,Sommer, W. F.,Mommers, E.Effects of a monophasic combined oral contraceptive containing nomegestrol acetate and 17beta-oestradiol compared with one containing levonorgestrel and ethinylestradiol on haemostasis, lipids and carbohydrate metabolism. 2011a. European Journal of Contraception and Reproductive Health Care	No relevant study population - participants did not have acne
Agren, U. M. A., M., Maenpaa-Liukko, K., Rantala, M. L.,Rautiainen, H.,Sommer, W. F.,Mommers, E.Effects of a monophasic combined oral contraceptive containing nomegestrol acetate and 17beta-oestradiol in comparison to one containing levonorgestrel and ethinylestradiol on markers of endocrine function. 2011b. European Journal of Contraception and Reproductive Health Care	No relevant study population - participants did not have acne
Ahmad, H. M. Analysis of clinical efficacy, side effects, and laboratory changes among patients with acne vulgaris receiving single versus twice daily dose of oral isotretinoin. 2015. Dermatologic Therapy	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ahmadvand, A. Y., A., Yasrebifar, F., Mohammadi, Y.,Mahjub, R.,Mehrpooya, M.Evaluating the effects of oral and topical simvastatin in the treatment of acne vulgaris: A double-blind, randomized, placebo-controlled clinical trial. 2018. Current Clinical Pharmacology	Intervention not relevant I Simvastatin
Ahmed, I. S., M. Topical adapalene cream 0.1% v/s isotretinoin 0.05% in the treatment of acne vulgaris: A randomized open-label clinical trial. 2009. Journal of Pakistan Association of Dermatologists	No relevant outcomes reported
Ahn, G. R., Kim, J. M., Park, S. J., Li, K., Kim, B. J. Selective Sebaceous Gland Electrothermolysis Using a Single Microneedle	Reported outcomes relevant for the network

Reference	Reason for exclusion
Radiofrequency Device for Acne Patients: A Prospective Randomized Controlled Study. 2019. Lasers in Surgery and Medicine.	meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Akamatsu, H. O., M., Nishijima, S., Asada, Y.,Takahashi, M.,Ushijima, T.,Niwa, Y.The inhibition of free radical generation by human neutrophils through the synergistic effects of metronidazole with palmitoleic acid: a possible mechanism of action of metronidazole in rosacea and acne. 1990. Archives of Dermatological Research	No relevant data reported - pharmokinetic study
Akaraphanth, R. K., W., Gritiyarangsan, P. Efficacy of ALA-PDT vs blue light in the treatment of acne. 2007. Photodermatology, Photoimmunology & Photomedicine	No relevant study design - not RCT
Akerlund, M.Clinical experience of a combined oral contraceptive with very low dose ethinyl estradiol. 1997. Acta Obstetricia et Gynecologica Scandinavica, Supplement	No relevant outcomes reported
Aksakal, A. B. K., M.,Onder, M.,Oztas, M. O.,Gurer, M. A.A comparative study of metronidazole 1% cream versus azelaic acid 20% cream in the treatment of acne. 1997. Gazi Medical Journal	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Albuquerque, R. G. d. R., M. A.,Hirotsu, C.,Hachul, H.,Bagatin, E.,Tufik, S.,Andersen, M. L.A randomized comparative trial of a combined oral contraceptive and azelaic acid to assess their effect on sleep quality in adult female acne patients. 2015. Archives of Dermatological Research	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Alexis, A. D. R., J. Q.,Desai, S. R.,Downie, J. B.,Draelos, Z. D.,Feser, C.,Forconi, R.,Fowler, J. F., Jr.,Gold, M.,Kaufman-Janette, J.,Lain, E.,Lee, M.,Ling, M.,Shamban, A. T.,Werschler, W. P.,Daniels, A.BPX-01 Minocycline Topical Gel Shows Promise for the Treatment of Moderate-to-severe Inflammatory Acne Vulgaris. 2018. The Journal of Clinical & Aesthetic Dermatology	No relevant intervention - intervention & class not available in the UK
Alexis, A. F. C.-B., F. E.,York, J. P.Adapalene/benzoyl peroxide gel 0.3%/2.5%: A safe and effective acne therapy in all skin phototypes. 2017. Journal of Drugs in Dermatology	No relevant data reported - post hock analysis according to Fitzpatrick skin type of Stein Gold 2016
Alexis, A. F. J., L. A.,Kerrouche, N.,Callender, V. D.A subgroup analysis to evaluate the efficacy and safety of adapalene-benzoyl peroxide topical gel in black subjects with moderate acne. 2014. Journal of Drugs in Dermatology	No relevant data reported - subgroup analysis of Thiboutot 2007, Gollnick 2009, Gold 2009
Alexis, A. F., Cook-Bolden, F., & Lin, T. Treatment of moderate-to-severe acne vulgaris in a hispanic population: a post-hoc analysis of the efficacy and tolerability of clindamycin 1.2%/benzoyl peroxide 3.75% gel. 2017. Journal of clinical and aesthetic dermatology	No relevant data reported - post hoc subgroup analysis for Hispanic population of Pariser 2014
Alirezai, M. M., J.,Jablonska, S.,Czernielewski, J.,Verschoore, M.Comparative study of the efficacy and tolerability of 0.1 and 0.03	Not in English language

Reference	Reason for exclusion
p.100 adapalene gel and 0.025 p.100 tretinoin gel in the treatment of acne. 1996. Annales de dermatologie ET de venereologie	
Alirezai, M. V., K.,Humbert, P.,Valensi, P.,Cambon, L.,Dupuy, P.A low-salt medical water reduces irritancy of retinoic acid in facial acne. 2000. European Journal of Dermatology	Intervention not targeted at acne but at treatment side effects
Allen, H.F., Mazzoni, C., Heptulla, R.A., Murray, M.A., Miller, N., Koenigs, L., Reiter, E.O. Randomized controlled trial evaluating response to metformin versus standard therapy in the treatment of adolescents with polycystic ovary syndrome. 2005. Journa of Pediatric Endocrinology and Metabolism	Not clear what proportion of participants had acne at baseline
Al-Mishari, M. A. Clinical and bacteriological evaluation of tetracycline and erythromycin in acne vulgaris. 1987. Clinical Therapeutics	Unclear if RCT
Amer, S. S., Nasr, M., Abdel-Aziz, R. T. A., Moftah, N. H., El Shaer, A., Polycarpou, E., Mamdouh, W., Sammour, O. Cosm-nutraceutical nanovesicles for acne treatment: Physicochemical characterization and exploratory clinical experimentation. 2020. International Journal of PharmaceuticsInt J Pharm	No relevant study design - not RCT
Amiri, M., Nahidi, F., Bidhendi-Yarandi, R., Khalili, D., Tohidi, M., Ramezani Tehrani, F.A comparison of the effects of oral contraceptives on the clinical and biochemical manifestations of polycystic ovary syndrome: A crossover randomized controlled trial. 2020. Human Reproduction	No relevant outcomes reported
An, W. X. Z., Z. H. Curative observation on herbal tea combined with ear acupoint in treating 120 middle school students with acne. 2016. Western journal of traditional chinese medicine[xi bu zhong yi yao]	Not in English language
Anadolu, R. Y. S., T.,Tarimci, N.,Birol, A.,Erdem, C.Improved efficacy and tolerability of retinoic acid in acne vulgaris: A new topical formulation with cyclodextrin complex PSI. 2004. Journal of the European Academy of Dermatology and Venereology	Insufficient information about severity of acne at baseline and study is not relevant for PCOS, maintenance or refractory treatments
Anonymous, Management of acne vulgaris. 1966. Drug & Therapeutics Bulletin	Duplicate record
Anonymous, Pharmacokinetic profile, safety, and tolerability of clascoterone topical cream 1% in subjects with moderate-to-severe acne vulgaris: an open-label phase IIa study. 2019. Journal of the American Academy of Dermatology	No relevant article type - conference abstract
Anonymous, Phase III Clinical Study of Clindamycin Phosphate Topical Gel (CLDM-T) in the Treatment of Acne Vulgaris: randomized Comparatie Study with Nadifloxacin Cream as a Control Drug. 1999b. Rinsho iyaku (journal of clinical therapeutics and medicines)	Not in English language
Anonymous, Retinoic acid in the treatment of acne. A report from the General Practitioner Research Group. 1974. Practitioner	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Anonymous, The Clinical Phase II Study of CLDM-T Gel in the Treatment of Acne Vulgaris: double-Blind Comparative Study, Evaluation of Efficacy, Safety and Optimal Concentration of CLDM-T Gel in the Treatment of Acne Vulgaris. 1999a. Rinsho iyaku (journal of clinical therapeutics and medicines)	Not in English language
Anonymous, Treatment of moderate-to-severe facial acne vulgaris	No relevant article type -

Reference	Reason for exclusion
with the use of a solid-state fractional 589/1,319-nm laser. 2018. Journal of the American Academy of Dermatology	conference abstract
Ansarin, H. S., S.,Behzadi, A. H.,Sadigh, N.,Hasanloo, J.Doxycycline plus levamisole: combination treatment for severe nodulocystic acne. 2008. Journal of drugs in dermatology : JDD	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Anstee, P. K., G. T.A prospective randomized study comparing the clinical effects of a norethisterone and a levonorgestrel containing low dose oestrogen oral contraceptive pills. 1993. Australian and New Zealand Journal of Obstetrics and Gynaecology	No relevant study population - participants did not have acne
Antoniou, C. D., C.,Sotiriadis, D.,Kalokasidis, K.,Kontochristopoulos, G.,Petridis, A.,Rigopoulos, D.,Vezina, D.,Nikolis, A.A multicenter, randomized, split-face clinical trial evaluating the efficacy and safety of chromophore gel-assisted blue light phototherapy for the treatment of acne. 2016. International Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Anyachukwu, C. C. O., O. K. K. Efficacy of adjunct (laser) therapy to topical agents among Southern Nigerian acne vulgaris patients. 2014. Acupuncture and Related Therapies	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ash, C. H., A.,Drew, S.,Whittall, R.A randomized controlled study for the treatment of acne vulgaris using high-intensity 414 nm solid state diode arrays. 2015. Journal of cosmetic and laser therapy	Unclear what treatment the control group received (over the counter products)
Aydin, F. C., T.,Senturk, N.,Yasar Turanli, A.Comparison of clinical efficacy of tretinoin 0.025% gel and adapalene 0.1% gel in the treatment of acne vulgaris. 2002. Ondokuz mayis universitesi tip dergisi	Not in English language
Aydinlik, S. L.-F., U.,Lehnert, J.Reduced estrogen ovulation inhibitor in acne therapy. Double-blind study comparing Diane-35 to Diane. 1986. Fortschritte der medizin	Not in English language
Aziz-Jalali, M. H. T., S. M.,Djavid, G. E.Comparison of red and infrared low-level laser therapy in the treatment of acne vulgaris. 2012. Indian Journal of Dermatology	No relevant study design as the study does not appear to be randomised - the same treatment was always applied to a give side of the face
Babaeinejad, S. K., E.,Fouladi, R. F.Comparison of therapeutic effects of oral doxycycline and azithromycin in patients with moderate acne vulgaris: What is the role of age?. 2011. Journal of Dermatological Treatment	No relevant study population - sample includes people with moderate acne but baseline severity not reported according to

Reference	Reason for exclusion
	lesion counts and study is not relevant for PCOS, maintenance or refractory treatments
Bae, B. G. P., C. O.,Shin, H.,Lee, S. H.,Lee, Y. S.,Lee, S. J.,Chung, K. Y.,Lee, K. H.,Lee, J. H.Salicylic acid peels versus Jessner's solution for acne vulgaris: a comparative study. 2013. Dermatologic surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Barak-Shinar, D. D., Z. D.A randomized controlled study of a novel botanical acne spot treatment. 2017. Journal of Drugs in Dermatology	No relevant intervention - study product was based on 10% herbal botanical ingredients with anti-inflammatory and anti-bacterial activity
Barranco, V. P.Effect of androgen-dominant and estrogen-dominant oral contraceptives on acne. 1974. Cutis; cutaneous medicine for the practitioner	No relevant study population - no information on the baseline severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Bassett, I. B. P., D. L.,Barnetson, R. S.A comparative study of tea-tree oil versus benzoylperoxide in the treatment of acne. 1990. Medical Journal of Australia	No relevant intervention - tea-tree oil
Baugh, W. P. K., W. D.Nonablative phototherapy for acne vulgaris using the KTP 532 nm laser. 2005. Dermatologic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Baumann, L. S. O., C.,Yatskayer, M.,Dahl, A.,Figueras, K.Comparison of clindamycin 1% and benzoyl peroxide 5% gel to a novel composition containing salicylic acid, capryloyl salicylic acid, HEPES, glycolic acid, citric acid, and dioic acid in the treatment of acne vulgaris. 2013. Journal of drugs in dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Behrangi, E. A., E.,Tavakoli, T.,Mehran, G.,Atefi, N.,Esmaeeli, S.,Azizian, Z.Comparing efficacy of montelukast versus doxycycline in treatment of moderate acne. 2015. Journal of Research in Medical Sciences	No relevant intervention - montelukast
Behrangi, E., Sadeghi, S., Sadeghzadeh-Bazargan, A., Goodarzi, A., Ghassemi, M., Sepasgozar, S., Rohaninasab, M. The effect of metformin in the treatment of intractable and late onset acne: A comparison with oral isotretinoin. 2019. Iranian Journal of	No relevant data reported - reports combined results for those with treatment-resistant acne and those

Reference	Reason for exclusion
Dermatology	with severe acne with late onset acne; no subgroups reported and study is not relevant for PCOS, maintenance or refractory treatments
Belknap, B. S.Treatment of acne with 5% benzoyl peroxide gel or 0.05% retinoic acid cream. 1979. Cutis	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Belum, V. R. M., M. A.,Dusza, S. W.,Cercek, A.,Kemeny, N. E.,Lacouture, M. E.A prospective, randomized, double-blinded, split-face/chest study of prophylactic topical dapsone 5% gel versus moisturizer for the prevention of cetuximab-induced acneiform rash. 2017. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with metastatic colorectal cancer or head and neck squamous cell carcinoma
Bernstein, E. F.A pilot investigation comparing low-energy, double pass 1,450 nm laser treatment of acne to conventional single-pass, high-energy treatment. 2007. Lasers in Surgery and Medicine	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Bernstein, J. E. S., A. R.Topically applied erythromycin in inflammatory acne vulgaris. 1980. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Bershad, S. K. S., G.,Parente, J. E.,Tan, M. H.,Sherer, D. W.,Persaud, A. N.,Lebwohl, M.Successful treatment of acne vulgaris using a new method: results of a randomized vehicle-controlled trial of short-contact therapy with 0.1% tazarotene gel. 2002. Archives of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Bettoli, V. B., A.,Zauli, S.,Toni, G.,Ricci, M.,Giari, S.,Virgili, A.Maintenance therapy for acne vulgaris: efficacy of a 12-month treatment with adapalene-benzoyl peroxide after oral isotretinoin and a review of the literature. 2013. Dermatology	Duplicate record
Bhatia, N. P., R.Randomized, observer-blind, split-face compatibility study with clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel and facial foundation makeup. 2015. Journal of Clinical and Aesthetic Dermatology	No relevant comparison - split face 6-hour RCT that examines cosmetic compatibility of make up with topical clindamycin and BPO gel
Bhavsar, B. C., B.,Sanmukhani, J.,Dogra, A.,Haq, R.,Mehta, S.,Mukherjee, S.,Subramanian, V.,Sheikh, S.,Mittal, R.Clindamycin 1% Nano-emulsion Gel Formulation for the Treatment of Acne Vulgaris: Results of a Randomized, Active Controlled, Multicentre, Phase IV Clinical Trial. 2014. Journal of Clinical and Diagnostic	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS,

Reference	Reason for exclusion
Research JCDR	maintenance or refractory treatments
Bissonnette, R. B., C., Seite, S.,Nigen, S.,Provost, N.,Maari, C.,Rougier, A.Randomized study comparing the efficacy and tolerance of a lipophillic hydroxy acid derivative of salicylic acid and 5% benzoyl peroxide in the treatment of facial acne vulgaris. 2009. Journal of Cosmetic Dermatology	No relevant intervention - intervention & class not available in the UK
Bissonnette, R. M., C., Nigen, S.,Provost, N.,Bolduc, C.Photodynamic therapy with methylaminolevulinate 80 mg/g without occlusion improves acne vulgaris. 2010. Journal of Drugs in Dermatology	No relevant comparison - photodynamic therapy with methylaminolevulinate with occlusion vs without occlusion
Bissonnette, R. P., Y., Drew, J.,Hofland, H.,Tan, J.Olumacostat glasaretil, a novel topical sebum inhibitor, in the treatment of acne vulgaris: A phase IIa, multicenter, randomized, vehicle-controlled study. 2017. Journal of the American Academy of Dermatology	No relevant intervention - intervention not licensed in the UK
Biswas, S. M., K. K., Dutta, R. N.,Sarkar, D. K.Comparative evaluation of the efficacy of four topical medications individually or in combination to treat grade I acne vulgaris. 2009. Journal of the Indian Medical Association	No relevant outcomes reported
Biyun, C.The clinical observation of treating acne vulgaris with "xiao cuo fang". 2004. Zhong yao cai = Zhongyaocai [Journal of Chinese medicinal materials]	Not in English language
Bladon, P. T. B., B. M., Cunliffe, W. J.Topical azelaic acid and the treatment of acne: A clinical and laboratory comparison with oral tetracycline. 1986. British Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Blaney, D. J. C., C. H. Topical use of tetracycline in the treatment of acne. A double blind study comparing topical and oral tetracycline therapy and placebo. 1976. Archives of Dermatology	No relevant intervention - intervention & class not available in the UK
Bleeker, J. H., L.,Vincent, J.Effect of systemic erythromycin stearate on the inflammatory lesions and skin surface fatty acids in acne vulgaris. 1981. Dermatologica	No relevant study population - sample includes people with mild to severe acne
Bodokh, I. J., Y., Lacour, J. Ph,Ortonne, J. P.Minocycline induces an increase in the number of excreting pilosebaceous follicles in acne vulgaris. A randomised study. 1997. Acta Dermato-Venereologica	No relevant data reported - pharmokinetic study
Bojar, R. A. E., E. A., Jones, C. E.,Cunliffe, W. J.,Holland, K. T.Inhibition of erythromycin-resistant propionibacteria on the skin of acne patients by topical erythromycin with and without zinc. 1994. British Journal of Dermatology	Efficacy outcomes reported in figures only
Borglund, E. H., O., Nord, C. E.Impact of topical clindamycin and systemic tetracycline on the skin and colon microflora in patients with acne vulgaris. 1984. Scandinavian Journal of Infectious Diseases	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Borglund, E. K., B., Larsson-Stymne, B.,Strand, A.,Veien, N. K.,Jakobsen, H. B.Topical meclocycline sulfosalicylate, benzoyl peroxide, and a combination of the two in the treatment of acne vulgaris. 1991. Acta Dermato-Venereologica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS,

Reference	Reason for exclusion
	maintenance or refractory treatments
Borhan, W. H. H., H. A.,Aboelnour, N. H.Efficacy of pulsed dye laser on acne vulgaris. 2014. Journal of american science	Insufficient information about treatment (unspecified topical antibiotic)
Botsali, A. K., P.,Uran, P.The effects of isotretinoin on affective and cognitive functions are disparate in adolescent acne vulgaris patients. 2019. Journal of Dermatological Treatment.	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Bouloc, A. R., E.,Imko-Walczuk, B.,Moga, A.,Chadoutaud, B.,Dreno, B.A skincare combined with combination of adapalene and benzoyl peroxide provides a significant adjunctive efficacy and local tolerance benefit in adult women with mild acne. 2017. Journal of the European Academy of Dermatology and Venereology	No relevant intervention - compares emolients
Bourne, M. S.Comparison of two lotions for acne vulgaris. 1979. Practitioner	No relevant intervention - intervention & class not available in the UK
Bowman, S. G., M.,Nasir, A.,Vamvakias, G.Comparison of clindamycin/benzoyl peroxide, tretinoin plus clindamycin, and the combination of clindamycin/benzoyl peroxide and tretinoin plus clindamycin in the treatment of acne vulgaris: a randomized, blinded study. 2005. Journal of drugs in dermatology : JDD	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Bradford, L. G. M., L. F.Topical application of vitamin A acid in acne vulgaris. 1974. Southern Medical Journal	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Bran, E. L. R. A., A. Therapeutic effectiveness of clindamycin phosphate (1% solution) compared with tetracycline (solution) administered topically in the treatment of acne vulgaris. 1986. Medicina cutanea ibero-latino-americana	Not in English language
Brand, B. G., R.,Baker, M. D.,Poncet, M.,Greenspan, A.,Georgeian, K.,Soloff, A. M.Cumulative irritancy comparison of adapalene gel 0.1% versus other retinoid products when applied in combination with topical antimicrobial agents. 2003a. Journal of the American Academy of Dermatology	No relevant study population - participants did not have acne
Brand, B. G., R.,Baker, M. D.,Poncet, M.,Greenspan, A.,Georgeian, K.,Soto, P.,Arsonnaud, S.Cumulative Irritancy Potential of Adapalene Cream 0.1% Compared with Adapalene Gel 0.1% and Several Tretinoin Formulations. 2003b. Cutis	No relevant study population - participants did not have acne
Brand, E. L. R., A. Study of the therapeutic effectiveness of clindamycin phosphate (1% solution) versus tetracycline (solution) administered topically in the treatment of acne vulgaris. 1986. Medicina cutÃ¡nea ibero-latino-americana	Not in English language

Reference	Reason for exclusion
Brandt, H. A., P.,Ahokas, T.,Forstrom, L.,Jarvinen, T.,Keskitalo, R.,Lehtonen, L.,Plosila, M.,Rita, H.,Suramo, M. L.Erythromycin acistrate - An alternative oral treatment for acne. 1994. Journal of Dermatological Treatment	No relevant comparison - suboptimal dose
Breneman, D. L. A., M. C. Successful treatment of acne vulgaris in women with a new topical sodium sulfacetamide/sulfur lotion. 1993. International Journal of Dermatology	No relevant study design - not RCT
Breno, B. K., A.,Richard, A.,Rougier, A.Interest of a new salicylic acid derivative in the prevention of acne relapses. 2002. European journal of dermatology : EJD	No relevant article type - conference abstract
Brickman, S. S. L., W. D.,Gareau, J. Y.A double-blind evaluation of a topical antibiotic preparation in acne. 1980. Current Therapeutic Research - Clinical and Experimental	No relevant intervention - intervention & class not available in the UK
Brodell, R. T. S., B. J.,Rafal, E.,Toth, D.,Tyring, S.,Wertheimer, A.,Kerrouche, N.,Bucher, D.A fixed-dose combination of adapalene 0.1%BPO 2.5% allows an early and sustained improvement in quality of life and patient treatment satisfaction in severe acne. 2012. Journal of Dermatological Treatment	No relevant outcomes reported
Brogden, R. N. S., T. M.,Avery, G. S.Benzoyl peroxide acne lotions : an independent report. 1974. Drugs	No relevant article type - expert review
Brookes, D. B. M., R. M.,Sheil, L. P.,Flowers, I. M.,Poulter, G. A. Comparison of Tretinoin and a composite formulation in the treatment of acne. 1978. British Journal of Clinical Practice	No relevant study population - insufficient details reported to determine acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Bubna, A. K.Metformin - For the dermatologist. 2016. Indian Journal of Pharmacology	Duplicate record
Bucknall, J. H. M., P. N. Comparison of tretinoin solution and benzoyl peroxide lotion in the treatment of acne vulgaris. 1977. Current Medical Research & Opinion	Not obtainable
Budden, M. G. Topical and oral tetracycline in the treatment of acne vulgaris. 1988. Practitioner	No relevant intervention - intervention & class not available in the UK
Burke, B. E., E. A.,Cunliffe, W. J.Benzoylperoxide versus topical erythromycin in the treatment of acne vulgaris. 1983. British Journal of Dermatology	No relevant study design - not RCT
Burkhart, C. G. B., C. N.Treatment of acne vulgaris without antibiotics: tertiary amine-benzoyl peroxide combination vs. benzoyl peroxide alone (Proactiv Solution). 2007. International Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Burton, J. E., G.A placebo-controlled study to evaluate the efficacy of topical tetracycline and oral tetracycline in the treatment of mild to moderate acne. 1990. Journal of International Medical Research	No relevant intervention - intervention & class not available in the UK
Burton, J. L. P., R. J.,Harris, J. I.Effect of 1% cyproterone acetate in Cetomacrogol cream BPC (formula A) on sebum excretion rate in patients with acne. 1976. British Journal of Dermatology	No relevant data reported - pharmokinetic study
Callender, V. D.Fitzpatrick skin types and clindamycin phosphate	No relevant data reported -

Reference	Reason for exclusion
1.2%/benzoyl peroxide gel: Efficacy and tolerability of treatment in moderate to severe acne. 2012a. Journal of Drugs in Dermatology	post hoc analysis reporting results for people receiving clindamycin 2.1%/BPO 2.5% gel
Cambazard, F.Clinical efficacy of Velac, a new tretinoin and clindamycin phosphate gel in acne vulgaris. 1998. Journal of the European Academy of Dermatology & Venereology	No relevant study design - non-systematic review of tretinoin treatment
Cannizzaro, M. V. D., A.,Garofalo, V.,Del Duca, E.,Bianchi, L.Reducing the oral Isotretinoin skin side effects: Efficacy of 8% omega-ceramides, hydrophilic sugars, 5% niacinamide cream Compound in acne patients. 2018. Giornale Italiano di Dermatologia e Venereologia	Not in English language
Cao, J., Yang, G., Wang, Y., Liu, J. Acupoint Stimulation for Acne: A Systematic Review of Randomized Controlled Trials. 2013. Med Acupunct. 2013	No relevant intervention - systematic review about acupoint stimulation techniques used to treat acne
Cao, J., Yang, G., Wang, Y., Ping Liu, J., Smith, C.A., Luo, H., Liu. Y. Complementary therapies for acne vulgaris. 2015. Cochrane Database Syst Rev	Not relevant intervention - systematic review about complementary and alternative medicine for acne
Cao, T. T., E. S.,Chan, Y. H.,Yosipovitch, G.,Tey, H. L.Anti-pruritic efficacies of doxycycline and erythromycin in the treatment of acne vulgaris: a randomized single-blinded pilot study. 2018. Indian journal of dermatology, venereology and leprology	No relevant study design - not RCT
Carlborg, L. Cyproterone acetate versus Levonorgestrel combined with ethinyl estradiol in the treatment of acne. Results of a multicenter study. 1986. Acta Obstetricia et Gynecologica Scandinavica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Carlborg, L. Cyproterone acetate versus levonorgestrel combined with ethinylestradiol in the treatment of acne. Results of a multicenter study. 1987. Contraception fertilite sexualite	Duplicate record
Carmina, E. L., R. A.A comparison of the relative efficacy of antiandrogens for the treatment of acne in hyperandrogenic women. 2002. Clinical Endocrinology	Duplicate record
Caron, D. S., V.,Clucas, A.,Verschoore, M.Skin tolerance of adapalene 0.1% gel in combination with other topical antiacne treatments. 1997a. Journal of the American Academy of Dermatology	No relevant study population - participants did not have acne
Caron, D. S., V.,Kerrouche, N.,Clucas, A.Split-face comparison of adapalene 0. 1% gel and tretinoin 0.025% gel in acne patients. 1997b. Journal of the American Academy of Dermatology	No relevant outcomes reported
Cavicchini, S. C., R.Long-term treatment of acne with 20% azelaic acid cream. 1989. Acta Dermato-Venereologica, Supplement	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Cestone, E. M., A.,Zanoletti, V.,Zanardi, A.,Mantegazza, R.,Dossena, M.Acne RA-1,2, a novel UV-selective face cream for patients with acne: Efficacy and tolerability results of a randomized, placebo-controlled clinical study. 2017. Journal of Cosmetic Dermatology	Efficacy outcomes reported in figures only

Reference	Reason for exclusion
Chalker, D. K. S., A.,Smith, J. G., Jr.,Swann, R. W.A double-blind study of the effectiveness of a 3% erythromycin and 5% benzoyl peroxide combination in the treatment of acne vulgaris. 1983. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Chan, H. C., G.,Santos, J.,Dee, K.,Co, J. K.A randomized, double-blind, placebo-controlled trial to determine the efficacy and safety of lactoferrin with vitamin E and zinc as an oral therapy for mild to moderate acne vulgaris. 2017. International Journal of Dermatology	No relevant intervention - Lactoferrin + Vitamin E + Zinc
Chandrashekha, B. S. A., M.,Ruparelia, M.,Vaidya, P.,Aamir, R.,Shah, S.,Thilak, S.,Aurangabadkar, S.,Pal, S.,Saraswat, A.,et al.,Tretinoin nanogel 0.025% versus conventional gel 0.025% in patients with acne vulgaris: a randomized, active controlled, multicentre, parallel group, phase iv clinical trial. 2015. Journal of clinical and diagnostic research	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Chang, S. E. A., S. J.,Rhee, D. Y.,Choi, J. H.,Moon, K. C.,Suh, H. S.,Soyun, ChoTreatment of facial acne papules and pustules in Korean patients using an intense pulsed light device equipped with a 530- to 750-nm filter. 2007. Dermatologic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Chantalat, J., Liu, J. C. Six-week safety and efficacy evaluation of a synergistic microgel complex versus 10% benzoyl peroxide in the treatment of mild to moderate acne. Abstract P101. American Academy of Dermatology 64th Annual Meeting March 3-7, 2006. 2006. NA	No relevant article type - conference abstract
Charoenvisal, C. T., Y. Effects on acne of two oral contraceptives containing desogestrel and cyproterone acetate. 1996. International Journal of Fertility and Menopausal Studies	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Chi, C. I. Effects of Salvia miltiorrhiza extract on the improvement and prognosis of acne vulgaris. 2016. Http://www.who.int/trialsearch/trial2.aspx? Trialid=chictr-iir-16010104	No relevant intervention - Salvia miltiorrhiza extract
Chiou, W. L. Low intrinsic drug activity and dominant vehicle (placebo) effect in the topical treatment of acne vulgaris. 2012. International Journal of Clinical Pharmacology and Therapeutics	No relevant study design - not RCT
Chlebus, E., Serafin, M., Chlebus, M. Is maintenance treatment in adult acne important? Benefits from maintenance therapy with adapalene, and low doses of alpha and beta hydroxy acids. 2019. Journal of Dermatological Treatment	No relevant study design - the randomized comparison is of skin care regimen rather than maintenance treatment (adapalene in both groups)
Cho, S. B. L., J. H.,Choi, M. J.,Lee, K. Y.,Oh, S. H.Efficacy of the fractional photothermolysis system with dynamic operating mode on acne scars and enlarged facial pores. 2009. Dermatologic Surgery	Duplicate record
Choudhury, S. C., S.,Sarkar, D. K.,Dutta, R. N.Efficacy and safety of topical nadifloxacin and benzoyl peroxide versus clindamycin and	No relevant intervention - intervention & class not

Reference	Reason for exclusion
benzoyl peroxide in acne vulgaris: A randomized controlled trial. 2011. Indian Journal of Pharmacology	available in the UK
Christian, G. L. K., G. G. Clindamycin vs placebo as adjunctive therapy in moderately severe acne. 1975. Archives of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Christiansen, J. H., P.,Reymann, F.The retinoic acid derivative Ro 11 1430 in Acne vulgaris. A controlled multicenter trial against retinoic acid. 1977. Dermatologica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Christiansen, J. H., P.,Reymann, F.Treatment of acne vulgaris with the retinoic acid derivative Ro 11-1430. A controlled clinical trial against retinoic acid. 1976. Dermatologica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Christiansen, J. V. G., E.,Ludvigsen, K.,Konstman Meier, C. H.,Norholm, A.,Osmundsen, P. E.,Pedersen, D.,Rasmussen, K. A.,Reiter, H.,Reymann, F.,et al.,Topical vitamin A acid (Airol) and systemic oxytetracycline in the treatment of acne vulgaris. A controlled clinical trial. 1974a. Dermatologica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Christiansen, J. V. G., E.,Ludvigsen, K.,Meier, C. H.,Norholm, A.,Pedersen, D.,Rasmussen, K. A.,Reiter, H.,Reymann, F.,Sylvest, B.,et al.,Topical tretinoin, vitamin A acid (Airol) in acne vulgaris. A controlled clinical trial. 1974b. Dermatologica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Chu, A. H., F. J.,Plott, R. T.The comparative efficacy of benzoyl peroxide 5%/erythromycin 3% gel and erythromycin 4%/zinc 1.2% solution in the treatment of acne vulgaris. 1997. British Journal of Dermatology	No relevant study population - sample includes people with too narrow range of acne severity criteria and study is not relevant for PCOS, maintenance or refractory treatments
Chularojanamontri, L. T., P.,Kulthanan, K.,Varothai, S.,Winayanuwattikun, W.A double-blinded, randomized, vehicle-controlled study to access skin tolerability and efficacy of an anti-inflammatory moisturizer in treatment of acne with 0.1% adapalene gel. 2016. Journal of Dermatological Treatment	No relevant intervention - Adaplene with or without Eucerin mositurizer
Clucas, A. V., M.,Sorba, V.,Poncet, M.,Baker, M.,Czernielewski, J.Adapalene 0.1% gel is better tolerated than tretinoin 0.025% gel in acne patients. 1997. Journal of the American Academy of Dermatology	Duplicate publication from Cunliffe 1997 trial
Cochran, R. J. T., S. B.,Flannigan, S. A.Topical zinc therapy for acne vulgaris. 1985. International Journal of Dermatology	No relevant study design - not RCT
Colver, G. B. M., P. S.,Dawber, R. P.Cyproterone acetate and two	No relevant study

Reference	Reason for exclusion
doses of oestrogen in female acne; a double-blind comparison. 1988. British Journal of Dermatology	population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Coman, G. C. H., A. C.,Mazloom, S. E.,Chavan, R. N.,Kolodney, M. S.A randomized, split-face, controlled, double-blind, single-centre clinical study: transient addition of a topical corticosteroid to a topical retinoid in patients with acne to reduce initial irritation. 2017. British Journal of Dermatology	No relevant article type - letter to editor
Cook-Bolden, F. E. Efficacy and tolerability of a fixed combination of clindamycin phosphate (1.2%) and benzoyl peroxide (3.75%) aqueous gel in moderate or severe adolescent acne vulgaris. 2015. Journal of Clinical and Aesthetic Dermatology	No relevant data reported - post hoc age analysis of Pariser 2014
Cook-Bolden, F. E. Treatment of moderate to severe acne vulgaris in a Hispanic population: A post-hoc analysis of efficacy and tolerability of clindamycin phosphate 1.2%/benzoyl peroxide 2.5% gel. 2012. Journal of Drugs in Dermatology	No relevant data reported - post hoc subgroup analysis by ethnicity of Thiboutot 2008
Cook-Bolden, F. E. W., S. H.,Guenin, E.,Bhatt, V.Novel Tretinoin 0.05% Lotion for Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris in a Hispanic Population. 2019. Journal of drugs in dermatology : JDD	No relevant data reported - post hoc subgroup analysis of Hispanic participants in Tyring 2018
Cook-Bolden, F. E., Gold, M. H., Guenin, E. Tazarotene 0.045% Lotion for the Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris in Adult Males. 2020. Journal of drugs in dermatology : JDD	Not obtainable
Corlin, R. M., B.,Mack, H. A. Oral administration of low doses of 13-cis-retinoic acid in acne papulopustulosa. Results of a multicenter study. 1984. Der hautarzt; zeitschrift fur dermatologie, venerologie, und verwandte gebiete	Not in English language
Cotterill, J. A.Benzoyl peroxide. 1980. Acta Dermato-Venereologica. Supplementum	Duplicate record
Coughlin, C. C. S., S. M.,Horwinski, J.,Sfyroera, G.,Bugayev, J.,Grice, E. A.,Yan, A. C.The preadolescent acne microbiome: A prospective, randomized, pilot study investigating characterization and effects of acne therapy. 2017. Pediatric Dermatology	No relevant data reported - microbiome study
Cremoncini, C. V., E.,Libroia, A. Treatment of hirsutism and acne in women with two combinations of cyproterone acetate and ethinylestradiol. 1976. Acta Europaea Fertilitatis	No relevant study design - not RCT
Cullberg, G. H., L.,Mattsson, L. A.,Mobacken, H.,Samsioe, G. Effects of a low-dose desogestrel-ethinylestradiol combination on hirsutism, androgens and sex hormone binding globulin in women with a polycystic ovary syndrome. 1985. Acta Obstetricia et Gynecologica Scandinavica	No relevant study population – study focuses women with PCOS and hirsuitism rather than acne and study is not relevant for other evidence reviews
Cunliffe, W. J. B., B.,Dodman, B.,Gould, D. J.A double-blind trial of a zinc sulphate/citrate complex and tetracycline in the treatment of acne vulgaris. 1979. British Journal of Dermatology	No relevant study population - insufficient information reported about acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Cunliffe, W. J. C., J. A. Clindamycin as an alternative to tetracycline in severe acne vulgaris. 1973. Practitioner	No relevant study design - not RCT
Cunliffe, W. J. C., J. A.,Williamson, B. The effect of a medicated wash on acne, sebum excretion rate and skin surface lipid composition.	No relevant article type - letter to editor

Reference	Reason for exclusion
1972. British Journal of Dermatology	
Cunliffe, W. J. C., R.,Dreno, B.,Forstrom, L.,Heenen, M.,Orfanos, C. E.,Privat, Y.,Aguilar, A. R.,Meynadier, J.,Alirezai, M.,Jablonska, S.,Shalita, A.,Weiss, J. S.,Chalker, D. K.,Ellis, C. N.,Greenspan, A.,Katz, H. I.,Kantor, I.,Millikan, L. E.,Swinehart, J. M.,Swinyer, L.,Whitmore, C.,Czernielewski, J.,Verschoore, M.Clinical efficacy and safety comparison of adapalene gel and tretinoin gel in the treatment of acne vulgaris: Europe and U.S. multicenter trials. 1997a. Journal of the American Academy of Dermatology	No relevant study design - combined publication of Cunliffe 1997 & US trial
Cunliffe, W. J. C., R.,Dreno, B.,Forstrom, L.,Heenen, M.,Orfanos, C. E.,Privat, Y.,Robledo Aguilar, A.,Poncet, M.,Verschoore, M.Efficacy and safety comparison of adapalene (CD271) gel and tretinoin gel in the topical treatment of acne vulgaris. A European multicentre trial. 1997b. Journal of Dermatological Treatment	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Cunliffe, W. J. D., F. W.,Dunlap, F.,Gold, M. H.,Gratton, D.,Greenspan, A.Randomised, controlled trial of the efficacy and safety of adapalene gel 0.1% and tretinoin cream 0.05% in patients with acne vulgaris. 2002. European Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Cunliffe, W. J. F., R. A.,Greenwood, N. D.,Hetherington, C.,Holland, K. T.,Holmes, R. L.,Khan, S.,Roberts, C. D.,Williams, M.,Williamson, B.Tetracycline and acne vulgaris: a clinical and laboratory investigation. 1973. British Medical Journal	No relevant study population - insufficient details about acne severity reported and study is not relevant for PCOS, maintenance or refractory treatments
Cunliffe, W. J. G., D.,Goode, K.,Stables, G. I.,Boorman, G. C.A double-blind investigation of the potential systemic absorption of isotretinoin, when combined with chemical sunscreens, following topical application to patients with widespread acne of the face and trunk. 2001. Acta Dermato-Venereologica	No relevant data reported - pharmokinetic study
Cunliffe, W. J. G., E.,Belaich, S.,Meynadier, J.,Alirezai, M.,Thomas, L.A comparison of the efficacy and safety of lymecycline and minocycline in patients with moderately severe acne vulgaris. 1998. European Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Cunliffe, W. J. H., K. T.Clinical and laboratory studies on treatment with 20% azelaic acid cream for acne. 1989. Acta Dermato-Venereologica, Supplement	No relevant study design - not RCT
Cunliffe, W. J. S., C.,Forster, R. A. Topical benzoyl peroxide increases the sebum excretion rate in patients with acne. 1983. British Journal of Dermatology	No relevant data reported - pharmokinetic study

Reference	Reason for exclusion
Cunliffe, W. J.A new topical retinoid--why a new topical acne therapy?. 1998. British Journal of Dermatology	No relevant article type - commentary
Dainichi, T. K., A.,Ueda, S.,Tajiri, R.,Fumimori, T.,Kakuma, T.,Hashimoto, T.Skin tightening effect using fractional laser treatment: I. A randomized half-side pilot study on faces of patients with acne. 2010. Dermatologic Surgery	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Damkerngsuntorn, W., Rerknimitr, P., Panchaprateep, R., Tangkijngamvong, N., Kumtornrut, C., Kerr, S. J., Asawanonda, P., Tantisira, M. H., Khemawoot, P. The Effects of a Standardized Extract of Centella asiatica on Postlaser Resurfacing Wound Healing on the Face: A Split-Face, Double-Blind, Randomized, Placebo-Controlled Trial. 2020. Journal of Alternative & Complementary MedicineJ Altern Complement Med	No relevant intervention - laser with extract of Centella asiatica
Danto, J. L. M., W. S.,Stewart, W. D.,Nelson, A. J.A controlled trial of benzoyl peroxide and precipitated sulfur cream in acne vulgaris. 1966. Applied Therapeutics	No relevantstudy population - insufficient information to determine acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Darley, C. R. M., J. W.,Besser, G. M.,Munro, D. D.,Kirby, J. D.Low dose prednisolone or oestrogen in the treatment of women with late onset or persistent acne vulgaris. 1983. British Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Darne, S. H., E. L.,Seukeran, D. C.Evaluation of the clinical efficacy of the 1450 nm laser in acne vulgaris: A randomized split-face, investigator-blinded clinical trial. 2011. British Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Darne, S. H., E.,Seukeran, D. C.Treatment of inflammatory acne with a 1450-nm smoothbeam diode laser: A split-face randomized single-blinded controlled trial. 2009. British Journal of Dermatology	No relevant article type - conference abstract
Dayal, S., Kalra, K. D., Sahu, P. Comparative study of efficacy and safety of 45% mandelic acid versus 30% salicylic acid peels in mild-to-moderate acne vulgaris. 2019. Journal of Cosmetic DermatologyJ	Duplicate of Dayal 2020 first published online 2019
de Arruda, L. H. K., V.,Bastos Filho, A.,Mazzaro, C. B.A prospective, randomized, open and comparative study to evaluate the safety and efficacy of blue light treatment versus a topical benzoyl peroxide 5% formulation in patients with acne grade II and III. 2009. Anais brasileiros de dermatologia	Not in English language
De Leeuw, J. V. D. B., N.,Bjerring, P.,Martino Neumann, H. A. Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid 0.5% liposomal spray and intense pulsed light in combination with topical keratolytic agents. 2010. Journal of the European Academy of Dermatology and Venereology	No relevant data reported - article reports that study is RCT but does not report comparative data
Degreef, H. V. B., G. Double-blind evaluation of a miconazole -	Duplicate record

Reference	Reason for exclusion
benzoyl peroxide combination for the topical treatment of acne vulgaris. 1982a. Dermatologica	
Del Rosso JQ, Kircik L, Gallagher CJ.Comparative efficacy and tolerability of dapsone 5% gel in adult versus adolescent females with acne vulgaris. https://www.ncbi.nlm.nih.gov/pubmed/25610522	Posthoc analysis of Draelos 2007
Del Rosso, J. Q. Clindamycin phosphate 1.2%/tretinoin 0.025% gel for the treatment of acne vulgaris: Which patients are most likely to benefit the most?. 2015. Journal of Clinical and Aesthetic Dermatology	Duplicate record
Del Rosso, J. Q. K., L.,Gallagher, C. J.Comparative efficacy and tolerability of dapsone 5% gel in adult versus adolescent females with acne vulgaris. 2015. Journal of Clinical and Aesthetic Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Del Rosso, J. Q. Study results of benzoyl peroxide 5%/clindamycin 1% topical gel, adapalene 0.1% gel, and use in combination for acne vulgaris. 2007. Journal of drugs in dermatology : JDD	No relevant study population - no details of inclusion criteria reported and study is not relevant for PCOS, maintenance or refractory treatments
Del Rosso, J. Q. The use of topical azelaic acid for common skin disorders other than inflammatory rosacea. 2006. Cutis	Duplicate record
Deshmukh, S. N. B., V. A.,Mahajan, M. M.,Sujata Dudhgaonkar, D.,Mishra, D.Comparison of efficacy and safety of topical 1% nadifloxacin and tretinoin 0.025% combination therapy with 1% clindamycin and tretinoin 0.025% combination therapy in patients of mild-to-moderate acne. 2018. Perspectives in Clinical Research	No relevant intervention - intervention & class not available in the UK
DeVillez, R. L.Clinical comparison of the safety and efficacy of Brevoxyl gel and Benzamycin gel. 1992. Drug Investigation	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Dhawan, S. S. Comparison of 2 clindamycin 1%-benzoyl peroxide 5% topical gels used once daily in the management of acne vulgaris. 2009. Cutis; cutaneous medicine for the practitioner	No relevant comparison - clindamycin/BPO topical gel with the hydrating excipients dimethicone and glycerin vs without hydrating excipients
Dieben Th, O. M. V., L.,Theeuwes, A.,Coelingh Bennink, H. J. T.The effects of CTR-24, a biphasic oral contraceptive combination, compared to Diane-35 in women with acne. 1994. Contraception	No relevant study population - insufficient details about types of lesions to determine severity of participants
Divers, L. S.A new preparation for the topical treatment of acne vulgaris. Report of a year's study. 1966. Journal of the College of General Practitioners	No relevant study design - not RCT
Do Nascimento, L. V. G., A. C. M.,Magalhaes, G. M.,De Faria, F. A.,Guerra, R. M.,Almeida, F. D. C.Single-blind and comparative clinical study of the efficacy and safety of benzoyl peroxide 4% gel	No relevant study population - sample includes people with mild

Reference	Reason for exclusion
(BID) and adapalene 0.1% Gel (QD) in the treatment of acne vulgaris for 11 weeks. 2003. Journal of Dermatological Treatment	to severe acne
Dogra, A. S., V. K.,Minocha, Y. C.Comparative evaluation of retinoic acid, benzoyl peroxide and erythromycin lotion in acne vulgaris. 1993. Indian journal of dermatology, venerology and leprology	No relevant study population - sample includes people with mild to severe acne
Dominguez, J. H., M. T.,Celayo, J. L.,Dominguez-Soto, L.,Teixeira, F.Topical isotretinoin vs. topical retinoic acid in the treatment of acne vulgaris. 1998. International Journal of Dermatology	No relevant data - insufficient data reported
Donadini, A.Is topical antibiotic therapy associated with the same oral treatment useful in patients with acne?. 1989. Ann ital dermatol clin sper	Not in English language and also no relevant study design - not RCT
Dosik, J. E., H.,Stuart, I.Topical minocycline foam 4%: Results of four phase 1 studies evaluating the potential for phototoxicity, photoallergy, sensitization, and cumulative irritation. 2019. Journal of immunotoxicology	No relevant study population - participants did not have acne
Dosik, J. S. G., R. D.,Arsonnaud, S.Cumulative irritancy comparison of topical retinoid and antimicrobial combination therapies. 2006. Skinmed	No relevant study population - participants did not have acne
Dosik, J. S. H., K.,Arsonnaud, S.Cumulative irritation potential of adapalene 0.1% cream and gel compared with tazarotene cream 0.05% and 0.1%. 2005b. Cutis	No relevant study population - participants did not have acne
Dosik, J. S. H., K.,Arsonnaud, S.Cumulative irritation potential of adapalene 0.1% cream and gel compared with tretinoin microsphere 0.04% and 0.1%. 2005a. Cutis	No relevant study population - participants did not have acne
Draelos, Z. D. Assessing the value of botanical anti-inflammatory agents in an OTC acne treatment regimen. 2015. Journal of Drugs in Dermatology	No relevant comparison/intervention - compares over-the-counter skin care regimens with/without added botanicals
Draelos, Z. D. C., E.,Maloney, J. M.,Elewski, B.,Poulin, Y.,Lynde, C.,Garrett, S.Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. 2007. Journal of the American Academy of Dermatology	No relevant data reported - reports pooled results from 2 trials combined
Draelos, Z. D. C., V.,Young, C.,Dhawan, S. S.The effect of vehicle formulation on acne medication tolerability. 2008. Cutis	No relevant outcomes reported
Draelos, Z. D. E., K.,Rom, D.Five-day study to judge the short-term effect of a benzoyl peroxide 3% gel on acne lesions. 2016. Journal of cosmetic dermatology	No relevant outcomes reported
Draelos, Z. D. M., A.,Smiles, K.The effect of 2% niacinamide on facial sebum production. 2006. Journal of Cosmetic and Laser Therapy	No relevant study population - participants did not have acne
Draelos, Z. D. P., A.,Alio Saenz, A. B.Randomized tolerability analysis of clindamycin phosphate 1.2%-tretinoin 0.025% gel used with benzoyl peroxide wash 4% for acne vulgaris. 2010. Cutis	No relevant intervention - queous-based gel (clindamycin phosphate 1.2%-tretinoin 0.025%) when used in conjunction with a BPO wash 4%
Draelos, Z. D. R., D. A.,Kempers, S. E.,Bruce, S.,Peredo, M. I.,Downie, J.,Chang-Lin, J. E.,Berk, D. R.,Ruan, S.,Kaoukhov, A.Treatment response with once-daily topical dapsone gel, 7.5% for acne vulgaris: Subgroup analysis of pooled data from two randomized, double-blind stu. 2017. Journal of Drugs in Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS,

Reference	Reason for exclusion
	maintenance or refractory treatments
Draelos, Z. D. S., A. R.,Thiboutot, D.,Oresajo, C.,Yatskayer, M.,Raab, S.A multicenter, double-blind study to evaluate the efficacy and safety of 2 treatments in participants with mild to moderate acne vulgaris. 2012. Cutis; cutaneous medicine for the practitioner	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Drake, L. Comparative efficacy and tolerance of Cleocin T topical gel (clindamycin phosphate topical gel) versus oral minocycline in the treatment of acne vulgaris. 1990. Data on file (technical report from pharmacia and upjohn ltd)	No relevant article type - not published in peer reviewed journal
Dreno, B. B., V.,Ochsendorf, F.,Layton, A. M.,Perez, M.,Dakovic, R.,Gollnick, H.Efficacy and safety of clindamycin phosphate 1.2%/tretinoin 0.025% formulation for the treatment of acne vulgaris: Pooled analysis of data from three randomised, double-blind, parallel-group, phase III studies. 2014. European Journal of Dermatology	No relevant data reported - pooled analysis of 3 studies combined, 2 of which include people with mild to severe acne. Data for third study reported in Schleslinger 2009
Dreno, B. M., D.,Alirezai, M.,Amblard, P.,Auffret, N.,Beylot, C.,Bodokh, I.,Chivot, M.,Daniel, F.,Humbert, P.,Meynadier, J.,Poli, F.Multicenter randomized comparative double-blind controlled clinical trial of the safety and efficacy of zinc gluconate versus minocycline hydrochloride in the treatment of inflammatory acne vulgaris. 2001. Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Dreno, B. T., J.,Rivier, M.,Martel, P.,Bissonnette, R.Adapalene 0.1%/benzoyl peroxide 2.5% gel reduces the risk of atrophic scar formation in moderate inflammatory acne: a split-face randomized controlled trial. 2016. Journal of the european academy of dermatology and venereology : JEADV	Duplicate record
Dreno, B. T., J.,Rivier, M.,Martel, P.,Bissonnette, R.Adapalene 0.1%/benzoyl peroxide 2.5% gel reduces the risk of atrophic scar formation in moderate inflammatory acne: a split-face randomized controlled trial. 2017. Journal of the European Academy of Dermatology and Venereology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Dudhia, S. S., R. B.,Agrawal, P.,Shah, A.,Date, S.Efficacy and safety of clindamycin gel plus either benzoyl peroxide gel or adapalene gel in the treatment of acne: a randomized open-label study. 2015. Drugs and Therapy Perspectives	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Dunlap, F. E. B., M. D.,Plott, R. T.,Verschoore, M.Adapalene 0.1% gel has low skin irritation potential even when applied immediately after	No relevant comparison - compares adapalene 0.1% gel application immediately

Reference	Reason for exclusion
washing. 1998a. British Journal of Dermatology, Supplement	after washing to a delayed application
Dunlop, K. J. B., R. S.A comparative study of isolutrol versus benzoyl peroxide in the treatment of acne. 1995. The Australasian journal of dermatology	No relevant intervention - Isolutrol
Eady, E. A. B., B. M.,Pulling, K.,Cunliffe, W. J.The benefit of 2% salicylic acid lotion in acne - A placebo-controlled study. 1996a. Journal of dermatological treatment	No relevant data reported - for example, not possible to extract the number of participants in each treatment group
Eady, E. A. B., R. A.,Jones, C. E.,Cove, J. H.,Holland, K. T.,Cunliffe, W. J.The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant propionibacteria. 1996b. British Journal of Dermatology	No relevant outcomes reported
Eady, E. A. B., R. A.,Jones, C. E.,Cove, K. T.,Cunliffe, W. J.The effects of acne therapy with a combination of benzoyl peroxide and erythromycin on carriage of eryhtromycin resistant cutaneous propionobacteria. 1994. British journal of dermatology	No relevant article type - conference abstract
Ede, M.A double blind, comparative study of benzoyl peroxide, benzoyl peroxide chlorhydroxyquinoline, benzoyl peroxide chlorhydroxyquinoline hydrocortisone, and placebo lotions in acne. 1973. Current Therapeutic Research - Clinical and Experimental	No relevant intervention
Egan, N. L., M. C.,Baker, M. M.Randomized, controlled, bilateral (split-face) comparison trial of the tolerability and patient preference of adapalene gel 0.1% and tretinoin microsphere gel 0.1% for the treatment of acne vulgaris. 2001. Cutis; cutaneous medicine for the practitioner	No relevant study population - sample includes people with mild, moderate and severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Eichenfield, L. E. J., J. L.,Dirschka, T.,Taub, A. F.,Lynde, C.,Graeber, M.,Kerrouche, N.Treatment of 2,453 acne vulgaris patients aged 12-17 years with the fixed-dose adapalene-benzoyl peroxide combination topical gel: efficacy and safety. 2010a. Journal of Drugs in Dermatology: JDD	Subgroup analysis of Stein Gold 2016
Eichenfield, L. F. A. S., A. B.Safety and efficacy of clindamycin phosphate 1.2%-benzoyl peroxide 3% fixed-dose combination gel for the treatment of acne vulgaris: a phase 3, multicenter, randomized, double-blind, active- and vehicle-controlled study. 2011. Journal of Drugs in Dermatology: JDD	No relevant study population - sample includes people with mild to severe acne acne and study is not relevant for PCOS, maintenance or refractory treatments
Eichenfield, L. F. D., Z.,Lucky, A. W.,Herbert, A. A.,Sugarman, J.,Gold, S.,Rudisill, D.Treatment of acne in children 9-11 with a fixed dose combination. 2013b. Pediatric Dermatology	No relevant article type - conference abstract
Eichenfield, L. F. H., A. A.,Schachner, L.,Paller, A. S.,Rossi, A. B.,Lucky, A. W.Tretinoin microsphere gel 0.04% pump for treating acne vulgaris in preadolescents: A randomized, controlled study. 2012a. Pediatric Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Eichenfield, L. F. K., A. C.Moderate to severe acne in adolescents with skin of color: Benefits of a fixed combination clindamycin phosphate 1.2% and benzoyl peroxide 2.5% aqueous gel. 2012b. Journal of Drugs in Dermatology	No relevant data reported - subgroup analysis of Thiboutot 2008
Eichenfield, L. F. S., J. L.,Guenin, E.,Harris, S.,Bhatt, V.Novel tretinoin	No relevant data reported -

Reference	Reason for exclusion
0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris in a preadolescent population. 2019. Pediatric Dermatology	post hock analysis of Tyring 2018
Eichenfield, L. F. T., D.,Shalita, A.,Swinyert, L.,Tanghetti, E.,Tschen, E.,Parr, L.A three-step acne system containing solubilized benzoyl peroxide versus benzoyl peroxide/clindamycin in pediatric patients with acne. 2009a. Journal of clinical and aesthetic dermatology	No relevant data reported - subgroup analysis of Thiboutout 2009
Eichenfield, L. F. W., M.A novel gel formulation of 0.25% tretinoin and 1.2% clindamycin phosphate: Efficacy in acne vulgaris patients aged 12 to 18 years. 2009b. Pediatric Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Eichenfield, L. F., Sugarman, J. L., Guenin, E., Bhatt, V. Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris in a preadolescent population. 2019. Journal of Clinical and Aesthetic Dermatology	No relevant article type - conference abstract
El Aziz Ragab, M. A. O., S. S.,Collier, A.,El-Wafa, Raha,Gomaa, N.The effect of continuous high versus low dose oral isotretinoin regimens on dermcidin expression in patients with moderate to severe acne vulgaris. 2018. Dermatologic Therapy	No relevant article type - letter to editor
Elbaum, D. J.Comparison of the stability of topical isotretinoin and topical tretinoin and their efficacy in acne. 1988. Journal of the American Academy of Dermatology	No relevant study population - insuficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
El-Fakahany, H. M., W.,Abdallah, F.,Abdel-Raouf, H.,Abdelhakeem, M.Fractional microneedling: A novel method for enhancement of topical anesthesia before skin aesthetic procedures. 2016. Dermatologic Surgery	No relevant intervention - skin microneedling for treatment of atrophic scars
El-Latif, A. A. H., F. A.,Elshahed, A. R.,Mohamed, A. G.,Elsaie, M. L.Intense pulsed light versus benzoyl peroxide 5% gel in treatment of acne vulgaris. 2014. Lasers in Medical Science	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ellis, C. N. G., W. R.,Stone, D. Z.,Heezen-Wehner, J. L.A comparison of cleocin T solution cleocin T gel, and placebo in the treatment of acne vulgaris. 1988. Cutis	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ellis, C. N. L., J.,Katz, H. I.,Goldfarb, M. T.,Hickman, J.,Jones, T. M.,Tschen, E.Therapeutic studies with a new combination benzoyl peroxide/clindamycin topical gel in acne vulgaris. 2001b. Cutis	No relevant data - reports 3 trials but full article is not available; no information about number of participants assigned to each group in trials reported
Ellis, C. N. L., J.,Katz, H. I.,Goldfarb, M. T.,Hickman, J.,Jones, T. M.Therapeutic studies with a new combination benzoyl peroxide/clindamycin topical gel in acne vulgaris.(erratum appears in Cutis 2001 Mar;67(3): 257). 2001a. Cutis; cutaneous medicine for the	Duplicate record

Reference	Reason for exclusion
practitioner	
Ellis, C. N. M., L. E.,Smith, E. B.,Chalker, D. M.,Swinyer, L. J.,Katz, I. H.,Berger, R. S.,Mills, O. H.,Baker, M.,Verschoore, M.,et al.,Comparison of adapalene 0.1% solution and tretinoin 0.025% gel in the topical treatment of acne vulgaris. 1998. British journal of dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Elman, M. S., M.,Harth, Y.The effective treatment of acne vulgaris by a high-intensity, narrow band 405-420 nm light source. 2003. Journal of Cosmetic and Laser Therapy	No relevant data - reoprts data from 3 trials. No relevant population - sample includes people with mild to severe acne in first 2 trials, and insufficient details about types of lesions to determine severity of participants in one trial and study is not relevant for PCOS, maintenance or refractory treatments
ElRefaei, A. M. A. S., H. A.,Sorour, N. E.Salicylic-mandelic acid versus glycolic acid peels in Egyptian patients with acne vulgaris. 2015. Journal of the egyptian women's dermatologic society	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Enshaieh,The efficacy of 5% topical tea tree oil gel in mild to moderate acne vulgaris: a randomized, double-blind placebo-controlled study. 2007. NA	No relevant intervention - tea tree oil gel
Ereaux, L. P.A new lotion for the treatment of acne vulgaris. 1965. Canadian Medical Association journal	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ergin, S. E., C.,Baysal, V.,Yayli, G.An acne study focused on erythromycin: Benzoyl peroxide alone or with topical erythromycin against Propionibacterium acnes in acne vulgaris. 2001. Gazi Medical Journal	Outcomes reported in figures only
Erkkola, R. H., E.,Luikku, J.,Lumme, R.,Mannikko, H.,Aydinlik, S.Ovulation inhibitors containing cyproterone acetate or desogestrel in the treatment of hyperandrogenic symptoms. 1990. Acta Obstetricia et Gynecologica Scandinavica	No relevant study population - participants did not have acne
Ernst, E., Huntley, A. Tea tree oil: a systematic review of randomized clinical trials. 2000. Forsch Komplementarmed Klass Naturheilkd	No relevtan intervention - systematic review about tea tree oil for various dermatological conditions
Ersoy, L. K., A.,Kilic, I.,Koc, K.,Sen, S.Topical spironolactone in acne vulgaris. 1996. Nouvelles dermatologiques	Not in English language
Euctr, C. Z. Assessment of efficacy and safety of a new gel with 10 mg/g clindamycin and 30 mg/g benzoyl peroxide in comparison with the approved preparation DUACÃ‚Â® 10 mg/g + 30 mg/g Gel and the	No relevant study design - not RCT

Reference	Reason for exclusion
underlying vehicle in patients with mild to moderate acne. 2018. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2017-000521-13-CZ	
Euctr, F. R. Randomized double-blind study on the benefit of spironolactone for treating acne of adult woman. 2017. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2017-001392-22-FR	No relevant study design - not RCT
Exner, J. H. C., H.,Dahod, S.,Pochi, P. E.Topical erythromycin/zinc effect on acne and sebum secretion. 1983. Current Therapeutic Research - Clinical and Experimental	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Fabbrocini, G. I., R.,Faggiano, A.,Del Prete, M.,Donnarumma, M.,Marasca, C.,Marciello, F.,Savastano, R.,Monfrecola, G.,Colao, A.Low glycaemic diet and metformin therapy: A new approach in male subjects with acne resistant to common treatments. 2016. Clinical and Experimental Dermatology	No relevant intervention - metformin plus a hypocaloric diet
Fabbrocini, G. R., A. B.,Thouvenin, M. D.,Peraud, C.,Mengeaud, V.,Bacquey, A.,Saint Aroman, M.Fragility of epidermis: acne and post-procedure lesional skin. 2017. Journal of the European Academy of Dermatology and Venereology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Faghihi, G. J., K.,Tajmirriahi, N.,Abtahi-Naeini, B.,Nilforoshzadeh, M.,Radan, M.,Hosseini, S. M.The efficacy of oral isotretinoin versus cyproterone compound in female patients with acne and the triad of cutaneous hyperandrogenism: A randomized clinical trial. 2014. Advanced Biomedical Research	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Faghihi, G. K.-I., A.,Hosseini, S. M.,Radan, M. R.,Nilforoushzadeh, M. A. Efficacy of intense pulsed light combined with topical erythromycin solution 2% versus topical erythromycin solution 2% alone in the treatment of persistent facial erythematous acne macules. 2015. Journal of isfahan medical school	No relevant study design - not RCT
Faghihi, G. R., M.,Abtahi-Naeini, B.,Nilforoushzadeh, M. A.The efficacy of 5% dapsone gel plus oral isotretinoin versus oral isotretinoin alone in acne vulgaris: A randomized double-blind study. 2014. Advanced Biomedical Research	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Faghihi, G. V., A.,Asilian, A.,Radan, M. R.,Esteki, H.,Elahidoost, M.Comparative efficacy of filtered blue light (emitted from sunlight) and topical erythromycin solution in acne treatment: A randomized controlled clinical trial. 2011. Journal of Pakistan Association of	No relevant study design - not RCT (split face study but same treatments always applied to left &

Reference	Reason for exclusion
Dermatologists	right)
Faloia, E. F., S.,Mancini, V.,Morosini, P.,De Pirro, R.Treatment with a gonadotropin-releasing hormone agonist in acne or idiopathic hirsutism. 1993. Journal of Endocrinological Investigation	No relevant study design - not RCT
Falsetti, L. Acne treatment with a new estroprogestinic biphasic combination containing desogestrel. 1991. Acta Europaea Fertilitatis	Not obtainable
Fan, L. H., Xu, C. R.A randomised controlled trial of Bimaisen (Compound Erythromycin and Benzoyl Peroxide) versus metronidazole in the treatment of acne (Chinese). 1998. Journal of clinical dermatology	Not in English language
Fanta, D. S., N.Miconazole-benzoyl peroxide: a new combination for extending the topical therapy of acne. 1984. Zeitschrift fur hautkrankheiten	Not in English language
Farina, M. C., L.,Palumbo, M.,De Leo, V.,Morgante, G.,Cianci, A.Effectiveness of an oral contraceptive containing ethinyl-estradiol combined with drospirenone in the treatment of symptomatic hyperandrogenism. 2006. Italian journal of gynaecology and obstetrics	No relevant study popualtion - article reports 2 trials, both of which are in people with hyperandrogenism and study is not relevant for PCOS, maintenance or refractory treatments
Farrell, L. N. S., J. S.,Stranieri, A. M.The treatment of severe cystic acne with 13-cis-retinoic acid. Evaluation of sebum production and the clinical response in a multiple-dose trial. 1980. Journal of the American Academy of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Fatemi, F. N., J.,Nasab, S. S.,Nilforoushzadeh, M. A. Treatment of acne vulgaris using the combination of topical erythromycin and Miconazole. 2014. Journal of Skin and Stem Cell	Insufficent detail in reporting - unclear how many participants received each treatment
Fatum, B. H., H. H. V.,Mortensen, E.Topical treatment of acne vulgaris with the vitamin A acid derivate motretinide (Tasmaderm), tretinoin (Airol) and a placebo cream. 1980. Ugeskrift for laeger	Not in English language
Feldman, S. R. T., J.,Poulin, Y.,Dirschka, T.,Kerrouche, N.,Manna, V.The efficacy of adapalene-benzoyl peroxide combination increases with number of acne lesions. 2011. Journal of the American Academy of Dermatology	No relevant data reported - meta-analysis of Thiboutot 2007, Gollnick 2009, and Stein Gold 2009
Fenske, N. A. M., J. L. Cutaneous pigmentation due to minocycline hydrochloride. 1980. Journal of the American Academy of Dermatology	No relevant study design - not RCT
Ferahbas, A. U., S.,Aykol, D.,Borlu, M.,Uksal, U.Clinical Evaluation of Roxithromycin: A Double-Blind, Placebo-Controlled and Crossover Trial in Patients with Acne Vulgaris. 2004. Journal of Dermatology	No relevant study population - insufficient information reported about acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Fernandez, J. R. R., K.,Voronkov, M.,Feng, X.,Stock, J. B.,Stock, M.,Gordon, J. S.,Shroot, B.,Christensen, M. S.,Perez, E.SIG1273: a new cosmetic functional ingredient to reduce blemishes and Propionibacterium acnes in acne prone skin. 2012. Journal of	No relevant intervention - Disodium Tetramethylhexadecenyl succinyl Cysteine

Reference	Reason for exclusion
Cosmetic Dermatology	
Feucht, C. L. A., B. S.,Chalker, D. K.,Smith, J. G., Jr.Topical erythromycin with zinc in acne. A double-blind controlled study. 1980. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Fisher, A. A.Erythromycin "free base" -a nonsensitizing topical antibiotic for infected dermatoses and acne vulgaris. 1977. Cutis	No relevant article type - non-systematic review
Fisk, W.A., Lev-Tov, H.A., Sivamani, R.K. Botanical and phytochemical therapy of acne: a systematic review. 2014. Phytother Res	No relevant intervention - systematic review about the use of botanical agents in the treatment of acne
Fleischer, A. B. S., A.,Eichenfield, L. F.,Abramovits, W.,Lucky, A.,Garrett, S.Dapsone gel 5% in combination with adapalene gel 0.1%, benzoyl peroxide gel 4% or moisturizer for the treatment of acne vulgaris: a 12-week, randomized, double-blind study. 2010. Journal of drugs in dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Fluhr, J. W. B., B.,Gloor, M.,Hoffler, U.In-vitro and in-vivo efficacy of zinc acetate against Propionibacteria alone and in combination with erythromycin. 1999. Zentralblatt fur Bakteriologie	No relevant study population - sample includes people with mild to severe acne
Fonseca, E. F., C.,Camarasa, J. G.,Olmos, L.,Del Pinos, J.,Rodriguez, T.,San Martin, J. C.,Roman, P.,Asin, M.,Sambricio, F.,et al.,Erythromycin lauryl sulphate in combination with tretinoin in the topical treatment of acne vulgaris. A multicentre double-blind clinical trial. 1995b. Journal of dermatological treatment	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Fonseca, E. F., C.,Camarasa, J. G.Erythromycin lauryl sulphate in combination with tretinoin in the topical treatment of acne vulgaris. A multicentrie double-blind clinical trial. 1995a. Indian journal of dermatology, venerology and leprology	Duplicate record
Forbat, E. A.-N., F.Nonvascular uses of pulsed dye laser in clinical dermatology. 2019. Journal of Cosmetic Dermatology.	Duplicate record
Francomano, M. G., G.,Bertoni, L.,Seidenari, S.Instrumental and clinical assessment of the efficacy and tolerability of a topical product with benzoyl peroxide combined with a detergent for acneic skin. 2000. Giornale italiano di dermatologia e venereologia	Not in English language
Frank, S. B. Topical treatment of acne with a tetracycline preparations: results of a multi-group study. 1976. Cutis	No relevant study design - not RCT
Franz, E. R., B.,Weidner-Strahl, S.The effectiveness of topical antibacterials in acne: a double-blind clinical study. 1978. Journal of International Medical Research	Not obtainable
Fraser, N. B. M., R. A.,Stewart, T. W.,Thornton, E. J.Treatment of acne vulgaris comparing two similar lotion formulations, one with ('Actinac') and one without chloramphenicol. 1980. Current Medical Research & Opinion	No relevant comparison - Actinac with/without chloramphenicol
Fried, R. N., M.Acne quality of life and patient satisfaction following treatment with tretinoin pump. 2009. Journal of Drugs in Dermatology: JDD	No relevant study design - not RCT
Fu, W. W., Fang, L., Gu, J., Shun, J. F. Clinical efficacy and safety of 5% benzoyl peroxide gel combined with 0.1% adapalene gel in the	Not in English language

Reference	Reason for exclusion
treatment of acne vulgaris: a multicenter, randomized study. 2003. Chinese journal of dermatology	
Fulton, J. E., Jr.,Pablo, G.Topical antibacterial therapy for acne. Study of the family of erythromycins. 1974. Archives of Dermatology	No relevant data reported
Fyrand, O. J., H. B. Water-based versus alcohol-based benzoyl peroxide preparations in the treatment of acne vulgaris. 1986. Dermatologica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Galvin, S. A. G., R.,Baker, M.,Guibal, F.,Tuley, M. R.Comparative tolerance of adapalene 0.1% gel and six different tretinoin formulations. 1998. British Journal of Dermatology, Supplement	No relevant study population - participants did not have acne
Gammon, W. R. M., C.,Lantis, S.Comparative efficacy of oral erythromycin versus oral tetracycline in the treatment of acne vulgaris. A double-blind study. 1986. Journal of the American Academy of Dermatology	Dosage of erythromycin lower than BNF value
Gandola, M. A., G.,Barba, C.,Bassi, R.,Binazzi, M.,Landi, G.,Levi, L.,Randazzo, D.,Serri, F.,Villano, A. P.Topical vitamin A acid in the treatment of acne vulgaris (a controlled multicenter trial). 1976. Archives for dermatological research = archiv fur dermatologische forschung	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Gans, E. H. K., A. M. Comparative efficacy of clindamycin and benzoyl peroxide for in vivo suppression of Propionibacterium acnes. 2002. Journal of Dermatological Treatment	No relevant data reported - pharmokinetic study
Garg, V. K. S., S.,Sarkar, R.Glycolic acid peels versus salicylic-mandelic acid peels in active acne vulgaris and post-acne scarring and hyperpigmentation: a comparative study. 2009. Dermatologic Surgery	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Geiger, J. M. H., L.,Harms, M.,Saurat, J. H.Oral 13-cis retinoic acid is superior to 9-cis retinoic acid in sebosuppression in human beings. 1996. Journal of the American Academy of Dermatology	No relevant study population - participants did not have acne
Genina, E. A. B., A. N.,Simonenko, G. V.,Odoevskaya, O. D.,Tuchin, V. V.,Altshuler, G. B.Low-intensity indocyanine-green laser phototherapy of acne vulgaris: pilot study. 2004. Journal of biomedical optics	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ghovvati, M., Kord Afshari, G., Ahmad Nasrollahi, S., Firooz, A., Samadi, A., Karimi, M., Talebi, Z., Kolahdooz, S., Vazirian, M. Efficacy of topical cinnamon gel for the treatment of facial acne vulgaris: A preliminary study. 2019. Biomedical Research and Therapy	No relevant study design - not RCT
Gibson, J. R. D., C. R.,Harvey, S. G.,Barth, J.Oral trimethoprim versus oxytetracycline in the treatment of inflammatory acne vulgaris. 1982. British Journal of Dermatology	No relevant study population - insufficient information reported about acne severity and study is not relevant for PCOS, maintenance or refractory treatments

Reference	Reason for exclusion
Gibson, J. R.Azelaic acid 20% cream (AZELEX) and the medical management of acne vulgaris. 1997. Dermatology Nursing	No relevant article type - expert review
Gloor, M. H., A.,Friederich, H. C.Trial of benzoyl peroxide treatment of acne vulgaris. EXPERIMENTELLE UNTERSUCHUNGEN ZUR BENZOYLPEROXYDTHERAPIE DER ACNE VULGARIS. 1975. ZHAUTKR	Not in English language
Goforoushan, F. A., H.,Goldust, M.Efficacy of vitamin E to prevent dermal complications of isotretinoin. 2013. Pakistan Journal of Biological Sciences	No relevant comparison - compares efficacy of treatment to alleviate isotretinoin dermal complications
Goh, C. L. T., M. B.,Briantais, P.,Kaoukhov, A.,Soto, P.Adapalene gel 0.1% is better tolerated than tretinoin gel 0.025% among healthy volunteers of various ethnic origins. 2009. Journal of Dermatological Treatment	No relevant study population - participants did not have acne
Gold, L. S. B., H.,Rueda, M. J.,Kerrouche, N.,Dreno, B.Adapalene-benzoyl peroxide gel is efficacious and safe in adult female acne, with a profile comparable to that seen in teen-aged females. 2016. Journal of Clinical and Aesthetic Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Gold, L. S., Dhawan, S., Weiss, J., Draelos, Z. D., Ellman, H., Stuart, I.Open-label extension study evaluating long-term safety and efficacy of FMX101 4% minocycline foam for moderate-to-severe acne vulgaris. 2019. Journal of Clinical and Aesthetic Dermatology	No relevant data reported - reported reports results on open-label part of trial only
Gold, M. H. B., V. L.,Boring, M. M.,Bridges, T. M.,Biron, J. A.,Carter, L. N.The use of a novel intense pulsed light and heat source and ALA-PDT in the treatment of moderate to severe inflammatory acne vulgaris. 2004. Journal of Drugs in Dermatology: JDD	No relevant study design - not RCT
Gold, M. H. R., J.,Goldman, M. P.,Bridges, T. M.,Bradshaw, V. L.,Boring, M. M.,Guider, A. N.A multicenter clinical evaluation of the treatment of mild to moderate inflammatory acne vulgaris of the face with visible blue light in comparison to topical 1% clindamycin antibiotic solution. 2005. Journal of drugs in dermatology : JDD	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Gold, M. H. S., N. S.,Bradshaw, V. L.,Boring, M. M.A randomized, controlled, double-blind study of localized low-heat treatment of acne lesions. 2007. Cosmetic Dermatology	No relevant data reported - response study
Gold, M. H. S., W.,Biron, J. A.Clinical efficacy of home-use blue-light therapy for mild-to moderate acne. 2011. Journal of Cosmetic and Laser Therapy	No relevant intervention - only 2 individual lesions treated per patient
Gold, M. H., Korotkor., A.Sub-group analyses from a trial of a fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 3.75% gel for the treatment of moderate-to-severe acne vulgaris. 2015. Journal of Clinical and Aesthetic Dermatology	No relevant article type - non-systematic review
Gold, M. R. M., A. P.A randomised, double-blind, multicentre, multinational comparison of 2% fusidic acid lotion and 1% clindamycin lotion in patients with acne vulgaris on the face. 1996. European journal of clinical research	Not obtainable
Goldman, M. P. B., S. M.A single-center study of aminolevulinic acid and 417 NM photodynamic therapy in the treatment of moderate to	No relevant study design - not RCT

Reference	Reason for exclusion
severe acne vulgaris. 2003. Journal of Drugs in Dermatology: JDD	
Goldstein, J. A. S.-S., A.,Thomsen, R. J.,Pochi, P. E.,Shalita, A. R.,Strauss, J. S.Comparative effect of isotretinoin and etretinate on acne and sebaceous gland secretion. 1982. Journal of the American Academy of Dermatology	No relevant comparison - isotretinoin vs etretinate
Gollnick, H. G., K.Azelaic acid for the treatment of acne: Comparative trials. 1989. Journal of Dermatological Treatment	No relevant article type - expert review
Gollnick, H. P. G., K.,Zaumseil, R. P.Azelaic acid 15% gel in the treatment of acne vulgaris. Combined results of two double-blind clinical comparative studies. 2004. Journal der Deutschen Dermatologischen Gesellschaft [Journal of the German Society of Dermatology]	Not in English language
Gollnick, H. P. M. V., K.,Hermann, J.,Blume, U.,Hahn, H.,Haustein, U. F.,Orfanos, C. E.Topical quinolone OPC-7251: A clinical and microbiological study in acne. 1994. European Journal of Dermatology	No information on the baseline severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Goltz, R. W. C., G. M.,Schnieders, J. R.,Neidert, G. L.A comparison of Cleocin T 1 percent solution and Cleocin T 1 percent lotion in the treatment of acne vulgaris. 1985. Cutis	No relevant data - insufficient data reported
Goltz, R. W. K., S.Oral tetracycline treatment on bacterial flora in acne vulgaris. 1966. Archives of Dermatology	No relevant data reported - bacterial flora study
Gonzalez, P. V., R.,Cirigliano, M.The tolerability profile of clindamycin 1%/benzoyl peroxide 5% gel vs. adapalene 0.1%/benzoyl peroxide 2.5% gel for facial acne: Results of a randomized, single-blind, split-face study. 2012. Journal of Cosmetic Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Goodfellow, A. A.-Z., J.,Carter, G.Oral spironolactone improves acne vulgaris and reduces sebum excretion. 1984. British Journal of Dermatology	No relevant outcomes reported
Goreshi, R. S., A.,Ehst, B. D.A double-blind, randomized, bilateral comparison of skin irritancy following application of the combination acne products clindamycin/tretinoin and benzoyl peroxide/adapalene. 2012. Journal of Drugs in Dermatology	No relevant outcomes reported
Goswami, B. C. B., B.,Barua, A. B.,Olson, J. A. Topical retinoyl beta-glucuronide is an effective treatment of mild to moderate acne vulgaris in Asian-Indian patients. 1999. Skin Pharmacology & Applied Skin Physiology	No relevant intervention - retinoyl beta-glucuronide
Goujon, C. G., P.,Violin, L.,Larnier, C.Biometric and clinical comparative assay of Roaccutane gel (0.05% isotretinoin) versus Retacnyl cream (0.05% tretinoin) in the treatment of moderate retentional acne on the face. 1995. Nouvelles Dermatologiques	Not in English language
Gould, D. J. E., R.,Cunliffe, W. J.Oral tetracycline and retinoic acid gel in acne. 1978. Practitioner	No relevant study design - unclear if RCT
Graupe, K. C., W. J.,Gollnick, H. P.,Zaumseil, R. P.Efficacy and safety of topical azelaic acid (20 percent cream): an overview of results from European clinical trials and experimental reports. 1996. Cutis	No relevant study design - not RCT
Green, L. C., M.,Gwazdauskas, J. A.,Gonzalez, P.The tolerability profile of clindamycin 1%/benzoyl peroxide 5% gel vs. adapalene 0.1%/benzoyl peroxide 2.5% gel for facial acne: Results of two randomized, single-blind, split-face studies. 2012. Journal of Clinical and Aesthetic Dermatology	No relevant data reported - reports pooled results from 2 trials combined

Reference	Reason for exclusion
Green, L. J. D. R., J. Q.Efficacy and Tolerability of a Three-Step Acne System Containing a Solubilized Benzoyl Peroxide Lotion versus a Benzoyl Peroxide/Clindamycin Combination Product: An Investigator-Blind, Randomized, Parallel-Group Study. 2008. The Journal of Clinical & Aesthetic Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Green, L. K., L. H.,Gwazdauskas, J.Randomized, controlled, evaluator-blinded studies conducted to compare the efficacy and tolerability of 3 over-the-counter acne regimens in subjects with mild or moderate acne. 2013. Journal of drugs in dermatology	No relevant comparison - compares over-the-counter 3-part skin care regimens inclunding BPO, SAL etc which have been discontinued (MaxClarity, Proactiv, Murad)
Greenwood, R. B., B.,Cunliffe, W. J.Evaluation of a therapeutic strategy for the treatment of acne vulgaris with conventional therapy. 1986. British Journal of Dermatology	No relevant study design - not RCT
Gregory, A. N. T., C. R.,Leibowitz, K. R.,Lane, M.A study on the use of a novel light and heat energy system to treat acne vulgaris. 2004. Cosmetic Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Griffiths, C. E. E., J. T.,Bernard, B. A.,Rossio, P.,Cromie, M. A.,Finkel, L. J.,Shroot, B.,Voorhees, J. J.Comparison of CD271 (adapalene) and all-trans retinoic acid in human skin: dissociation of epidermal effects and CRABP-II mRNA expression. 1993. Journal of Investigative Dermatology	No relevant study population - participants did not have acne
Grimes, P. C., V.Tazarotene cream for postinflammatory hyperpigmentation and acne vulgaris in darker skin: A double-blind, randomized, vehicle-controlled study. 2006. Cutis	No relevant study population - sample includes people with post-inflammatory hyperpigmentation and acne and study is not relevant for PCOS, maintenance or refractory treatments
Grosshans, E. F., A.,Guibaud, B.Clinical evaluation of a topical ethyl lactate treatment of acne vulgaris (author's transl). 1978. Annales de dermatologie ET de venereologie	Not English language
Grosshans, E. M., R.,Mascaro, J. M.,Torras, H.,Meynadier, J.,Alirezai, M.,Finlay, A. Y.,Soto, P.,Poncet, M.,Verschoore, M.,Clucas, A.Evaluation of clinical efficacy and safety of adapalene 0.1% gel versus tretinoin 0.025% gel in the treatment of acne vulgaris, with particular reference to the onset of action and impact on quality of life. 1998. British Journal of Dermatology, Supplement	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Grove, G. Z., C.,Gwazdauskas, J.Tolerability and irritation potential of four topical acne regimens in healthy subjects. 2013. Journal of Drugs in Dermatology	No relevant study population - participants did not have acne

Reference	Reason for exclusion
Gruber, F. G.-G., H.,Kastelan, M.,Brajac, I.,Lenkovic, M.,Zamolo, G.Azithromycin compared with minocycline in the treatment of acne comedonica and papulo-pustulosa. 1998b. Journal of Chemotherapy	No relevant study design - not RCT
Gu, W. Z., X. Q.,Wu, J. D.Cuochuang Heji and acupuncture and cupping treatment on acne vulgaris. 2016b. Liaoning journal of traditional chinese medicine [liaoning zhong yi za zhi]	No relevant intervention - Cuochuang Heji and acupuncture
Gu,Cuochuang Heji and acupuncture and cupping treatment on acne vulgaris. 2016a. NA	Duplicate record
Guerrier, C. J. W. T., E. J.Double-blind comparison of two similar lotion formulations, one without and the other with hydrocortisone acetate ('Actinac') in the treatment of acne vulgaris. 1980. Current Medical Research and Opinion	No relevant comparison - Actinac with/without chloramphenicol
Guin, J. D.Topical clindamycin: A double-blind study comparing clindamycin phosphate with clindamycin hydrochloride. 1979. International Journal of Dermatology	No relevant study population - insufficient information to determine acne severity
Guin, J. D.Treatment of acne vulgaris with topical clindamycin phosphate: a double-blind study. 1981. International Journal of Dermatology	No relevant study population - insufficient information to determine acne severity
Gunning, D. B. B., A. B.,Lloyd, R. A.,Olson, J. A.Retinoyl beta-glucuronide: A nontoxic retinoid for the topical treatment of acne. 1994. Journal of Dermatological Treatment	No relevant intervention - retinoyl beta-glucuronide
Gupta, A. K. G., M. D.,Abramovits, W.Ziana (clindamycin phosphate 1.2% and tretinoin 0.025%)gel. 2007. SKINmed	No relevant study design - not RCT
Gwiezdzinski, Z. U., S.,Szelemej, R.2.5% Solution of flutamide (a nonsteroidal antiandrogen) in the topical treatment of acne vulgaris. A double-blind randomized study. 1997. Journal of Dermatological Treatment	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Habbema, L. K., B.,Menke, H. E.,Doornweerd, S.,De Boulle, K.A 4% erythromycin and zinc combination (Zineryt) versus 2% erythromycin (Eryderm) in acne vulgaris: A randomized, double-blind comparative study. 1989a. British Journal of Dermatology	No relevant data reported - study does not report number of participants randomised or who completed in each group
Habbema, L. K., B.,Menke, H. E.,Doornweerd, S.,De, B. K.A 4% erythromycin and zinc combination (Zineryt (R)) versus 2% erythromycin (Eryderm (R)) in acne vulgaris: a randomized, double-blind comparative study. 1989b. British journal of dermatology	Duplicate record
Haedersdal, M. T.-B., K.,Wiegell, S. R.,Wulf, H. C.Long-pulsed dye laser versus long-pulsed dye laser-assisted photodynamic therapy for acne vulgaris: A randomized controlled trial. 2008. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Hajheydari, Z. S., M.,Morteza-Semnani, K.,Soltani, A.Effect of Aloe vera topical gel combined with tretinoin in treatment of mild and moderate acne vulgaris: A randomized, double-blind, prospective trial. 2014. Journal of Dermatological Treatment	No relevant intervention - aloe vera
Halbe, H. W. d. M., N. R.,Bahamondes, L.,Petracco, A.,Lemgruber, M.,de Andrade, R. P.,da Cunha, D. C.,Guazelli, C. A.,Baracat, E. C.Efficacy and acceptability of two monophasic oral contraceptives containing ethinylestradiol and either desogestrel or gestodene. 1998.	No relevant study population - participants did not have acne

Reference	Reason for exclusion
The European journal of contraception & reproductive health care : the official journal of the European Society of Contraception	
Hammerstein, J. M., J.,Leo-Rossberg, I.,Moltz, L.,Zielske, F.Use of cyproterone acetate (CPA) in the treatment of acne, hirsutism and virilism. 1975. Journal of Steroid Biochemistry	No relevant study design - not RCT
Han, G., Armstrong, A. W., Desai, S. R., Guenin, E.Novel Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris in an Asian Population. 2019. Journal of drugs in dermatology : JDD	Not obtainable
Handojo, I.Retinoic acid cream (Airol cream) and benzoyl-peroxide in the treatment of acne vulgaris. 1979b. Southeast Asian Journal of Tropical Medicine & Public Health	No relevant study population - insufficient information to determine acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Handojo, I.The combined use of topical benzoyl peroxide and tretinoin in the treatment of acne vulgaris. 1979a. International Journal of Dermatology	No relevant study population - insufficient information to determine acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Harcup, J. W. C., J.The treatment of acne vulgaris in general practice. A double-blind assessment of co-trimoxazole and tetracycline. 1980. Practitioner	No relevant study population - insufficient information to determine acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Hare, P. J.Benzoyl peroxide gel compared with retinoic acid in acne vulgaris. 1975. British Journal of Clinical Practice	No relevant study design - not RCT
Harms, M. P., I.,Ceyrac, D.,Saurat, J. H.Isotretinoin ineffective topically. 1985. Lancet (london, england)	No relevant study design - not RCT
Harper, J. C. R., W. E.,Zeichner, J. A.,Guenin, E.,Bhatt, V.,Pillai, R.Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris: assessment of safety and tolerability in subgroups. 2019. Journal of Dermatological Treatment.	No relevant data reported - post hoc subgroup analyis by ethncity and sex of Tyring 2019
Harper, J. C., Baldwin, H., Stein Gold, L., Guenin, E.Efficacy and Tolerability of a Novel Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate or Severe Acne Vulgaris in Adult Females. 2019. Journal of drugs in dermatology : JDD	Not obtainable
Harper, J. C., Roberts, W. E., Zeichner, J. A., Guenin, E., Bhatt, V., Pillai, R.Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris: assessment of safety and tolerability in subgroups. 2020. Journal of Dermatological Treatment	No relevan data reported - reports post hoc analysis of Tyring 2018
Harper, J. C.Gender as a clinically relevant outcome variable in acne: benefits of a fixed combination clindamycin phosphate (1.2%) and benzoyl peroxide (2.5%) aqueous gel. 2012. Journal of Drugs in Dermatology: JDD	No relevant data reported - post hoc subgroup analysis presenting data for male and female groups straitified by age
Harper, J. C.The efficacy and tolerability of a fixed combination clindamycin (1.2%) and benzoyl peroxide (3.75%) aqueous gel in patients with facial acne vulgaris: Gender as a clinically relevant outcome variable. 2015. Journal of Drugs in Dermatology	No relevant data reported - post hoc subgroup analysis by gender of Pariser 2014
Hashimoto, Y. S., Y.,Mizuno, Y.,Hasegawa, T.,Matsuba, S.,Ikeda,	No relevant study design -

Reference	Reason for exclusion
S.,Monma, T.,Ueda, S.Salicylic acid peels in polyethylene glycol vehicle for the treatment of comedogenic acne in Japanese patients. 2008. Dermatologic Surgery	not RCT
Hatwal, A. B., R. P.,Agrawal, J. K.,Singh, G.,Bajpai, H. S.Spironolactone and cimetidine in treatment of acne. 1988. Acta Dermato-Venereologica	No relevant intervention - h2-receptor antagonist - cimetidine
Hayashi, N. K., E.,Nogita, T.,Fujiyama, M.,Kawashima, M.A randomized placebo-controlled investigator-blinded face split study of 20% azelaic acid cream to evaluate the efficacy and safety in Japanese patients with acne vulgaris. 2012. Journal of Dermatology	No relevant article type - conference abstract
Hayashi, N. K., I.,Siakpere, O.,Endo, A.,Hatanaka, T.,Yamada, M.,Kawashima, M.Clindamycin phosphate 1.2%/benzoyl peroxide 3% fixed-dose combination gel versus topical combination therapy of adapalene 0.1% gel and clindamycin phosphate 1.2% gel in the treatment of acne vulgaris in Japanese patients: A multicenter, randomized, investigator-blind, parallel-group study. 2018. Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Hayashi, N. K., M. Multicenter randomized controlled trial on combination therapy with 0.1% adapalene gel and oral antibiotics for acne vulgaris: Comparison of the efficacy of adapalene gel alone and in combination with oral faropenem. 2012. Journal of Dermatology	No relevant intervention - intervention & class not available in the UK
Hayashi, N. K., M. Study of the usefulness of moisturizers on adherence of acne patients treated with adapalene. 2014. Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Hayashi, N. K., M.Efficacy of oral antibiotics on acne vulgaris and their effects on quality of life: a multicenter randomized controlled trial using minocycline, roxithromycin and faropenem. 2011. Journal of Dermatology	No relevant intervention - intervention & class not available in the UK
Hebert, A., Thiboutot, D., Stein Gold, L., Cartwright, M., Gerloni, M., Fragasso, E., Mazzetti, A. Efficacy and Safety of Topical Clascoterone Cream, 1%, for Treatment in Patients with Facial Acne: Two Phase 3 Randomized Clinical Trials. 2020. JAMA Dermatology.	No relevant intervention - scoterone cream in the UK
Hellgren, L. V., J. Changes of skin surface lipids in acne vulgaris after treatment with trimethoprim-sulphamethoxazole. 1976. Dermatologische Monatsschrift	Not in English language
Hellgren, L. V., J.Topical erythromycin for acne vulgaris. 1980. Dermatologica	No relevant data reported - participants received intervention for between 4 and 8 weeks
Herndon, J. H., Jr.,Stephens, T. J.,Trookman, N. S.,Rizer, R. L.,Preston, N.,Caveney, S.,Gottschalk, R. W.A comparison of the tolerability of adapalene 0.1% cream and adapalene 0.1% lotion in healthy individuals. 2012. SKINmed	No relevant study population - participants did not have acne
Hersle, K. G., H.Minocycline in acne vulgaris: a double blind study. 1976. Current Therapeutic Research - Clinical and Experimental	No relevant study population - insufficient information to determine acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Heymann, W. R.Hyperandrogenism and the skin. 2004. Journal of the American Academy of Dermatology	No relevant study design - not RCT

Reference	Reason for exclusion
Hjorth, N. G., K.Azelaic acid for the treatment of acne. A clinical comparison with oral tetracycline. 1989. Acta Dermato-Venereologica. Supplementum	No relevant data - insufficient data reported
Hjorth, N. S., D.,Dela, K.Topical anhydrous aluminum chloride formulation in the treatment of acne vulgaris: A double-blind study. 1985. Cutis	No relevant study population - insufficient information reported about acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Hjorth, N. S., H.,Thomsen, K.,Dela, K.Meclosorb(), a new topical antibiotic agent in the treatment of acne vulgaris: A double-blind clinical study. 1984. Acta Dermato-Venereologica	No relevant study population - insufficient information reported about acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Ho, S. G. Y., C. K.,Chan, N. P.,Shek, S. Y.,Kono, T.,Chan, H. H.A retrospective analysis of the management of acne post-inflammatory hyperpigmentation using topical treatment, laser treatment, or combination topical and laser treatments in oriental patients. 2011. Lasers in Surgery & Medicine	Duplicate record
Hong, S. B. L., M. H.Topical aminolevulinic acid-photodynamic therapy for the treatment of acne vulgaris. 2005. Photodermatology, Photoimmunology & Photomedicine	No relevant study design - not RCT
Hongcharu, W. T., C. R.,Chang, Y.,Aghassi, D.,Suthamjariya, K.,Anderson, R. R.Topical ALA-photodynamic therapy for the treatment of acne vulgaris. 2000. Journal of Investigative Dermatology	Efficacy outcomes reported in figures only
Honorato, J. A., J. R.,Sandoval, C. A.,Quintanilla, E.Double-blind, randomized and controlled clinical trial on the efficacy of topical clindamycin in the treatment of acne. 1988. Revista de farmacologia clinica y experimental	Not in English language
Horfelt, C. S., B.,Larko, O.,Faergemann, J.,Wennberg, A. M.Photodynamic therapy for acne vulgaris: a pilot study of the dose-response and mechanism of action. 2007. Acta Dermato-Venereologica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Hubbell, C. G. H., E. R.,Rist, T.,White Jr, J. W.Efficacy of minocycline compared with tetracycline in treatment of acne vulgaris. 1982. Archives of Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Hughes, B. R.A double blind evaluation of topical isotretinoin, benzoyl peroxide and placebo in patients with acne. Abstract. 1989. British journal of dermatology	No relevant article type - conference abstract
Hurwitz, S.The combined effect of vitamin A acid and benzoyl peroxide in the treatment of acne. 1976. Cutis	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory

Reference	Reason for exclusion
	treatments
Ianosi, S. N., D.,Branisteanu, D. E.,Popescu, M.,Calina, D.,Zlatian, O.,Docea, A. O.,Marinas, M. C.,Iordache, A. M.,MitruÈ›, P.,et al.,Comparative efficacy of oral contraceptive versus local treatment versus intense pulsed light combined with vacuum in endocrine acne in women. 2018. Journal of biological regulators and homeostatic agents	No relevant outcomes reported
Ibbotson, S. H.Topical 5-aminolaevulinic acid photodynamic therapy for the treatment of skin conditions other than non-melanoma skin cancer. 2002. British Journal of Dermatology	Duplicate record
Iglesias, L.Everyday doxycycline (oral) for 16 weeks vs everyday doxycycline (oral) for the first 4 weeks and on alternate days for the next 12 weeks in the treatment of acne vulgaris. (Spanish). 1992. Actas dermo-sifiliograficas	Not in English language
Ikeno, H. O., K.Open study comparing sodium L-ascorbyl-2-phosphate 5% lotion versus adapalene 0.1% gel for acne vulgaris. 2007. Cosmetic Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ilknur, T. D., M.,Bicak, M. U.,Ozkan, S.Glycolic acid peels versus amino fruit acid peels for acne. 2010. Journal of Cosmetic and Laser Therapy	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
In Jae, J. D. J., H.,Dong Hyun, K.,Yoon, M. S.,Lee, H. J.Comparative study of buffered 50% glycolic acid (pH 3.0) + 0.5% salicylic acid solution vs Jessner's solution in patients with acne vulgaris. 2018. Journal of cosmetic dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Inman, P. G., B.,McNay, R. A.Acne and the pill. 1971. Newcjiedj	Not obtainable
Iraji, F. M., A.,Naji, S. M.,Siadat, A. H.The efficacy of topical cyproterone acetate alcohol lotion versus placebo in the treatment of the mild to moderate acne vulgaris: A double blind study. 2006. Dermatology Online Journal	No relevant intervention - topical cyproterone acetate alcohol lotion
Ito, K. M., S.,Hamada, M.,Tokunaga, T.,Kokuba, H.,Tashiro, K.,Yano, I.,Yasumoto, S.,Imafuku, S.Efficacy and Safety of the Traditional Japanese Medicine Keigairengyoto in the Treatment of Acne Vulgaris. 2018b. Dermatology Research and Practice	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ito,Efficacy and Safety of the Traditional Japanese Medicine Keigairengyoto in the Treatment of Acne Vulgaris. 2018a. NA	Duplicate record
Jaffary, F. F., G.,Saraeian, S.,Hosseini, S. M.Comparison the effectiveness of pyruvic acid 50% and salicylic acid 30% in the	Reported outcomes relevant for the network

Reference	Reason for exclusion
treatment of acne. 2016. Journal of research in medical sciences	meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Jaffary, F. N., M. A.,Koupaiee, H. S.,Faghihi, G.,Hosseini, S. M.,Sokhanvari, F.,Ansari, N.,Sadeghian, G.Omeprazole versus doxycycline combination therapy with topical erythromycin the treatment of acne vulgaris: a randomized clinical trial. 2017. Tehran university medical journal	Not in English language
Jaffe, G. V. G., J. J.,Constad, D.Benzoyl peroxide in the treatment of acne vulgaris: a double-blind, multi-centre comparative study of 'Quinoderm' cream and 'Quinoderm' cream with hydrocortisone versus their base vehicle alone and a benzoyl peroxide only gel preparation. 1989. Current Medical Research and Opinion	No relevant study design - not RCT
Jang, M. S. D., K. S.,Kang, J. S.,Jeon, Y. S.,Suh, K. S.,Kim, S. T.A comparative split-face study of photodynamic therapy with indocyanine green and indole-3-acetic acid for the treatment of acne vulgaris. 2011. British Journal of Dermatology	No relevant study design - not RCT
Jarratt, M. T. B., T.Efficacy and safety of clindamycin-tretinoin gel versus clindamycin or tretinoin alone in acne vulgaris: A randomized, double-blind, vehicle-controlled study. 2012. Journal of Drugs in Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Jarratt, M. T. J., T. M.,Chang-Lin, J. E.,Tong, W.,Berk, D. R.,Lin, V.,Kaoukhov, A.Safety and pharmacokinetics of once-daily dapsone gel, 7.5% in patients with moderate acne vulgaris. 2016. Journal of Drugs in Dermatology	No relevant study population - sample includes mild to severe acne. Participants had 20 to 50 inflammatory lesions (papules and pustules)
Jarratt, M. W., C. P.,Alio Saenz, A. B.Tazarotene foam versus tazarotene gel: A randomized relative bioavailability study in acne vulgaris. 2013. Clinical Drug Investigation	No relevant data reported - bioavailability study
Jawade, S. A. S., V. A.,Kondalkar, A. R.Efficacy and tolerability of adapalene 0.1%-benzoyl peroxide 2.5% combination gel in treatment of acne vulgaris in indian patients: A randomized investigator-blind controlled trial. 2016. Iranian Journal of Dermatology	No relevant study population - sample includes people mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Jelinek, J. J. Hydrocuorothiazide and the control of premenstrual exacerbation of acne. 1972. Arcilderii	No relevant study population -insuficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Ji, S. Z. T., P.,Li, G. Q.,Liu, L. L.,Chen, X. X.,Zhu, X. J.A comparison of 10% benzoyl peroxide cream and 5% benzoyl peroxide gel in the treatment of acne vulgaris. 2000. The chinese journal of clinical pharmacology	Not in English language
Jih, M. H. F., P. M.,Goldberg, L. H.,Robles, M.,Glaich, A. S.,Kimyai-	No relevant intervention -

Reference	Reason for exclusion
Asadi, A.The 1450-nm diode laser for facial inflammatory acne vulgaris: Dose-response and 12-month follow-up study. 2006. Journal of the American Academy of Dermatology	compares 2 fluences of 1450-nm laser
Jin, X. Y. D., W.,Hu, X.,Wang, J.,Zou, D. J.Changes of sex hormone levels in male acne patients with normal serum testosterone and effect of antiandrogen therapy. 2009. Academic journal of second military medical university	Not in English language
Johnson, K. H.Are oral contraceptives (OCPs) with antiandrogenic progestins preferred over other OCPs in patients with acne?. 2002. Journal of Family Practice	No relevant study design - not RCT
Jones, D. H. K., K.,Miller, A. J.,Cunliffe, W. J.A dose-response study of 13-cis-retinoic acid in acne vulgaris. 1983. British Journal of Dermatology	Not possible to extract relevant data
Jones, T. M. J., S.,Alio Saenz, A. B.Bioavailability of clindamycin from a new clindamycin phosphate 1.2%-benzoyl peroxide 3% combination gel. 2013. Clinical Pharmacology in Drug Development	No relevant data reported - pharmokinetic study
Jorizzo, J. G., R.,Nighland, M.Tretinoin microsphere gel in younger acne patients. 2008. Journal of drugs in dermatology : JDD	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Juhlin, L. M., G.,Ohman, S.Topical triamcinolone acetonide and chlorhydroxyquinoline in acne. 1968. Acta Derm	No relevant study population - insufficient information to determine acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Jung, J. Y. H., J. S.,Ahn, C. H.,Yoon, J. Y.,Kwon, H. H.,Suh, D. H.Prospective randomized controlled clinical and histopathological study of acne vulgaris treated with dual mode of quasi-long pulse and Q-switched 1064-nm Nd:YAG laser assisted with a topically applied carbon suspension. 2012. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Jung, J. Y. K., H. H.,Yeom, K. B.,Yoon, M. Y.,Suh, D. H.Clinical and histological evaluation of 1% nadifloxacin cream in the treatment of acne vulgaris in Korean patients. 2011. International Journal of Dermatology	No relevant intervention - intervention & class not available in the UK
Jung, J. Y. L., J. H.,Ryu, D. J.,Lee, S. J.,Bang, D.,Cho, S. B.Lower-fluence, higher-density versus higher-fluence, lower-density treatment with a 10,600-nm carbon dioxide fractional laser system: A split-face, evaluator-blinded study. 2010a. Dermatologic Surgery	Duplicate record
Jung, J. Y. Y., M. Y.,Hong, J. S.,Suh, D. H.Treatment of acne vulgaris with a low fluence 1064-nm Nd: YAG laser after applying carbon suspension. 2010b. Journal of Dermatology. Conference: 1st Eastern Asia Dermatology Congress, EADC2010. Fukuoka Japan. Conference Publication:	No relevant article type - conference abstract
Jurairattanaporn, N. C., T.,Ophaswongse, S.,Udompataikul, M.Comparative trial of silver nanoparticle gel and 1% clindamycin gel when use in combination with 2.5% benzoyl peroxide in patients with moderate acne vulgaris. 2017. Journal of the Medical Association of	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-

Reference	Reason for exclusion
Thailand	severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Jurzyk, R. S. S., R. L.,Rose, L. I.Antiandrogens in the treatment of acne and hirsutism. 1992. American Family Physician	No relevant studyd design - not RCT
Kabir, M. S., S.,Raza, A.,Kanwal, S.,Tanvir, T.Comparison of efficacy of adapalene (0.1% gel) monotherapy ve adapalene (0.1%) plus benzyl peroxide (2.5%) combination therapy for treatment of mild to moderate acne vulgaris. 2018. Pakistan Journal of Medical and Health Sciences	No relevant data reported
Kainz, J. T. B., G.,Auer-Grumbach, P.,Lackner, V.,Perl-Convalexius, S.,Popa, R.,Wolfesberger, B.Azelaic acid 20 % cream: effects on quality of life and disease severity in adult female acne patients. 2016. Journal der Deutschen Dermatologischen Gesellschaft	Duplicate record
Kakita, L. Tazarotene versus tretinoin or adapalene in the treatment of acne vulgaris. 2000. Journal of the American Academy of Dermatology	No relevant article type - commentary article
Kaminaka, C. U., M.,Matsunaka, H.,Furukawa, F.,Yamomoto, Y.Clinical evaluation of glycolic acid chemical peeling in patients with acne vulgaris: a randomized, double-blind, placebo-controlled, split-face comparative study. 2014. Dermatologic surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Kang, A. L., A.,Herrmann, J.,Moy, R.Treatment of moderate-to-severe facial acne vulgaris with solid-state fractional 589/1,319-nm laser. 2019. Journal of Clinical and Aesthetic Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Kantikosum, K. C., Y.,Chottawornsak, N.,Asawanonda, P.The efficacy of glycolic acid, salicylic acid, gluconolactone, and licochalcone a combined with 0.1% adapalene vs adapalene monotherapy in mild-to-moderate acne vulgaris: A double-blinded within-person comparative study. 2019. Clinical, Cosmetic and Investigational Dermatology	No relevant study design - not RCT
Kantner, V. S., E. Topical effects of oxytetracycline in acne vulgaris. 1970. Ceskoslovenska dermatologie	Not in English language
Kar, B. R. T., S.,Panda, M.Comparative study of oral isotretinoin versus oral isotretinoin + 20% salicylic Acid peel in the treatment of active acne. 2013. Journal of Cutaneous & Aestheic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Karoglan, A., Paetzold, B., Pereira de Lima, J., Bruggemann, H., Tuting, T., Schanze, D., Guell, M., Gollnick, H. Safety and Efficacy of	No relevant study desgin - the first phase was not

Reference	Reason for exclusion
Topically Applied Selected Cutibacterium acnes Strains over Five Weeks in Patients with Acne Vulgaris: An Open-label, Pilot Study. 2019. Acta Dermato-Venereologica	randomised and the interventions are not relevant in the second phase
Karsai, S. S., L.,Raulin, C.The pulsed-dye laser as an adjuvant treatment modality in acne vulgaris: A randomized controlled single-blinded trial. 2010. British Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Katsambas, A. T., A. A.,Stratigos, J.Topical clindamycin phosphate compared with oral tetracycline in the treatment of acne vulgaris. 1987. British Journal of Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Katz, H. I. K., S.,Akin, M. D.,Dunlap, F.,Whiting, D.,Norbart, T. C.Effect of a desogestrel-containing oral contraceptive on the skin. 2000. European Journal of Contraception & Reproductive Health Care	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kawashima, M. H., H.,Alio Saenz, A. B.,Ono, M.,Yamada, M.Clindamycin phosphate 1.2%-benzoyl peroxide 3.0% fixed-dose combination gel has an effective and acceptable safety and tolerability profile for the treatment of acne vulgaris in Japanese patients: A phase III, multicentre, randomised, single-blinded, active-controlled, parallel-group study. 2015. British Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kawashima, M. H., H.,Alio Saenz, A. B.,Ono, M.,Yamada, M.Is benzoyl peroxide 3% topical gel effective and safe in the treatment of acne vulgaris in Japanese patients? A multicenter, randomized, double-blind, vehicle-controlled, parallel-group study. 2014. Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kawashima, M. H., S.,Czernielewski, J.,Miyachi, Y.Adapalene gel 0.1% - Topical retinoid-like molecule - For the treatment of Japanese patients with acne vulgaris: A multicenter, randomized, investigator-blinded, dose-ranging study. 2007. Skin Research	No relevant population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kawashima, M. H., S.,Loesche, C.,Miyachi, Y.Adapalene gel 0.1% is effective and safe for Japanese patients with acne vulgaris: A randomized, multicenter, investigator-blinded, controlled study. 2008. Journal of Dermatological Science	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kawashima, M. N., T.,Katsuramaki, T.Open-label, randomized,	No relevant study

Reference	Reason for exclusion
multicenter, phase III study to evaluate the safety and efficacy of benzoyl peroxide gel in long-term use in patients with acne vulgaris: A secondary publication. 2017a. Journal of Dermatology	population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kawashima, M. S., S.,Furukawa, F.,Matsunaga, K.,Akamatsu, H.,Igarashi, A.,Tsunemi, Y.,Hayashi, N.,Yamamoto, Y.,Nagare, T.,et al.,Twelve-week, multicenter, placebo-controlled, randomized, double-blind, parallel-group, comparative phase II/III study of benzoyl peroxide gel in patients with acne vulgaris: a secondary publication. 2017b. Journal of dermatology	No relevant study population - includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kawashima, M. Y., M.,Parish, C.Clindamycin 1%/benzoyl peroxide 3% gel, a new topical combination product, is effective in Japanese patients with acne vulgaris. 2013. Journal of Investigative Dermatology	No relevant article type - conference abstract
Kayhan, S. S., I.,Saracoglu, Z. N.,Aksu, A. E. K.,Tozun, M.Comparison of safety and efficacy of oral azithromycin-topical adapalene versus oral doxycycline-topical adapalene in the treatment of acne vulgaris and determination of the effects of these treatments on patients' quality of life. 2012. Turkderm deri hastaliklari ve frengi arsivi	Not in English language
Kaymak, Y. T., E.,Taner, Y.Comparison of depression, anxiety and life quality in acne vulgaris patients who were treated with either isotretinoin or topical agents. 2009. International Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kelidari, H. R. S., M.,Hajheydari, Z.,Akbari, J.,Morteza-Semnani, K.,Akhtari, J.,Valizadeh, H.,Asare-Addo, K.,Nokhodchi, A.Spironolactone loaded nanostructured lipid carrier gel for effective treatment of mild and moderate acne vulgaris: A randomized, double-blind, prospective trial. 2016. Colloids and Surfaces B: Biointerfaces	No relevant intervention - intervention & class not available in the UK
Kelly, S. D., E.,Fearns, S.,McKinnon, C.,Carter, R.,Gerlinger, C.,Smithers, A.Effects of oral contraceptives containing ethinylestradiol with either drospirenone or levonorgestrel on various parameters associated with well-being in healthy women: a randomized, single-blind, parallel-group, multicentre study. 2010. Clinical drug investigation	No relevant study population - participants did not have acne
Kerscher, M. R., T.,Bayrhammer, J.,Schramm, G.Effects of an oral contraceptive containing chlormadinone and ethinylestradiol on acne-prone skin of women of different age groups: an open-label, single-centre, phase IV study. 2008. Clinical Drug Investigation	No relevant study deisgn - not RCT
Kessler, E. F., K.,Chia, C.,Rogers, C.,Anna Glaser, D.Comparison of alpha- and beta-hydroxy acid chemical peels in the treatment of mild to moderately severe facial acne vulgaris. 2008. Dermatologic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Khaki, I., Valiani, M., Mohammadbeigi, A.Evaluation the effect of auriculotherapy on the clinical signs of single girls with polycystic	No relevant intervention - acupuncture

Reference	Reason for exclusion
ovary syndrome: A single-blinded clinical trial. 2019. Clinical Cancer Investigation Journal	
Khan, M. K., N. U.,Anwar, M. I.,Noor, S. M.A comparison of the efficacy of topical adapalene gel 0.1% with tretinoin gel 0.025% in mild acne vulgaris. 2017. Journal of Pakistan Association of Dermatologists	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Kharfi, M. T., N. B.,Zeglaoui, F.,Ezzine, N.,Mokhtar, I.,Kamoun, F.,Kamoun, M. R.Evaluate the efficacy and safety of topical glycolic acid (Glyco A 12%) and retinoin acid (Kefrane 0'05%) on facial acne lesions. 2001a. Tunisie medicale	Not in English language
Kharfi, M. T., N.,Zeglaoui, F.,Ezzine, N.,Mokhtar, I.,Kamoun, F.,Kamoun, M. R.Comparative study of the efficacy and tolerance of 12% glycolic acid cream and 0.05% retinoic acid cream for polymorphic acne. 2001b. Tunisie medicale	Not in English language
Khodaeiani, E. F., R. F.,Amirnia, M.,Saeidi, M.,Karimi, E. R.Topical 4% nicotinamide vs. 1% clindamycin in moderate inflammatory acne vulgaris. 2013. International Journal of Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Khodaeinai, E. B., S.,Amirnia, M.,Shokry, J.,Karimi, L. R.,Fouladi, D. F.,Sedaghat, K.Efficacy of 10% azelaic acid gel with hydro-alcoholic or alcohol-free bases in mild to moderate acne vulgaris; the first clinical trial. 2014. Journal of Medical Sciences (Faisalabad)	Outcomes reported in figures only
Kim, B. J. L., H. G.,Woo, S. M.,Youn, J. I.,Suh, D. H.Pilot study on photodynamic therapy for acne using indocyanine green and diode laser. 2009. Journal of Dermatology	Data reported in figures only
Kim, B. K., H.,Kim, J. E.,Lee, S. H.Retinyl retinoate, a retinoid derivative improves acne vulgaris in double-blind, vehicle-controlled clinical Study. 2013. Tissue engineering and regenerative medicine	No relevant study design - not RCT
Kim, S. J. B., J. H.,Koh, J. S.,Bae, M. I.,Lee, S. J.,Shin, M. K.The effect of physically applied alpha hydroxyl acids on the skin pore and comedone. 2015. International journal of cosmetic science	No relevant study population - sample includes people with acne-prone skin, no further details reported and study is not relevant for PCOS, maintenance or refractory treatments
Kim, S. W. M., S. E.,Kim, J. A.,Eun, H. C.Glycolic acid versus Jessner's solution: which is better for facial acne patients? A randomized prospective clinical trial of split-face model therapy. 1999. Dermatologic surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments

Reference	Reason for exclusion
Kim, W. J. P., J. M.,Ko, H. C.,Kim, B. S.,Kim, M. B.,Song, M.A split-faced, observer-blinded comparison study of topical adapalene/benzoyl peroxide and adapalene in the treatment of Asian acne patients. 2013. Journal of Drugs in Dermatology: JDD	No relevant article type - letter to editor
King, K. J., D. H.,Daltrey, D. C.,Cunliffe, W. J.A double-blind study of the effects of 13-cis-retinoic acid on acne, sebum excretion rate and microbial population. 1982. British Journal of Dermatology	No relevant data reported - sebum excretion study
Kircik, L. H. B., V.,Martin, G.,Pillai, R.Randomized, double-blind, split-face study to compare the irritation potential of two topical acne formulations over a 21-day treatment period. 2016. Journal of Drugs in Dermatology	No relevant study population - participants did not have acne
Kircik, L. H.Comparative efficacy and safety results of two topical combination acne regimens. 2009b. Journal of Drugs in Dermatology	No relevant data reported - study recruited participants for 4 (n=23) or 12 wk (n=42) trial of BPO/CLIND gel vs solubilized BPO gel but reports data for all participants
Kircik, L. H.Fixed Combination of Clindamycin Phosphate 1.2% and Benzoyl Peroxide 3.75% Aqueous Gel: Long-Term Use in Adult Females With Moderate Acne Vulgaris. 2017. Journal of Drugs in Dermatology: JDD	No relevant study design - not RCT
Kircik, L. H.Tretinoin microsphere gel pump 0.04% versus tazarotene cream 0.05% in the treatment of mild-to-moderate facial acne vulgaris. 2009. Journal of Drugs in Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Kligman, A. M. F., J. E., Jr.,Plewig, G.Topical vitamin A acid in acne vulgaris. 1969. Archives of Dermatology	No relevant study design - not RCT
Kligman, A. M. P., G.,Mills, O. H., Jr.Topically applied tretinoin for senile (solar) comedones. 1971. Archives of Dermatology	No relevant study design - not RCT
Kligman, A. M.Comparison of a topical benzoyl peroxide gel, oral minocycline, oral doxycycline and a combination for suppression of P. acnes in acne patients. 1998. Journal of dermatological treatment	No relevant outcmoes reported - bacterial counts
Knutson, D. D. S., L. J.,Smoot, W. H.Meclocycline sulfosalicylate. Topical antibiotic agent for the treatment of acne vulgaris. 1981. Cutis	No relevant article type - non-systematic review
Ko, H. C. S., M.,Seo, S. H.,Oh, C. K.,Kwon, K. S.,Kim, M. B.Prospective, open-label, comparative study of clindamycin 1%/benzoyl peroxide 5% gel with adapalene 0.1% gel in Asian acne patients: Efficacy and tolerability. 2009. Journal of the European Academy of Dermatology and Venereology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Kobayashi, M. N., T.,Fukamachi, K.,Nakamura, M.,Tokura, Y.Efficacy of combined topical treatment of acne vulgaris with adapalene and nadifloxacin: A randomized study. 2011. Journal of Dermatology	No relevant intervention - intervention & class not available in the UK
Koltun, W. L., A. W.,Thiboutot, D.,Niknian, M.,Sampson-Landers, C.,Korner, P.,Marr, J.Efficacy and safety of 3 mg drospirenone/20 mcg	No relevant study population - sample does

Reference	Reason for exclusion
ethinylestradiol oral contraceptive administered in 24/4 regimen in the treatment of acne vulgaris: a randomized, double-blind, placebo-controlled trial. 2008. Contraception	not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Koltun, W. M., J. M.,Marr, J.,Kunz, M.Treatment of moderate acne vulgaris using a combined oral contraceptive containing ethinylestradiol 20 mug plus drospirenone 3 mg administered in a 24/4 regimen: A pooled analysis. 2011. European Journal of Obstetrics and Gynecology and Reproductive Biology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kotrajaras, R.Comparative study in the treatment of acne vulgaris with cyproterone acetate, tetracycline and vitamin A acid. 1982. Journal of the Medical Association of Thailand	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Krausz, A. F., A. J.Cutaneous hyperandrogenism: role of antiandrogen therapy in acne, hirsutism, and androgenetic alopecia. 2013. Journal of Drugs in Dermatology: JDD	No relevant article type - non-systematic review
Kriplani, A. T., J.,Agrawal, N.,Kulshrestha, V.,Ammini, A. C.,Kumar, G.A comparative study of Diane-35 plus spironolactone and Diane-35 plus finasteride in cases of hirsutism and acne. 2009. International journal of endocrinology and metabolism	No relevant study population - only 38% of participants have acne
Krishnan, G.Comparison of two concentrations of tretinoin solution in the topical treatment of acne vulgaris. 1976. Practitioner	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Kubeyinje, E. P.Topical tretinoin compared with topical clindamycin phosphate in the treatment of acne and acne-associated hyperpigmentation in Arabs. 1997. Journal of dermatological treatment	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Kubota, Y. M., A.,Shirahige, Y.,Nakai, K.,Katsuura, J.,Moriue, T.,Murakami, Y.,Matsunaka, H.,Yoneda, K.Effect of sequential application of topical adapalene and clindamycin phosphate in the treatment of Japanese patients with acne vulgaris. 2012. Journal of Dermatological Treatment	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kuflik, E. G.Benzoyl peroxide gel in acne therapy. 1976. Cutis	No relevant study design - not RCT
Kurokawa, I. A., H.,Nishijima, S.,Asada, Y.,Kawabata, S.Clinical and bacteriologic evaluation of OPC-7251 in patients with acne: A double-blind group comparison study versus cream base. 1991. Journal of the American Academy of Dermatology	Duplicate record

Reference	Reason for exclusion
Kus, S. Y., D.,Aytug, A.Comparison of efficacy of azithromycin vs. doxycycline in the treatment of acne vulgaris. 2005. Clinical and Experimental Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kwon, H. H. C., S. C.,Jung, J. Y.,Bae, Y. I.,Park, G. H.Comparison of novel dual mode vs conventional single pass of a 1450-nm diode laser in the treatment of acne vulgaris for Korean patients: A 20-week prospective, randomized, split-face study. 2018. Journal of Cosmetic Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kwon, H. H. L., J. B.,Yoon, J. Y.,Park, S. Y.,Ryu, H. H.,Park, B. M.,Kim, Y. J.,Suh, D. H.The clinical and histological effect of home-use, combination blue-red LED phototherapy for mild-to-moderate acne vulgaris in Korean patients: A double-blind, randomized controlled trial. 2013. British Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kwon, H. H. M., K. R.,Park, S. Y.,Yoon, J. Y.,Suh, D. H.,Lee, J. B.Daylight photodynamic therapy with 1.5% 3-butenyl 5-aminolevulinate gel as a convenient, effective and safe therapy in acne treatment: A double-blind randomized controlled trial. 2016. Journal of Dermatology	No relevant study population - sample includes mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kwon, H. H. P., H. Y.,Choi, S. C.,Bae, Y.,Jung, J. Y.,Park, G. H.Novel device-based acne treatments: comparison of a 1450-nm diode laser and microneedling radiofrequency on mild-to-moderate acne vulgaris and seborrhoea in Korean patients through a 20-week prospective, randomized, split-face study. 2018. Journal of the European Academy of Dermatology and Venereology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Kwon, H. H. P., S. Y.,Yoon, J. Y.,Min, S.,Suh, D. H.Do tutorials on application method enhance adapalene-benzoyl peroxide combination gel tolerability in the treatment of acne?. 2015. Journal of Dermatology	No relevant comparator - compares efficacy of adding training module to intervention
Kwon, I. K., S.,Lee, D.Photodynamic therapy using chlorophyll-a in the treatment of acne vulgaris: A randomized, single-blind, split-face study. 2014. Journal of Investigative Dermatology	No relevant article type - conference abstract
Kwon,Comparison of clinical and histological effects between lactobacillus-fermented Chamaecyparis obtusa and tea tree oil for the treatment of acne: an eight-week double-blind randomized controlled split-face study. 2014. NA	No relevant intervention and comparison - Lactobacillus-fermented Chamaecyparis obtusa vs tea tree oil
L. Ghoshal, S. Banerjee, S. Ghosh, D. Gangopadhyay and S. JanaComparative evaluation of effectiveness of adapalene and azithromycin, alone or in combination, in acne vulgaris. 2007. Indian Journal of Dermatology	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments

Reference	Reason for exclusion
Lachnit-Fixson, U. K., J.Therapy of androgenization symptoms: double blind study of an antiandrogen preparation (SH B 209 AB) against neogynon (author's transl). 1977. Medizinische klinik	Not in English language
Lain, E., Day, D., Harper, J., Guenin, E.Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris: Impact of Gender and Race on Efficacy and Safety. 2019. Journal of drugs in dermatology : JDD	Not obtainable
Langner, A. B., G. C.,Stapor, V.,Wolska, H.,Fraczykowska, M.Isotretinoin cream 0.05% and 0.1% in the treatment of acne vulgaris. 1994. Journal of Dermatological Treatment	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Laquieze, S. C., J.,Rueda, M. J.Beneficial effect of a moisturizing cream as adjunctive treatment to oral isotretinoin or topical tretinoin in the management of acne. 2006. Journal of drugs in dermatology : JDD	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Lassus, A.Local treatment of acne. A clinical study and evaluation of the effect of different concentrations of benzoyl peroxide gel. 1981. Current Medical Research & Opinion	Not an RCT
Lee SH, Huh CH, Park KC, Youn SW.Effects of repetitive superficial chemical peels on facial sebum secretion in acne patients.. 2006. J Eur Acad Dermatol Venereol	No relevant outcomes repoted - sebum levels only
Lee, E. J. L., H. K.,Shin, M. K.,Suh, D. H.,Lee, S. J.,Kim, N. I.An open-label, split-face trial evaluating efficacy and safty of photopneumatic therapy for the treatment of acne. 2012. Annals of Dermatology	No relevant study design - not RCT
Lee, H. E. K., J. Y.,Kim, Y. H.,Yoo, S. R.,Moon, S. H.,Kim, N. I.,Park, C.,Kim, J. H.,Koh, H. J.,Park, W. S.,Ro, Y. S.A double-blind randomized controlled comparison of apddr-0901, a novel cosmeceutical formulation, and 0.1% adapalene gel in the treatment of mild-to-moderate acne vulgaris. 2011a. European Journal of Dermatology	No relevant intervention - intervention & class not available in the UK
Lee, H. J., Kim, J. Y., Park, K. D., Lee, W. J.Randomized controlled double-blind study of a cleanser composed of 5-aminolevulinic acid and peptides on mild and moderate acne vulgaris. 2019a. Journal of Cosmetic Dermatology.	No relevant intervention - cleanser
Lee, J. W. Y., K. H.,Park, K. Y.,Han, T. Y.,Li, K.,Seo, S. J.,Hong, C. K.Effectiveness of conventional, low-dose and intermittent oral isotretinoin in the treatment of acne: A randomized, controlled comparative study. 2011b. British Journal of Dermatology	No relevant study population - insufficient details to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Lee, S. Y. C.The efficacy of full-spectrum light generated by electrical discharge between two carbon arc rods for the treatment of acne compared to 1% topical clindamycin. 2010. Lasers in Surgery and Medicine	No relevant article type - conference abstract
Lee, S. Y., Park, A. Y., Shin, J. Y., Lee, H. J., Kim, J. E., Lee, S. H., Lee, J. S.Comparison of the efficacy of azithromycin versus	No relevant artcile type - conference abstract

Reference	Reason for exclusion
doxycycline in acne vulgaris. 2019b. Journal of the American Academy of Dermatology	
Lee, W. J. J., H. J.,Kim, J. Y.,Lee, S. J.,Kim, D. W.Effect of photodynamic therapy on inflammatory acne using 3% liposomal 5-aminolevulinic acid emulsion and intense-pulsed light: A pilot study. 2012. Journal of Dermatology	No relevant article type - letter to editor
Lekakh, O. M., A. M.,Novice, K.,Kamalpour, J.,Sadeghian, A.,Mondo, D.,Kalnicky, C.,Guo, R.,Peterson, A.,Tung, R.Treatment of Acne Vulgaris With Salicylic Acid Chemical Peel and Pulsed Dye Laser: A Split Face, Rater-Blinded, Randomized Controlled Trial. 2015. Journal of Lasers in Medical Sciences	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Lekwuttikarn, R. T., T.,Chatproedprai, S.,Wananukul, S.Randomized, controlled trial split-faced study of 595-nm pulsed dye laser in the treatment of acne vulgaris and acne erythema in adolescents and early adulthood. 2017. International Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Lemay, A. A., D. F.,Roberts, J. L.,Harrison, D. D.The efficacy of an oral contraceptive containing 20ug ethinyl estradiol and 100ug levonorgestrel for the treatment of moderate acne. 2000. Gynecological endocrinology	No relevant article type - conference abstract
Lesher, J. L., Jr.,Chalker, D. K.,Smith, J. G., Jr.,Guenther, L. C.,Ellis, C. N.,Voorhees, J. J.,Shalita, A. R.,Klauda, H. C.An evaluation of a 2% erythromycin ointment in the topical therapy of acne vulgaris. 1985. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Lester, R. S. S., G. D.,Light, M. J.Isotretinoin and tetracycline in the management of severe nodulocystic acne. 1985. International Journal of Dermatology	Dosage of tetracycline lower than BNF value
Leu, F. S., U.,Fournet, M.,Truffat, C.Random sample study of the effect of two concentrations of retinoic acid on acne vulgaris. 1974. Medecine ET hygiene	Not in English language
Levesque, A. H., I.,Seite, S.,Rougier, A.,Bissonnette, R.Randomized trial comparing a chemical peel containing a lipophilic hydroxy acid derivative of salicylic acid with a salicylic acid peel in subjects with comedonal acne. 2011. Journal of cosmetic dermatology	No relevant intervention - lipohydroxy acid
Lew-Kaya, D. A. R., L. L.,Sefton, J.,Stern, K.Once-daily erythromycin 2% gel in the treatment of acne vulgaris: Two double-blind comparisons with tretinoin 0.01% gel. 1992. Advances in Therapy	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments

Reference	Reason for exclusion
Leyden, J. G., G. L.Randomized facial tolerability studies comparing gel formulations of retinoids used to treat acne vulgaris. 2001. Cutis; cutaneous medicine for the practitioner	No relevant study population - participants did not have acne
Leyden, J. J. B., R. S.,Dunlap, F. E.,Ellis, C. N.,Connolly, M. A.,Levy, S. F.Comparison of the efficacy and safety of a combination topical gel formulation of benzoyl peroxide and clindamycin with benzoyl peroxide, clindamycin and vehicle gel in the treatments of acne vulgaris. 2001. American Journal of Clinical Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Leyden, J. J. G., E. H.Evaluation of the antimicrobial effects in vivo of Triaz Gel (benzoyl peroxide special gel), Cleocin-T Lotion (clindamycin phosphate lotion), and Azelex Cream (azelaic acid cream) in humans. 1997. Journal of Dermatological Treatment	No relevant outcomes reported - bacterial counts
Leyden, J. J. G., R.,Nighland, M.Cumulative irritation potential of topical retinoid formulations. 2008. Journal of drugs in dermatology : JDD	No relevant study population - participants did not have acne
Leyden, J. J. H., J. G.,Jarratt, M. T.,Stewart, D. M.,Levy, S. F.The efficacy and safety of a combination benzoyl peroxide/clindamycin topical gel compared with benzoyl peroxide alone and a benzoyl peroxide/erythromycin combination product. 2001. Journal of Cutaneous Medicine and Surgery	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Leyden, J. J. K., L.,Yaroshinsky, A.Two randomized, double-blind, controlled trials of 2219 subjects to compare the combination clindamycin/tretinoin hydrogel with each agent alone and vehicle for the treatment of acne vulgaris. 2006. Journal of the American Academy of Dermatology	No relevant data reported - study reports combined results of 2 RCTs
Leyden, J. J. N., M.,Rossi, A. B.,Ramaswamy, R.Irritation potential of tretinoin gel microsphere pump versus adapalene plus benzoyl peroxide gel. 2010. Journal of Drugs in Dermatology	No relevant study population - participants did not have acne
Leyden, J. J. T., E. A.,Miller, B.,Ung, M.,Berson, D.,Lee, J.Once-daily tazarotene 0.1 % gel versus once-daily tretinoin 0.1 % microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. 2002. Cutis; cutaneous medicine for the practitioner	Not obtainable
Leyden, J. J. W., M.A novel gel formulation of clindamycin phosphate-tretinoin is not associated with acne flaring. 2008. Cutis	No relevant outcomes reported - reports 2-wk treatment-related flaring outcomes of 12-week RCT reported in Schlessinger 2007
Leyden, J. J.Topical treatment for the inflamed lesion in acne, rosacea, and pseudofolliculitis barbae. 2004. Cutis	No relevant article type - introduction to supplement
Leyden, J. W., M.,Baldwin, E. K.Tolerability of clindamycin/tretinoin gel vs. tretinoin microsphere gel and adapalene gel. 2009. Journal of Drugs in Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Leyden, J., Levy, S.The development of antibiotic resistance in Propionibacterium acnes. 2001. Cutis	Not reported how many people were randomised in each arm; no tables available; also the outcome is bacteria counts

Reference	Reason for exclusion
	which is not relevant
Li,Effects of Qingfei Liangxue Fa on sebum excretion rate and free fatty acid of patients with acne vulgaris. 2004. NA	No relevant intervention - complementary therapy
Liani, L. P., J. S.Evaluation of topical erythromycin and topical lactate with or without systemic ketoconazole in acne vulgaris. 1992. Indian journal of dermatology, venereology and leprology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Liddell, K.Benzoyl peroxide gel in the treatment of acne vulgaris. 1974. British Journal of Clinical Practice	Not obtainable
Lihong, S.He-Ne laser auricular irradiation plus body acupuncture for treatment of acne vulgaris in 36 cases. 2006. Journal of Traditional Chinese Medicine	No relevant intervention - laser plus acupuncture
Lim, C. C. P., D. G. C.,Adamson, J.A sustained release tetracycline preparation in acne vulgaris. 1974. Practitioner	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Lim, S. K. H., J. M.,Lee, Y. H.,Lee, Y.,Seo, Y. J.,Kim, C. D.,Lee, J. H.,Im, M.Comparison of Vitamin D Levels in Patients with and without Acne: a Case-Control Study Combined with a Randomized Controlled Trial. 2016. PloS one	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Lin, Z. R. Z., W.,You, S. F.,Xiao, Y.Clinical observation on pricking blood and acupoint injection in treating acne. 2016. Western journal of traditional chinese medicine [xi bu zhong yi yao za zhi]	Not in English language
Liu, H., Yu, H., Xia, J., Liu, L., Liu, G. J., Sang, H., Peinemann, F.Topical azelaic acid, salicylic acid, nicotinamide, sulphur, zinc and fruit acid (alphaÃ¢Â€Â• hydroxy acid) for acne. 2020. Cochrane Database of Systematic Reviews	Systematic review - references were checked for relevance
Liu, L. H. F., X.,An, Y. X.,Zhang, J.,Wang, C. M.,Yang, R. Y.Randomized trial of three phototherapy methods for the treatment of acne vulgaris in chinese patients. 2014. Photodermatology Photoimmunology and Photomedicine	No relevant outcome data reported - interventions provided until >90% improvement observed in participants
Lookingbill, D. P. A., B. B.,Ellis, C. N.,Jegasothy, B. V.,Lucky, A. W.,Ortiz- Ferrer, L. C.,Savin, R. C.,Shupack, J. L.,Stiller, M. J.,Zone, J. J.,Landis, J. R.,Ramaswamy, R.,Cherill, R. J.,Pochi, P. E.Inocoterone and acne: The effect of a topical antiandrogen: Results of a multicenter clinical trial. 1992. Archives of Dermatology	No relevant intervention - never marketed
Lookingbill, D. P. C., D. K.,Lindholm, J. S.,Katz, H. I.,Kempers, S. E.,Huerter, C. J.,Swinehart, J. M.,Schelling, D. J.,Klauda, H. C.Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: Combined results of two double-blind investigations. 1997. Journal of the American Academy of Dermatology	No relevant intervention - never marketed
Lu, J. L., Z.Acupuncture combined with cupping and circling moxibustion for 40 cases of acne. 2018. World Journal of Acupuncture - Moxibustion	No relevant intervention - acupuncture-cupping
Lubtikulthum, P. K., N.,Udompataikul, M.A comparative study on the	No relevant intervention -

Reference	Reason for exclusion
effectiveness of herbal extracts vs 2.5% benzoyl peroxide in the treatment of mild to moderate acne vulgaris. 2019. Journal of Cosmetic Dermatology.	topical herbal extract
Lucky, A. W. C., S. I.,Funicella, T.,Jarratt, M. T.,Jones, T.,Reddick, M. E.Double-blind, vehicle-controlled, multicenter comparison of two 0.025% tretinoin creams in patients with acne vulgaris. 1998a. Journal of the American Academy of Dermatology	Outcomes reported in figures only
Lucky, A. W. C., S. I.,Jarratt, M. T.,Quigley, J. W.Comparative efficacy and safety of two 0.025% tretinoin gels: Results from a multicenter, double-blind, parallel study. 1998b. Journal of the American Academy of Dermatology	Outcomes reported in figures only
Lucky, A. W. H., T. A.,Olson, W. H.,Robisch, D. M.,Lebwohl, M.,Swinyer, L. J.Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. 1997. Journal of the American Academy of Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Lucky, A. W. K., W.,Thiboutot, D.,Niknian, M.,Sampson-Landers, C.,Korner, P.,Marr, J.A combined oral contraceptive containing 3-mg drospirenone/20-mug ethinyl estradiol in the treatment of acne vulgaris: A randomized, double-blind, placebo-controlled study evaluating lesion counts and participant self-assessment. 2008. Cutis	Outcomes reported in figures only
Lucky, A. W. M., J. M.,Roberts, J.,Taylor, S.,Jones, T.,Ling, M.,Garrett, S.Dapsone gel 5% for the treatment of acne vulgaris: safety and efficacy of long-term (1 year) treatment. 2007. Journal of drugs in dermatology : JDD	No relevant study design - not RCT
Lucky, A. W. S., J.Comparison of micronized tretinoin gel 0.05% and tretinoin gel microsphere 0.1% in young adolescents with acne: A post hoc analysis of efficacy and tolerability data. 2011. Cutis	Outcomes reported in figures only
Lueangarun, S. S., K.,Tempark, T.,Managit, C.,Sithisarn, P.Clinical efficacy of 0.5% topical mangosteen extract in nanoparticle loaded gel in treatment of mild-to-moderate acne vulgaris: A 12-week, split-face, double-blinded, randomized, controlled trial. 2019. Journal of Cosmetic Dermatology.	Non relevant intervention – alpha-mangostin
Lyons, R. E.Comparative effectiveness of benzoyl peroxide and tretinoin in acne vulgaris. 1978. International Journal of Dermatology	No relevant study population - insufficient details reported to determine severity of acne
Ma, L. X., L. H.,Yu, B.,Yin, R.,Chen, L.,Wu, Y.,Tan, Z. J.,Liu, Y. B.,Tian, H. Q.,Li, H. Z.,Lin, T.,Wang, X. L.,Li, Y. H.,Wang, W. Z.,Yang, H. L.,Lai, W.Low-dose topical 5-aminolevulinic acid photodynamic therapy in the treatment of different severity of acne vulgaris. 2013. Photodiagnosis and Photodynamic Therapy	No relevant study design - not RCT
Ma, X. H. Z., S. L.,Zhou, G. M.Clinical observation on treatment of female delayed acne vulgaris with qingre cuochuang tablet. 2004. Zhongguo zhong xi yi jie he za zhi zhongguo zhongxiyi jiehe zazhi = chinese journal of integrated traditional and western medicine	Not in English language
Ma, Y. L., Y.,Wang, Q.,Ren, J.,Xiang, L.Prospective study of topical 5-aminolevulinic acid photodynamic therapy for the treatment of severe adolescent acne in Chinese patients. 2015. Journal of Dermatology	No relevant study deisgn - not RCT
MacDonald, R. H. M., H.,Ray, S. K.Clinical trial of Actinac in acne. 1976. British Journal of Clinical Practice	No relevant study population - sample includes people with mild

Reference	Reason for exclusion
	to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Mackey, J. P.A small double-blind trial of an anovulant agent in acne vulgaris. 1975. Irish Medical Journal	No relevant study design - not RCT
Magin,Topical and oral CAM in acne: A review of the empirical evidence and a consideration of its context. 2006. NA	No relevant intervention - systematic review about complementary and alternative medicines for acne
Mahran, H. G., Drbala, K. M.Efficacy of twelve sessions of 905nm infrared laser on acne vulgaris. 2019. Annals of Clinical and Analytical Medicine	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Maiti, R. S., C. S.,Ashique Rahman, M. A.,Srinivasan, A.,Parida, S.,Hota, D.Efficacy and Safety of Tazarotene 0.1% Plus Clindamycin 1% Gel Versus Adapalene 0.1% Plus Clindamycin 1% Gel in Facial Acne Vulgaris: A Randomized, Controlled Clinical Trial. 2017. Clinical Drug Investigation	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Maloney, J. M. A., D. I.,Flack, M.,McLaughlin-Miley, C.,Sevilla, C.,Derman, R.Use of a low-dose oral contraceptive containing norethindrone acetate and ethinyl estradiol in the treatment of moderate acne vulgaris. 2001. Clinical journal of women's health	Not obtainable
Maloney, J. M. D. J., P.,Watson, D.,Niknian, M.,Lee-Rugh, S.,Sampson-Landers, C.,Korner, P.A randomized controlled trial of a low-dose combined oral contraceptive containing 3 mg drospirenone plus 20 mug ethinylestradiol in the treatment of acne vulgaris: Lesion counts, investigator ratings and subject self-assessment. 2009a. Journal of Drugs in Dermatology	Duplicate record
Maloney, J. M. D., P., Jr.,Watson, D.,Niknian, M.,Lee-Rugh, S.,Sampson-Landers, C.,Korner, P.A randomized controlled trial of a low-dose combined oral contraceptive containing 3 mg drospirenone plus 20 microg ethinylestradiol in the treatment of acne vulgaris: lesion counts, investigator ratings and subject self-assessment. 2009b. Journal of Drugs in Dermatology: JDD	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Maloney, J. M. D., P.,Watson, D.,Niknian, M.,Lee-Rugh, S.,Sampson-Landers, C.,Korner, P.Treatment of acne using A 3-milligram drospirenone/20-microgram ethinyl estradiol oral contraceptive administered in a 24/4 regimen: A randomized controlled trial. 2008. Obstetrics and Gynecology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Mandekou-Lefaki, I. D., F.,Teknetzis, A.,Euthimiadou,	No relevant study design -

Reference	Reason for exclusion
R.,Karakatsanis, G.Low-dose schema of isotretinoin in acne vulgaris. 2003. International Journal of Clinical Pharmacology Research	not RCT
Mandy, S.A.A comparison of the efficacy and safety of tretinoin cream 0.025% and 0.05%. 1990. Advances in Therapy	No relevant data reported - post hoc analysis of non-randomised comparison of 2 RCTs
Mandy, S.Tretinoin in acne vulgaris. 1975. Modern Problems in Paediatrics	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Mango, D. R., S.,Manna, P.,Miggiano, G. A.,Serra, G. B.Clinical and hormonal effects of ethinylestradiol combined with gestodene and desogestrel in young women with acne vulgaris. 1996. Contraception	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Mansour, D. V., C.,Sommer, W.,Weisberg, E.,Taneepanichskul, S.,Melis, G. B.,SundstrÃ¶m-Poromaa, I.,Korver, T.Efficacy and tolerability of a monophasic combined oral contraceptive containing nomegestrol acetate and 17Î²-oestradiol in a 24/4 regimen, in comparison to an oral contraceptive containing ethinylestradiol and drospirenone in a 21/7 regimen. 2011b. European journal of contraception & reproductive health care	Duplicate record
Mansour, D. V., C.,Sommer, W.,Weisberg, E.,Taneepanichskul, S.,Melis, G. B.,Sundstrom-Poromaa, I.,Korver, T.Efficacy and tolerability of a monophasic combined oral contraceptive containing nomegestrol acetate and 17beta-oestradiol in a 24/4 regimen, in comparison to an oral contraceptive containing ethinylestradiol and drospirenone in a 21/7 regimen. 2011a. European Journal of Contraception and Reproductive Health Care	No relevant study population - participants did not have acne
Mansurul, A. M. I., A. Z. M.Effect of spironolactone on acne vulgaris - A double blind study. 2000. Bangladesh Journal of Dermatology, Venereology and Leprology	Not obtainable
Marazzi, P. B., G.,Donald, A.,Davies, H.Clinical evaluation of Double Strength IsotrexinTM versus Benzamycin in the topical treatment of mild to moderate acne vulgaris. 2002b. Journal of Dermatological Treatment	Duplicate record
Marcinkiewicz, J. W.-P., A.,Walczewska, M.,Lipko-Godlewska, S.,Jachowicz, R.,Maciejewska, A.,Bialecka, A.,Kasprowicz, A.Topical taurine bromamine, a new candidate in the treatment of moderate inflammatory acne vulgaris: a pilot study. 2008. European Journal of Dermatology	No relevant intervention - taurine bromaminenot available in the UK
Marcinkiewicz, J.Taurine bromamine: a new therapeutic option in inflammatory skin diseases. 2009. Polskie Archiwum Medycyny Wewnetrznej	No relevant study design - not RCT
Marczyk, B. M., P.,Budzisz, E.,Rotsztejn, H.Comparative study of the effect of 50% pyruvic and 30% salicylic peels on the skin lipid film in patients with acne vulgaris. 2014. Journal of Cosmetic Dermatology	No relevant data reported - sebum secretion study
Mareledwane, N. G.A randomized, open-label, comparative study of oral doxycycline 100 mg vs. 5% topical benzoyl peroxide in the treatment of mild to moderate acne vulgaris. 2006. International Journal of Dermatology	No relevant data reported

Reference	Reason for exclusion
Marous, Mr.R., Flaten, H.K., Sledge, B., Rietcheck, H.R., Dellavalle, R., Suneja, T., Dunnick, C.Complementary and Alternative Methods for Treatment of Acne Vulgaris: a Systematic Review. 2018. Current Dermatology Reports	No relevant intervention - systematic review about complementary and alternative medicines for acne
Marron, S. E. T.-A., L.,Boira, S. Anxiety, depression, quality of life and patient satisfaction in acne patients treated with oral isotretinoin. 2013. Acta Dermato-Venereologica	No relevant study design - not RCT
Marsden, J. R. L., M. F.,Ford, G. P.,Shuster, S.Effect of low dose cyproterone acetate on the response of acne to isotretinoin. 1984. British Journal of Dermatology	No relevant study design - not RCT
Matsunaga, K. L., Y. H.,Chan, R.,Kerrouche, N.,Paliargues, F.Adjunctive usage of a non-comedogenic moisturizer with adapalene gel 0.1% improves local tolerance: A randomized, investigator-blinded, split-face study in healthy Asian subjects. 2013. Journal of Dermatological Treatment	No relevant study population – participants did not have acne
Mazzarello, V. D., M. G.,Ferrari, M.,Piga, G.,Usai, D.,Zanetti, S.,Sotgiu, M. A.Treatment of acne with a combination of propolis, tea tree oil, and aloe vera compared to erythromycin cream: Two double-blind investigations. 2018. Clinical Pharmacology: Advances and Applications	No relevant intervention - a cream based on three natural extracts vs 3% erythromycin cream vs placebo cream but no useful data for comparison of erythromycin cream and placebo reported
Mazzarello, V., Gavini, E., Rassu, G., Donadu, M. G., Usai, D., Piu, G., Pomponi, V., Sucato, F., Zanetti, S., Montesu, M. A. Clinical Assessment of New Topical Cream Containing Two Essential Oils Combined with Tretinoin in the Treatment of Acne. 2020. Clinical, Cosmetic and Investigational Dermatology CCIDClin Cosmet Investig Dermatol	No relevant intervention - a galenic compound containing 2 essential oils (Myrtus communis L. and Origanum vulgare)
Mazzetti, A. M., L.,Gerloni, M.,Cartwright, M.A Phase 2b, Randomized, Double-Blind Vehicle Controlled, Dose Escalation Study Evaluating Clascoterone 0.1%, 0.5%, and 1% Topical Cream in Subjects With Facial Acne. 2019. Journal of drugs in dermatology : JDD	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Mazzetti, A., Moro, L., Gerloni, M., Cartwright, M.Pharmacokinetic Profile, Safety, and Tolerability of Clascoterone (Cortexolone 17-alpha propionate, CB-03-01) Topical Cream, 1% in Subjects With Acne Vulgaris: An Open-Label Phase 2a Study. 2019. Journal of Drugs in Dermatology: JDDJ Drugs Dermatol	Not obtainable
McGillis, T. J. R., M. J.,Reisner, R. M.,Sternberg, T. H.,Stirling, N. C.,Winer, L. H.Topical Vitamin A Acid in the Management of Comedo Acne. 1971. Cutis; cutaneous medicine for the practitioner	Not obtainable
McHugh, R. C. R., A.,Sangha, N. D.,McCarty, M. A.,Utterback, R.,Rohrback, J. M.,Osborne, B. E.,Fleischer, A. B., Jr.,Feldman, S. R.A topical azithromycin preparation for the treatment of acne vulgaris and rosacea. 2004. Journal of Dermatological Treatment	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
McKenzie, M. W. B., D. C.,Popovich, N. G.Topical clindamycin formulations for the treatment of acne vulgaris. An evaluation. 1981. Archives of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS,

Reference	Reason for exclusion
	maintenance or refractory treatments
Mehran, G., Sepasgozar, S., Rohaninasab, M., Goodarzi, A., Ghassemi, M., Fotooei, M., Behrangi, E.Comparison between the therapeutic effect of microneedling versus tretinoin in patients with comedonal acne: A randomized clinical trial. 2019. Iranian Journal of Dermatology	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Meigel, W. G., H.,Wokalek, H.Oral treatment of acne conglobata with isotretinoin. Results of the German Multicenter Study. 1983. Der hautarzt; zeitschrift fur dermatologie, venerologie, und verwandte gebiete	Not in English language
Merkviladze, N. G., T.,Tushurashvili, P.,Ekaladze, E.,Jojua, N.The efficacy of topical drugs in treatment of noninflammatory acne vulgaris. 2010. Georgian Medical News	No relevant study design - not RCT
Merritt, B. B., C. N.,Morrell, D. S.Use of isotretinoin for acne vulgaris. 2009. Pediatric Annals	No relevant study design - not RCT
Michaelsson, G. J., L.,Ljunghall, K.A double-blind study of the effect of zinc and oxytetracycline in acne vulgaris. 1977a. British Journal of Dermatology	No relevant comparison - compares oral zinc and tetracyclines
Michaelsson, G. J., L.,Vahlquist, A.Effects of oral zinc and vitamin A in acne. 1977b. Archives of Dermatology	No relevant comparison - compares oral zinc sulfate alone and in combination with vitamin A
Michaelsson, G.Oral zinc in acne. 1980. Acta dermato-venereologica	No relevant article type - non-systematic review
Mikhael, E. M. M., M. Y. Evaluation of the effect of topical atorvastatin solution for the treatment of papulopustular acne. 2013. International Journal of Current Pharmaceutical Research	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Milikan, L. E.A double-blind study of Betadine skin cleanser in acne vulgaris. 1976. Cutis	No relevant intervention - Betadine skin cleanser
Miller, J. A. J., H. S.T reatment of hirsutism and acne with cyproterone acetate. 1986a. Clinics in Endocrinology & Metabolism	No relevant article type - non-systematic review
Miller, S. T. S., J. J.Low-dose doxycycline moderately effective for acne. 2003. Journal of Family Practice	No relevant study design - not RCT
Millikan, L. E. A., R.Use of Buf-Puf and benzoyl peroxide in the treatment of acne. 1981. Cutis	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Mills Jr, O. H. M., R. R.,Kligman, A. M.Acne vulgaris. Oral therapy with tetracycline and topical therapy with vitamin A. 1972. Archives of dermatology	No relevant data - insufficient data reported
Mills Jr, O. T., C.,Cardin, C. W.,Smiles, K. A.,Leyden, J. J.Bacterial resistance and therapeutic outcome following three months of topical acne therapy with 2% erythromycin gel versus its vehicle. 2002. Acta Dermato-Venereologica	Outcomes reported in figures only
Mills, O. H., Jr.,Kligman, A. M.Treatment of acne vulgaris with topically	No relevant study design -

Reference	Reason for exclusion
applied erythromycin and tretinoin. 1978. Acta Dermato-Venereologica	not RCT
Min, S. P., S. Y.,Yoon, J. Y.,Suh, D. H.Comparison of fractional microneedling radiofrequency and bipolar radiofrequency on acne and acne scar and investigation of mechanism: comparative randomized controlled clinical trial. 2015. Archives of Dermatological Research	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Mirnezami, M. R., H.Is Oral Omega-3 Effective in Reducing Mucocutaneous Side Effects of Isotretinoin in Patients with Acne Vulgaris?. 2018. Dermatology Research and Practice	No relevant intervention - oral omega-3
Mitra, A. S., G. I.Topical photodynamic therapy for non-cancerous skin conditions. 2006. Photodiagnosis and Photodynamic Therapy	Duplicate record
Miyachi, Y. M., F.,Mita, T.,Bai, L.,Ikoma, A.Efficacy and safety of a fixed dose combination gel of adapalene 0.1% and benzoyl peroxide 2.5% in Japanese patients with acne vulgaris-a multicenter, randomzed, double-blinded, active-controlled, parallel group phase III study. 2016. Skin research	Not English language
Mobacken, H. H., K.Topical treatment of acne vulgaris with clindamycin. 1985. Lakartidningen	Not in English language
Moftah, N. H. I., S. M.,Wahba, N. H.Intense pulsed light versus photodynamic therapy using liposomal methylene blue gel for the treatment of truncal acne vulgaris: a comparative randomized split body study. 2016. Archives of Dermatological Research	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Mohammadi, S. F., S.,Pardakhty, A.,Khalili, M.,Mohebbi, A.,Yousefian, M. R.,Aflatoonian, M.A survey to compare the efficacy of niosomal erythromycin alone versus combination of erythromycin and zinc acetate in the treatment of acne vulgaris. 2017. Journal of Kerman University of Medical Sciences	Outcomes reported in figures only
Mohan Kumar, P., Savitha, A. K., Suthanthira Kannan, S. To compare the side effect profile of azithromycin pulse therapy with doxycycline in acne vulgaris treatment: An open labelled, randomised, parallel group, hospital based study. 2019. Indian Journal of Public Health Research and Development	No relevant study population - sample includes participants with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Mokhtari, F. F., G.,Basiri, A.,Farhadi, S.,Nilforoushzadeh, M.,Behfar, S.Comparison effect of azithromycin gel 2% with clindamycin gel 1% in patients with acne. 2016. Advanced Biomedical Research	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Mokhtari, F., Shajari, A., Iraji, F., Faghihi, G., Siadat, A. H., Sadeghian, G., Adibi, N.The effectiveness of adapalene 0.1% with intense pulsed light versus benzoyl peroxide 5% with intense pulsed light in the treatment of acne vulgaris: A comparative study. 2019.	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in

Reference	Reason for exclusion
Journal of Research in Medical SciencesJ	the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Moltz, L. K., E.Medium dose oral cyproterone acetate therapy in women with moderate hyperandrogenism. 1984. Geburtshilfe und frauenheilkunde	Not in English language
Moneib, H. T., A. A.,Youssef, S. S.,Fawzy, M. M.Randomized split-face controlled study to evaluate 1550-nm fractionated erbium glass laser for treatment of acne vulgaris-an image analysis evaluation. 2014. Dermatologic Surgery	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Monib, K. M. E. D., Hussein, M. S.Nd:YAG laser vs IPL in inflammatory and noninflammatory acne lesion treatment. 2019. Journal of Cosmetic Dermatology.	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Monk, B. E. A., J. A.,Caldwell, I. W.,Green, B.,Pelta, D.,Leonard, J.,Du Vivier, A.,Johnson, K.,Tolowinska, I.Efficacy of low-dose cyproterone acetate compared with minocycline in the treatment of acne vulgaris. 1987. Clinical & Experimental Dermatology	No relevant intervention - suboptimal dose of minocycline only taken for 21 days each month
Montes, L. F.Acne vulgaris: treatment with topical benzoyl peroxide acetone gel. 1977. Cutis	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Moore, C. L., C.,Moltz, L.,Oettel, M.,Klinger, G.,Schreiber, G.Antiandrogenic properties of the dienogest-containing oral contraceptive Valette. 1999. Drugs of Today	Not obtainable
Moravvej, H. H., A. M.,Yousefi, M.,Givrad, S.Efficacy of doxycycline versus azithromycin in the treatment of moderate facial acne vulgaris. 2012. Iranian Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Morel, P. V., M. P.,Beylot, C.,Bonerandi, J. J.,Dreno, B.,Lehucher-Ceyrac, D.,Slimani, S.,Dupuy, P.Clinical efficacy and safety of a topical combination of retinaldehyde 0.1% with erythromycin 4% in acne vulgaris. 1999. Clinical and Experimental Dermatology	No relevant intervention - topical retinaldehyde gel
Morganti, P. B., E.,Guarneri, B.,Guarneri, F.,Fabrizi, G.,Palombo, P.,Palombo, M.Topical clindamycin 1% vs. linoleic acid-rich phosphatidylcholine and nicotinamide 4% in the treatment of acne: A	No relevant data reported

Reference	Reason for exclusion
multicentre-randomized trial. 2011. International Journal of Cosmetic Science	
Morganti, P. R., S. D.,Bruno, C.,Cardillo, A.Ethyl lactate and benzoyl peroxide in acne vulgaris. 1988. Journal of Applied Cosmetology	No relevant study population - insufficient details to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Mugglestone, C. J. R., E. L.The treatment of acne with an anti-androgen/oestrogen combination. 1982. Clinical & Experimental Dermatology	Dosage of tetracycline lower than BNF value
Muhlemann, M. F. C., G. D.,Cream, J. J.,Wise, P.Oral spironolactone: An effective treatment for acne vulgaris in women. 1986. British Journal of Dermatology	No relevant data reported - randomised cross-over trial, data for first phase not reported separately from data from second phase
Murff, H. J.Combination therapies are more effective than monotherapy for mild to moderate acne. 2008. Journal of Clinical Outcomes Management	No relevant article type - commentary on an RCT
Naieni, F. F. A., H.Comparison of three different regimens of oral azithromycin in the treatment of acne vulgaris. 2012. Journal of isfahan medical school	Not in English language
Nandimath, M. K. R., N. B.Comparision of clinical efficacy of topical clindamycin with adapalene and adapalene alone in treatment of mild to moderate facial acne vulgaris. 2013. International Journal of Pharma and Bio Sciences	Not obtainable
Narurkar, V. A. B., K. R.,Cohen, J. L.An open-label trial examining the efficacy and safety of a pre- and postprocedure topical five-product system (Clinique Medical Optimizing Regimen) specifically formulated to complement laser/light-based facial cosmetic procedures. 2010. Journal of Cosmetic & Laser Therapy	No relevant study population - participants scheduled to undergo facial physical treatment cosmetic procedure
Nelson, R. M. R., A. E.Hirsutism and acne treated by an androgen antagonist. 1970. Obstetrics & Gynecology	No relevant study design - not RCT
Ng, C. H. T., M. M.,Celi, E.,Tate, B.,Schweitzer, I.Prospective study of depressive symptoms and quality of life in acne vulgaris patients treated with isotretinoin compared to antibiotic and topical therapy. 2002. Australasian Journal of Dermatology	No relevant study design - not RCT
Ng, P. P. G., C. L.Treatment outcome of acne vulgaris with oral isotretinoin in 89 patients. 1999. International Journal of Dermatology	No relevant study design - not RCT
Niazi, S. S., A.Comparison of efficacy of fixed low-dose regimens (daily vs alternate day) of oral isotretinoin in mild to moderate acne vulgaris. 2015. Journal of Pakistan Association of Dermatologists	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Nicklas, C. R., R.,Cardenas, C.,Hasson, A.Comparison of efficacy of aminolaevulinic acid photodynamic therapy vs. adapalene gel plus oral doxycycline for treatment of moderate acne vulgaris-A simple, blind, randomized, and controlled trial. 2018. Photodermatology photoimmunology and photomedicine	Duplicate record

Reference	Reason for exclusion
Nielsen, P. G.Treatment of female acne vulgaris with a cream containing the antiandrogen canrenone. 1983. Dermatologica	No relevant article type - letter to editor
Nighland, M. G., R.Tretinoin microsphere gel in facial acne vulgaris: a meta-analysis. 2008. Journal of drugs in dermatology : JDD	No relevant data reported - reports pooled results from 3 trials combined
NilFroushzadeh, M. A. S., A. H.,Baradaran, E. H.,Moradi, S.Clindamycin lotion alone versus combination lotion of clindamycin phosphate plus tretinoin versus combination lotion of clindamycin phosphate plus salicylic acid in the topical treatment of mild to moderate acne vulgaris: a randomized control trial. 2009. Indian journal of dermatology, venereology and leprology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Niren, N. M. T., H. M.The Nicomide Improvement in Clinical Outcomes Study (NICOS): results of an 8-week trial. 2006. Cutis	No relevant study design - not RCT
Nitzan, Y. B. C., A. D.Zinc in skin pathology and care. 2006. Journal of Dermatological Treatment	Duplicate record
Nofal, E. N., A.,Gharib, K.,Nasr, M.,Abdelshafy, A.,Elsaid, E.Combination chemical peels are more effective than single chemical peel in treatment of mild-to-moderate acne vulgaris: A split face comparative clinical trial. 2018. Journal of Cosmetic Dermatology	No relevant study design - not RCT
Nordin, K. F., T.,Rylander, C.Ro 11-1430, a new retinoic acid derivative for the topical treatment of acne. 1981. Dermatologica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Norris, J. F. H., B. R.,Basey, A. J.,Cunliffe, W. J.A comparison of the effectiveness of topical tetracycline, benzoyl-peroxide gel and oral oxytetracycline in the treatment of acne. 1991. Clinical & Experimental Dermatology	No relevant intervention - topical tetracycline and 250 mg of oral oxytetracycline
Nyirady, J. G., R. M.,Nighland, M.,Berger, R. S.,Jorizzo, J. L.,Kim, Y. H.,Martin, A. G.,Pandya, A. G.,Schulz, K. K.,Strauss, J. S.A comparative trial of two retinoids commonly used in the treatment of acne vulgaris. 2001. Journal of Dermatological Treatment	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Nyirady, J. N., M.,Payonk, G.,Pote, J.,Phillips, S.,Grossman, R.A comparative evaluation of tretinoin gel microsphere, 0.1%, versus tretinoin cream, 0.025%, in reducing facial shine. 2000. Cutis; cutaneous medicine for the practitioner	No relevant study population - sample includes people with facial oiliness
Ochsendorf, F.Clindamycin phosphate 1.2% / tretinoin 0.025%: a novel fixed-dose combination treatment for acne vulgaris. 2015. Journal of the European Academy of Dermatology & Venereology	No relevant study design - not RCT
Oh, S. H. R., D. J.,Han, E. C.,Lee, K. H.,Lee, J. H.A comparative study of topical 5-aminolevulinic acid incubation times in photodynamic therapy with intense pulsed light for the treatment of inflammatory acne. 2009. Dermatologic Surgery	Split face study - but randomised treatments not compared directly in the same participants.
Olafsson, J. H. G., J.,Eggertsdottir, G. E.,Kristjansson, F.Doxycycline versus minocycline in the treatment of acne vulgaris: A double-blind study. 1989. Journal of Dermatological Treatment	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in

Reference	Reason for exclusion
	the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Olivier, S. D., A.,Bierschwale, H.,Archer, D.Efficacy of a low-dose oral contraceptive (20mcg ethinyl estradiol/100 mcg levonorgestrel) for the treatment of moderate acne. 2003. International journal of obstetrics & gynecology	No relevant article type - conference abstract
Olson, W. H. L., J. S.,Robisch, D. M.The duration of response to norgestimate and ethinyl estradiol in the treatment of acne vulgaris. 1998. International Journal of Fertility and Women's Medicine	No relevant data reported - reports combined results from Redmond 1997 and Lucky 1997 trials
Oprica, C. E., L.,Hagstromer, L.,Nord, C. E.Clinical and microbiological comparisons of isotretinoin vs. tetracycline in acne vulgaris. 2007. Acta Dermato-Venereologica	No relevant data - insufficient data reported
Orafidiya, L. O. A., E. O.,Oyedele, A. O.,Babalola, O. O.,Onayemi, O.Preliminary clinical tests on topical preparations of Ocimum gratissimum linn leaf essential oil for the treatment of acne vulgaris. 2002. Clinical Drug Investigation	No relevant study population - no information about severity of acne reported and study is not relevant for PCOS, maintenance or refractory treatments
Orafidiya,The effect of aloe vera gel on the anti-acne properties of the essential oil of Ocimum gratissimum Linn leaf - A preliminary clinical investigation. 2004. NA	No relevant intervention - Ocimum oil lotion and aloe gel
Orringer, J. S. K., S.,Hamilton, T.,Schumacher, W.,Cho, S.,Hammerberg, C.,Fisher, G. J.,Karimipour, D. J.,Johnson, T. M.,Voorhees, J. J.Treatment of acne vulgaris with a pulsed dye laser: A randomized controlled trial. 2004. Journal of the American Medical Association	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Orringer, J. S. K., S.,Maier, L.,Johnson, T. M.,Sachs, D. L.,Karimipour, D. J.,Helfrich, Y. R.,Hamilton, T.,Voorhees, J. J.A randomized, controlled, split-face clinical trial of 1320-nm Nd:YAG laser therapy in the treatment of acne vulgaris. 2007. Journal of the American Academy of Dermatology	No relevant study population - sample includes people mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Orringer, J. S. S., D. L.,Bailey, E.,Kang, S.,Hamilton, T.,Voorhees, J. J.Photodynamic therapy for acne vulgaris: A randomized, controlled, split-face clinical trial of topical aminolevulinic acid and pulsed dye laser therapy. 2010. Journal of Cosmetic Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Owens, D. W.Clinical evaluation of topical vitamin A acid in therapy of acne vulgaris. 1973. Texas Medicine	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory

Reference	Reason for exclusion
	treatments
Ozgen, Z. Y. G., O.A randomized, double-blind comparison of nadifloxacin 1% cream alone and with benzoyl peroxide 5% lotion in the treatment of mild to moderate facial acne vulgaris. 2013. Marmara Medical Journal	No relevant intervention - nadifloxacin 1% cream not available in the UK
Ozkan, M. D., G.,Sabuncu, I.,Saracoglu, N.,Akgun, Y.,Urer, S. M.Clinical efficacy of topical clindamycin phosphate and azelaic acid on acne vulgaris and emergence of resistant coagulase-negative staphylococci. 2000. Turkish Journal of Medical Sciences	Duplicate record
Ozolins, M. E., E. A.,Avery, A.,Cunliffe, W. J.,O'Neill, C.,Simpson, N. B.,Williams, H. C.Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne. 2005. Health technology assessment (Winchester, England)	No relevant article type - executive summary of Ozolins 2004 trial
PÃ©rez LÃ³pez, M. M. V., J. M.A new salt of erythromycin (A-137 or erythromycin lauryl sulfate) in the topical treatment of acne. 1982. Medicina cutanea ibero-latino-americana	Not in English language
Packman, A. M. B., R. H.,Dunlap, F. E.,Kraus, S. J.,Webster, G. F.Treatment of acne vulgaris: Combination of 3% erythromycin and 5% benzoyl peroxide in a gel compared to clindamycin phosphate lotion. 1996. International Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Padilla, R. S. M., J. M.,Becker, L. E.Topical tetracycline hydrochloride vs. topical clindamycin phosphate in the treatment of acne: a comparative study. 1981. International Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Pai, I. F. W., Y. C.,Lu, Y. C.Clinical trial of cyproterone acetate-ethinyl oestradiol compound on androgen dependent skin disorders. 1982. Taiwan i Hsueh Hui Tsa Chih - Journal of the Formosan Medical Association	Not in English language
Palacios, S. W., L.,Parke, S.,Machlitt, A.,Romer, T.,Bitzer, J.Efficacy and safety of a novel oral contraceptive based on oestradiol (oestradiol valerate/dienogest): A Phase III trial. 2010. European Journal of Obstetrics and Gynecology and Reproductive Biology	No relevant study population - participants did not have acne
Palatsi, R. H., E.,Liukko, P.,Malmiharju, T.,Mattila, L.,Riihiluoma, P.,Ylostalo, P.Serum total and unbound testosterone and sex hormone binding globulin (SHBG) in female acne patients treated with two different oral contraceptives. 1984. Acta Dermato-Venereologica	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Palatsi, R. R., M.,Kivinen, S.Pituitary function and DHEA-S in male acne and DHEA-S, prolactin and cortisol before and after oral contraceptive treatment in female acne. 1986. Acta Dermato-Venereologica	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Pandey, D. A., S.Efficacy of isotretinoin and antihistamine versus isotretinoin alone in the treatment of moderate to severe acne: A randomised control trial. 2019. Kathmandu University Medical Journal	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in

Reference	Reason for exclusion
	the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Panzer, J. D. P., W.,Meek, T. J.,Derbes, V. J.,Atkinson, W.Acne treatment: A comparative efficacy trial of clindamycin and tetracycline. 1977. Cutis	No relevant data - insufficient data reported
Pariser, D. B., A.,Fried, R.,Jarratt, M. T.,Kempers, S.,Kircik, L.,Lucky, A. W.,Rafal, E.,Rendon, M.,Weiss, J.,et al.,Tretinoin gel microsphere pump 0.04% plus 5% benzoyl peroxide wash for treatment of acne vulgaris: morning/morning regimen is as effective and safe as morning/evening regimen. 2010. Journal of drugs in dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Pariser, D. C., L. E.,Johnson, L. A.,Gottschalk, R. W.Adapalene 0.1% gel compared to tazarotene 0.1% cream in the treatment of acne vulgaris. 2008. Journal of drugs in dermatology : JDD	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Pariser, D. M., Green, L. J., Lain, E. L., Schmitz, C., Chinigo, A. S., McNamee, B., Berk, D. R.Safety and tolerability of sarecycline for the treatment of acne vulgaris: results from a phase III, multicenter, open-label study and a phase I phototoxicity study. 2019. Journal of Clinical and Aesthetic Dermatology	No relevant study design - participants were not randomised on entry to the study and study is not relevant for PCOS, maintenance or refractory treatments
Park, K. Y. K., E. J.,Seo, S. J.,Hong, C. K.Comparison of fractional, nonablative, 1550-nm laser and 595-nm pulsed dye laser for the treatment of facial erythema resulting from acne: A split-face, evaluator-blinded, randomized pilot study. 2014. Journal of Cosmetic and Laser Therapy	No relevant study population - sample includes people with acne erythema
Parker, F.A comparison of clindamycin 1% solution versus clindamycin 1% gel in the treatment of acne vulgaris. 1987. International Journal of Dermatology	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Pastrana-Ruiz, M. E. V.-M., M. E.,Hojyo-Tomoka, M. T.,Dom inguez-Soto, L.Antibiotics for the treatment of acne. Double-blind comparative study with a 1% solution of clindamycin phosphate versus 500 mg oral tetracycline in patients with moderate acne. 1989. Dermatologia revista mexicana	Not in English language
Patel, V. B. M., A. N.,Marfatia, Y. S.Preparation and comparative clinical evaluation of liposomal gel of benzoyl peroxide for acne. 2001a. Drug Development and Industrial Pharmacy	No relevant study design - not RCT
Patel, V. B. M., A.,Marfatia, Y. S.Clinical assessment of the combination therapy with liposomal gels of tretinoin and benzoyl peroxide in acne. 2001b. AAPS PharmSciTech	No relevant study design - not RCT
Paver, K.Complications from combined oral tetracycline and oral	Not obtainable

Reference	Reason for exclusion
corticoid therapy in acne vulgaris. 1970. Medical Journal of Australia	
Pavithra, G. U., G. M.,Rukmini, M. S.A randomized controlled trial of topical benzoyl peroxide 2.5% gel with a low glycemic load diet versus topical benzoyl peroxide 2.5% gel with a normal diet in acne (grades 1-3). 2018. Indian Journal of Dermatology, Venereology & Leprology	No relevant study population - insufficient details reported to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Peachey, R. D. C., B. L.Topical retinoic acid in the treatment of acne vulgaris. 1971. British Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Peck, G. L. O., T. G.,Butkus, D.,Pandya, M.,Arnaud-Battandier, J.,Gross, E. G.,Windhorst, D. B.,Cheripko, J.Isotretinoin versus placebo in the treatment of cystic acne. A randomized double-blind study. 1982b. Journal of the American Academy of Dermatology	No relevant data - insufficient data reported
Peck, G. L. O., T. G.,Butkus, D.Isotretinoin versus placebo in the treatment of cystic acne. 1982a. Journal of the American Academy of Dermatology	Duplicate record
Pedace, F. J. S., R.Topical retinoic acid in acne vulgaris. 1971. The British journal of dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Peereboom-Wynia, J. D. R. C., P. J. G.,Bernsen, R.A new alcohol-free preparation of benzoyl peroxide gel (Basiron) for acne vulgaris. A double blind trial. 1984. TGO - Tijdschrift voor Therapie Geneesmiddel en Onderzoek	Not in English language
Peker, M. T., H. B.,Arca, E.,Erbil, A. H.,Gur, A. R.Efficacy of topical erythromycin, tetracycline and clindamycin in the treatment of acne vulgaris. 2004. Deri hastaliklari ve frengi arsivi	Not in English language
Perez, M. A., F.,De Moragas, J. M.A double blind study comparing clindamycin-phosphate versus oral tetracycline in acne treatment. 1987b. Medicina cutanea ibero-latino-americana	Not in English language
Perez, M. A., F.,De Moragas, J. M.Comparative double-blind study of topical clindamycin phosphate and oral tetracycline in the treatment of acne. 1987a. Medicina cutanea ibero-latino-americana	Not in English language
Petit, L. P.-F., C.,Uhoda, E.,Vroome, V.,Cauwenbergh, G.,Pierard, G. E.Coping with mild inflammatory catamenial acne: a clinical and bioinstrumental split-face assessment. 2004. Skin Research & Technology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Pierard-Franchimont, C. G., V.,Arrese, J. E.,Martalo, O.,Braham, C.,Slachmuylders, P.,Pierard, G. E.Lymecycline and minocycline in inflammatory acne: A randomized, double-blind intent-to-treat study on clinical and in vivo antibacterial efficacy. 2002. Skin Pharmacology	Antibiotic dosages lower than BNF values

Reference	Reason for exclusion
and Applied Skin Physiology	
Pierard-Franchimont, C. H., F.,Fraiture, A. L.,Fumal, I.,Pierard, G. E.Split-face clinical and bio-instrumental comparison of 0.1% adapalene and 0.05% tretinoin in facial acne. 1999. Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Pinto, C. S., F.,Orellana, J. J.,Gonzalez, S.,Hasson, A.Efficacy of red light alone and methyl-aminolaevulinate-photodynamic therapy for the treatment of mild and moderate facial acne. 2013. Indian Journal of Dermatology, Venereology & Leprology	No relevant study design - not RCT
Pisani, M. G., V.,Grimaldi, F. F.Treatment of acne vulgaris with an ointment containing azelaic acid (12%), L-carnitine (2%), enoxolone (1%): double-blind study versus placebo. TRATTAMENTO DELL'ACNE VOLGARE CON UNA CREMA A BASE DI ACIDO AZELAICO (12%), L-CZRNITINA (2%), ENOXOLONE (1%): STUDIO IN DOPPIO CIECO VERSUS PLACEBO. 1991. Chron dermatol	Not in English language
Plewig, G. D., H.,Pfleger, M.,Michelsen, S.,Kligman, A. M.Low dose isotretinoin combined with tretinoin is effective to correct abnormalities of acne. 2004. Journal der Deutschen Dermatologischen Gesellschaft	Not in English language
Plewig, G. H., K. T.,Nenoff, P.Clinical and bacteriological evaluation of nadifloxacin 1% cream in patients with acne vulgaris: A double-blind, phase III comparison study versus erythromycin 2% cream. 2006. European Journal of Dermatology	No relevant intervention - nadifloxacin 1% cream not available in the UK
Plewig, G.Dermabrasion for nodular cutaneous elastosis with cysts and comedones. 1972. Archives of Dermatology	Not obtainable
Plewig, G.Vitamin A acid. Topical treatment in acne vulgaris. 1969. Pennsylvania Medicine	No relevant population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Pochi, P. E. B., F. K.,Ellis, C. N.,Stoughton, R. B.,Whitmore, C. G.,Saatjian, G. D.,Sefton, J.Erythromycin 2 percent gel in the treatment of acne vulgaris. 1988. Cutis	Not obtainable
Podfigurna, 2019Clinical, hormonal and metabolic parameters in women with PCOS with different combined oral contraceptives (containing chlormadinone acetate versus drospirenone). 2019. Journal of Endocrinological Investigation	Duplicate of Podfigurna 2020
Polakova, K. F., A.,Sayag, M.,Jourdan, E.Adermocosmetic containing bakuchiol, Ginkgo biloba extract and mannitol improves the efficacy of adapalene in patients with acne vulgaris: Result from a controlled randomized trial. 2015. Clinical, Cosmetic and Investigational Dermatology	No relevant intervention - bakuchiol, Ginkgo biloba extract, and mannitol complex
Pollock, B. T., D.,Stringer, M. R.,Bojar, R. A.,Goulden, V.,Stables, G. I.,Cunliffe, W. J.Topical aminolaevulinic acid-photodynamic therapy for the treatment of acne vulgaris: A study of clinical efficacy and mechanism of action. 2004. British Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and

Reference	Reason for exclusion
	refractory treatments
Ponzio, H. A. B., R. T.,Bozko, M. P.Clinical evaluation of a line of products for the control of acne in teenagers. 1994. Anais brasileiros de dermatologia	Not in English language
Poulos, E. T. T., F. J.Acne vulgaris. Double blind trial comparing tetracycline and clindamycin. 1976. Archives of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Prasad, S. M., A.,Kubavat, A.,Kelkar, A.,Modi, A.,Swarnkar, B.,Bajaj, B.,Vedamurthy, M.,Sheikh, S.,Mittal, R.Efficacy and safety of a nano-emulsion gel formulation of adapalene 0.1% and clindamycin 1% combination in acne vulgaris: A randomized, open label, active-controlled, multicentric, phase IV clinical trial. 2012. Indian Journal of Dermatology, Venereology and Leprology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Prendiville, J. S. L., R. A.,Russell-Jones, R.A comparison of dapsone with 13-cis retinoic acid in the treatment of nodular cystic acne. 1988. Clinical and Experimental Dermatology	No relevant data reported - group numbers not reported
Pria, S. D. G., R. B.,Mahesh, V. B.An antiandrogen in acne and idiopathic hirsutism. 1969. Journal of Investigative Dermatology	No relevant study design - not RCT
Priano, L. B., S.,Isola, V.,Grazioli, I.,Melzi, G.,Massone, L.Topical spironolactone 5% versus benzoylperoxide 5% + miconazole 2% in the therapy of acne: double-blind, controlled study to evaluate the efficacy and the eventual systemic absorption. 1993. Giornale italiano di dermatologia e venereologia	Not in English language
Prince, R. A. B., D. A.,Hepler, C. D.,Feldick, H. G.Clinical trial of topical erythromycin in inflammatory acne. 1981. Drug Intelligence & Clinical Pharmacy	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Prince, R. A. H., J. M.,Maroc, J. A.Comparative trial of benzoyl peroxide versus benzoyl peroxide with urea in inflammatory acne. 1982. Cutis	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Privitera, G. B., S.,Del Mastro, S.Clinical and pharmacokinetic evaluation of josamycin in the treatment of inflammatory acne. 1989. Journal of Chemotherapy	No relevant study deisgn - not RCT
Rafanelli, A. G., I.,Melzi, G.A controlled study spironolactone vs progesterone in the topical treatment of acne. 1993. Giornale italiano di dermatologia e venereologia	Not in English language
Rafiei R, Yaghoobi RAzithromycin versus tetracycline in the treatment of acne vulgaris.. 2006. J Dermatolog Treat	No relevant intervention - suboptimal dose of tetracycline
Raimer, S. M., J. M.,Bourcier, M.,Wilson, D.,Papp, K.,Siegfried, E.,Garrett, S.Efficacy and safety of dapsone gel 5% for the treatment	No relevant study population - sample

Reference	Reason for exclusion
of acne vulgaris in adolescents. 2008. Cutis	includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Rajka, G.On therapeutic approaches to some special types of acne. 1985. Acta Dermato-Venereologica. Supplementum	No relevant study deisgn - not RCT
Raoof, J., Hooper, D., Moore, A., Zaiac, M., Sullivan, T., Kircik, L., Lain, E., Jankicevic, J., Stuart, I.FMX101 4% topical minocycline foam for the treatment of moderate-to-severe acne vulgaris: efficacy and safety from a Phase III randomized, doubleblind, vehicle-controlled study. 2019. Journal of Clinical and Aesthetic Dermatology	No relevant article type - conference abstract
Raoof, T. J. H., D.,Moore, A.,Zaiac, M.,Sullivan, T.,Kircik, L.,Lain, E.,Jankicevic, J.,Stuart, I.Efficacy and Safety of a Novel Topical Minocycline Foam for the Treatment of Moderate-to-Severe Acne Vulgaris: A Phase 3 Study. 2019. Journal of the American Academy of Dermatology.	No relevant intervention - FMX101 4% topical minocycline foam not available in the UK
Raoof, T. J., Hooper, D., Moore, A., Zaiac, M., Sullivan, T., Kircik, L., Lain, E., Jankicevic, J., Stuart, I.Efficacy and safety of a novel topical minocycline foam for the treatment of moderate to severe acne vulgaris: A phase 3 study. 2020. Journal of the American Academy of Dermatology	No relevant intervention - FMX101 4% topical minocycline foam not available in the UK
Rapaport, M. P., S. M.,Reisner, R. M.Evaluation of topical erythromycin and oral tetracycline in acne vulgaris. 1982. Cutis; cutaneous medicine for the practitioner	No relevant intervention - suboptimal dose of tetracycline
Rassai, S. R., E.,Ramirez-Fort, M. K.,Feily, A.Adjuvant Narrow Band UVB Improves the Efficacy of Oral Azithromycin for the Treatment of Moderate to Severe Inflammatory Facial Acne Vulgaris. 2014. Journal of Cutaneous & Aestheic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Rea, S. T., S.,Frittelli, V.,Gunnarsson, R.A feasibility study for a triple-blind randomized controlled trial investigating the effects of oral isotretinoin on mood and quality of life in patients with acne vulgaris. 2017. Clinical and experimental dermatology	No releavant study design - not RCT
Rea, S. T., S.,Frittelli, V.,Gunnarsson, R.A feasibility study for a triple-blind randomized controlled trial investigating the effects of oral isotretinoin on mood and quality of life in patients with acne vulgaris. 2018. Clinical and Experimental Dermatology	Duplicate record
Rebillo, T. H., J. L.Skin surface glycerol levels in acne vulgaris. 1978. Journal of Investigative Dermatology	No relevant study design - not RCT
Redmond, G. P. G., G. P.,Gupta, M. K.,Bedocs, N. M.,Parker, R.,Skibinski, C.,Bergfeld, W.Treatment of androgenic disorders with dexamethasone: dose-response relationship for suppression of dehydroepiandrosterone sulfate. 1990. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with hirsuitism or alopecia, only 11% participants with acne
Reinel, D. B., H.A new drug combination for the topical treatment of acne. Miconazole 2% + benzoyl peroxide 5% versus benzoyl peroxide 5%--a double-blind study. 1985. Zeitschrift fur hautkrankheiten	Not in English language
Richter, C. T., C.,Hillmann, K.,Dobos, G.,Stroux, A.,Kottner, J.,Blume-Peytavi, U.Reduction of Inflammatory and Noninflammatory Lesions with Topical Tyrothricin 0.1% in the Treatment of Mild to Severe Acne	No relevant intervention - topical Tyrothricin;nNo relevant study population -

Reference	Reason for exclusion
Papulopustulosa: A Randomized Controlled Clinical Trial. 2016. Skin Pharmacology and Physiology	sample includes people with mild to severe acne
Richter, J. R. F., L. R.,Kiistala, U. O.,Jung, E. G.Efficacy of the fixed 1.2% clindamycin phosphate, 0.025% tretinoin gel formulation (Velac) and a proprietary 0.025% tretinoin gel formulation (Aberela) in the topical control of facial acne. 1998b. Journal of the European Academy of Dermatology and Venereology	Duplicate record
Rietschel, R. L. D., S. H.Benzoyl peroxide reactions in an acne study group. 1982. Contact Dermatitis	No relevant data reported - pharmokinetic study
Rietschel, R. L. D., S. H.Clindamycin phosphate used in combination with tretinoin in the treatment of acne. 1983. International Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Rist, T. D., M. W.Study design and selection criteria in the BEST study. 2003. Cutis	No relevant data reported
Rivkin, L. R., M.Clinical evaluation of a new erythromycin solution for acne vulgaris. 1980. Cutis	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Riyanto, P. S., P.,Lelyana, R.Advantage of soybean isoflavone as antiandrogen on acne vulgaris. 2015. Dermato-Endocrinology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Robinson, S. K., Z.,Tang, M. M.Metformin as an adjunct therapy for the treatment of moderate to severe acne vulgaris: A randomized open-labeled study. 2019. Dermatologic Therapy	Dosage of tetracycline lower than BNF value
Robledo Aguilar, A. L. B., E.,del Pino Gamboa, J.,Sambricio Guiu, F.,Rodriguez Pichardo, A.,Sotillo Gago, I.,Chaparro Martinez, A.,Garcia Aparicio, P. G.Multicentric comparative study of the efficacy and tolerance of clindamycin phosphate 1% topical solution and tetracycline topical solution for the treatment of acne vulgaris. 1988. Current therapeutic research - clinical and experimental	No relevant intervention - tetracycline topical solutio not available in the UK
Rocha, M. A. D. G., L. R. S.,Sanudo, A.,Bagatin, E.Modulation of Toll Like Receptor-2 on sebaceous gland by the treatment of adult female acne. 2017a. Dermato-endocrinology	No relevant study design - not RCT
Rocha, M. C., K. H. M.,Carvalho, V. M.,Bagatin, E.ADT-G as a promising biomarker for peripheral hyperandrogenism in adult female acne. 2017b. Dermato-endocrinology	No relevant data reported - pharmokinetic study
Rocha, M. S., A.,Bagatin, E.The effect on acne quality of life of topical azelaic acid 15% gel versus a combined oral contraceptive in adult female acne: A randomized trial. 2017c. Dermato-endocrinology	No relevant data reported - quality of life data only
Rojanamatin, J. C., P.Treatment of inflammatory facial acne vulgaris with intense pulsed light and short contact of topical 5-aminolevulinic acid: a pilot study. 2006. Dermatologic Surgery	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory

Reference	Reason for exclusion
	treatments
Romiti, N.Use of the aromatic retinoid Ro-11-1430 for acne therapy. 1978. Pharmatherapeutica	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Ruamrak, C. L., N.,Natakankitkul, S.Comparison of clinical efficacies of sodium ascorbyl phosphate, retinol and their combination in acne treatment. 2009. International Journal of Cosmetic Science	No relevant study population - sample includes people with mild to severe acne; No relevant intervention - topical sodium ascorbyl phosphate
Ruxton,A novel topical ingredient derived from seaweed significantly reduces symptoms of acne vulgaris: a general literature review. 2013. NA	No relevant intervention - marine-derived ingredients for acne
Ryou, J. H. L., S. J.,Park, Y. M.,Kim, H. O.,Kim, H. S.Acne-photodynamic therapy with intra-lesional injection of 5-aminolevulinic acid. 2009. Photodermatology, Photoimmunology & Photomedicine	No relevant study design - not RCT
Sadick, N. S. L., Z.,Laver, L.Treatment of mild-to-moderate acne vulgaris using a combined light and heat energy device: Home-use clinical study. 2010c. Journal of Cosmetic and Laser Therapy	No relevant article type - conference abstract
Sadick, N., Edison, B. L., John, G., Bohnert, K. L., Green, B.An Advanced, Physician-Strength Retinol Peel Improves Signs of Aging and Acne Across a Range of Skin Types Including Melasma and Skin of Color. 2019. Journal of Drugs in Dermatology: JDDJ Drugs Dermatol	Not obtainable
Sadick, N.An open-label, split-face study comparing the safety and efficacy of levulan kerastick (aminolevulonic acid) plus a 532 nm KTP laser to a 532 nm KTP laser alone for the treatment of moderate facial acne. 2010a. Journal of Drugs in Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Saihan, E. M. B., J. L.,Meyrick, G.,Speller, D. C.,Thornton, E.,Chestney, V.The effect of a topical antibiotic preparation in acne vulgaris--a controlled clinical and laboratory study. 1981. British Journal of Clinical Practice	No relevant intervention - actinac discontinued in the UK
Salagnac, V. L., F.,De, L. O.,Le, C. Y.,Kalis, B.Topical treatment of actinic ageing with vitamin A acid at various concentrations. TRAITEMENT DU VIEILLISSEMENT ACTINIQUE PAR LA VITAMINE A ACIDE TOPIQUE A DIFFERENTES CONCENTRATIONS. 1991. REV. FR. GYNECOL. OBSTET.	Not in English language
Sampaio, S. A. P. M., H. C. B.,Freitas, T. H. P.,Totoli, Sasm,Martins, MrfcA multicenter trial comparing the efficacy and tolerance of isotretinoin gel 0,05% and tretinoin cream 0.05% in the treatment of acne vulgaris. 1997. Revista brasileira de medicina	Not in English language
Sanam, M. Z., O.Desogestrel+ethinylestradiol versus levonorgestrel +ethinylestradiol: Which one has better affect on acne, hirsutism, and weight change. 2011. Saudi Medical Journal	No relevant study population - participants did not have acne
Santos, M. A. B., V. G.,Santos, G.Effectiveness of photodynamic	No relevant study

Reference	Reason for exclusion
therapy with topical 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone in the treatment of acne vulgaris: comparative study. 2005. Dermatologic Surgery	population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Santos-Caetano, J. P. C., M. R.A Randomized Controlled Tolerability Study to Evaluate Reformulated Benzoyl Peroxide Face Washes for Acne Vulgaris. 2019. Journal of drugs in dermatology : JDD	No relevant intervention - intervention is washed off the face
Sardesai Vkambli, V.Comparison of efficacy of topical clindamycin and nicotinamide combination with plain clindamycin for the treatment of acne vulgaris and acne resistant to topical antibiotics. 2003. Indian journal of dermatology, venereology and leprology	No relevant study design - not RCT
Sauer, G. C.Prospective study on the safety of long-term tetracycline therapy for acne. 1981. Cutis	No relevant study design - not RCT
Sayyafan, M. S. R., M.,Salmanpour, R.Clinical assessment of topical erythromycin gel with and without zinc acetate for treating mild-to-moderate acne vulgaris. 2019. Journal of Dermatological Treatment.	No relevant study design - not RCT
Sayyafran, 2019 Clinical assessment of topical erythromycin gel with and without zinc acetate for treating mild-to-moderate acne vulgaris. 2019. Journal of Dermatological Treatment	Duplication of Sayyafan 2019
Schachner, L. E., W.,Kittles, C.,Mertz, P.Topical erythromycin and zinc therapy for acne. 1990a. Journal of the American Academy of Dermatology	No relevant data - insufficient data reported
Schachner, L. P., A.,Kittles, C.A clinical trial comparing the safety and efficacy of a topical erythromycin-zinc formulation with a topical clindamycin formulation. 1990b. Journal of the American Academy of Dermatology	No relevant data - insufficient data reported
Scheinfeld, N.ABSORICA (isotretinoin): a new form. 2013. SKINmed	No relevant study design - not RCT
Schlessinger, J. M., A.,Gold, M.,Leonardi, C.,Eichenfield, L.,Plott, R. T.,Leyden, J.,Wortzman, M.Clinical safety and efficacy studies of a novel formulation combining 1.2% clindamycin phosphate and 0.025% tretinoin for the treatment of acne vulgaris. 2007. Journal of drugs in dermatology : JDD	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Schutte, H. C., W. J.,Forster, R. A.The short-term effects of benzoyl peroxide lotion on the resolution of inflamed acne lesions. 1982. British Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne
Schwanitz, H. J. M., E.Internal versus topical tetracycline therapy of acne. 1984. Zeitschrift fur hautkrankheiten	Not in English language
Scott, A. M., Stehlik, P., Clark, J., Zhang, D., Yang, Z., Hoffmann, T., Mar, C. D., Glasziou, P.Blue-Light Therapy for Acne Vulgaris: A Systematic Review and Meta-Analysis. 2019. Annals of Family Medicine	Systematic review - references were checked for relevance
Semprini, A., Braithwaite, B., Corin, A., Sheahan, D., Tofield, C., Helm, C., Montgomery, B., Fingleton, J., Weatherall, M., Beasley, R. Randomised controlled trial of topical kanuka honey for the treatment of acne. 2016. BMJ Open	No relevant intervention - compairson of addition of topical 90% medicalgrade kanuka honey and 10% glycerine to standard antibacterial soap wash with antibacterial soap wash alone
Sen, A. K., S.,Chatterjee, R. N.,Sarkar, M.,Bhattacharjee, S.,Ram, A.	No relevant article type -

Reference	Reason for exclusion
K.Acomparativestudyof efficacy and safetyoftopical clindamycingelversus combination of clindamycingeland benzoylperoxidecreamin patients ofmildtomoderateacnevulgaris. 2013. Indian Journal of Pharmacology	conference abstract
Shafiq, Y. N., B. S.,Rizwani, G. H.,Usman, M.,Shah, B. A.,Aslam, M.,Hina, B.Anti-acne activity of Casuarina equisetifolia bark extract: a randomized clinical trial. 2014. Bangladesh journal of pharmacology	No relevant intervention - Casuarina equisetifolia bark extract (5% cream)
Shaheen, J. A. K., M.,Kareem, A.,Ahmad, M.,Ansari, N. U. H.,Ahmad, I.Clinical evaluation of roxithromyin in acne vulgaris: Comparison of daily versus alternate day regimen. 2005. Journal of Pakistan Association of Dermatologists	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Shahid, J. K., T.Tretinoin cream versus benzoyl peroxide(10%) gel in the tropical treatment of mild acne vulgaris. 1996. Biomedica	Not obtainable
Shahlita, A. R. S., E. B.,Bauer, E.Topical erythromycin v clindamycin therapy for acne. A multicenter, double-blind comparison. 1984. Archives of Dermatology	No relevant study population - insufficient information to determine severity of acne
Shahmoradi, Z. I., F.,Siadat, A. H.,Ghorbaini, A.,Nilforoushzadeh, M. A.Comparison of topical 5% nicotinamid and 2% clindamycin gels in the treatment of the mild to moderate acne vulgaris: a double-blinded randomized clinical trial. 2015. Journal of isfahan medical school	Not in English language
Shahmoradi, Z. I., F.,Siadat, A. H.,Ghorbaini, A.Comparison of topical 5% nicotinamid gel versus 2% clindamycin gel in the treatment of the mild-moderate acne vulgaris: A double-blinded randomized clinical trial. 2013. Journal of Research in Medical Sciences	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Shalita, A. M., B.,Menter, A.,Abramovits, W.,Loven, K.,Kakita, L.Tazarotene cream versus adapalene cream in the treatment of facial acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. 2005. Journal of drugs in dermatology : JDD	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Shalita, A. R. B., D. S.,Thiboutot, D. M.,Leyden, J. J.,Parizadeh, D.,Sefton, J.,Walker, P. S.,Gibson, J. R.Effects of tazarotene 0.1% cream in the treatment of facial acne vulgaris: Pooled results from two multicenter, double-blind, randomized, vehicle-controlled, parallel-group trials. 2004. Clinical Therapeutics	No relevant data reported - reports pooled result from 2 trials combined
Shalita, A. R. C., D. K.,Parish, L. C.,Bernstein, J. E.,Evans, C. S.The effects of topical nicotinamide on acne vulgaris. 1992. Journal of investigative dermatology	No relevant article type - conference abstract
Shalita, A. R. R., E. S.,Anderson, D. N.,Yavel, R.,Landow, S.,Lee, W. L.Compared efficacy and safety of tretinoin 0.1% microsphere gel alone and in combination with benzoyl peroxide 6% cleanser for the treatment of acne vulgaris. 2003. Cutis	No relevantinternvention - facial cleanser; No relevant study population - insufficient information to determine seveirty of acne and study is not relevant for PCOS, maintenance or refractory treatments

Reference	Reason for exclusion
Shalita, A. R.Comparison of a salicylic acid cleanser and a benzoyl peroxide wash in the treatment of acne vulgaris. 1989. Clinical therapeutics	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Shalita, A. R.Comparison of a salicylic acid cleanser and a benzoyl peroxide wash in the treatment of acne vulgaris: COMPARACAO ENTRE SISTEMA DE LIMPEZA COM ACIDO SALICILICO E SOLUCAO DE PEROXIDO DE BENZOILA NO TRATAMENTO DO ACNE VULGARIS. 1998. Revista brasileira de medicina	Not in English language
Shalita, A. W., J. S.,Chalker, D. K.,Ellis, C. N.,Greenspan, A.,Katz, H. I.,Kantor, I.,Millikan, L. E.,Swinehart, T.,Swinyer, L.,et al.,A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: a multicenter trial. 1996. Journal of the American Academy of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Sharma, A. D. G., P. D.,Sundaram, M.,Janaki, V. R.,Rege, V. L.,Bilimoria, F. E.,Arora, J.Topical lincomycin gel in acne vulgaris: A multicentric placebo controlled study. 2003. Indian Journal of Dermatology, Venereology and Leprology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Sharquie,Treatment of acne vulgaris with 2% topical tea lotion. 2006. NA	No relevant intervention - 2% tea lotion
Sheehan-Dare, R. A. P.-S., J. W.,Cunliffe, W. J.A comparative study between topical clindamycin and oral minocycline in the treatment of acne vulgaris. 1989. Round table series - royal society of medicine	Duplicate record
Sheehan-Dare, R. A. P.-S., J.,Cunliffe, W. J.A double-blind comparison of topical clindamycin and oral minocycline in the treatment of acne vulgaris. 1990. Acta Dermato-Venereologica	No relevant data - insufficient data reported
Shen, W. T., Wu, Y., He, H. Q., Yu, Y., Qin, H. H., Fei, J. B., Wang, G. J.Efficacy and safety of artemether emulsion for the treatment of mild-to-moderate acne vulgaris: a randomized pilot study. 2020. Journal of Dermatological Treatment	No relevant intervention - artemether
Shetti, S. A. N., H. N.,Hanumantharaya, N.A randomized, open-label, comparative study of efficacy of low-dose continuous versus low-dose intermittent oral isotretinoin therapy in moderate-to-severe acne vulgaris. 2017. National Journal of Physiology, Pharmacy and Pharmacology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Shie Morteza, M., Hayati, Z., Namazi, N., Abdollahimajd, F.Efficacy	No relevant intervention -

Reference	Reason for exclusion
and safety of oral silymarin in comparison with oral doxycycline and their combination therapy in the treatment of acne vulgaris. 2019. Dermatologic Therapy	silymarin
Shin JU, Lee SH, Jung JY, Lee JH.A split-face comparison of a fractional microneedle radiofrequency device and fractional carbon dioxide laser therapy in acne patients.. 2012. J Cosmet Laser Ther	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Shwetha, H. G., A.A comparative study of efficacy and safety of combination of topical 1% clindamycin and 0.1% adapalene with 1% clindamycin and 2.5% benzoyl peroxide in mild to moderate acne in a tertiary care hospital. 2013. Indian Journal of Pharmacology	No relevant article type - conference abstract
Sidgiddi, 2019Efficacy of oral isotretinoin in combination with desloratadine in the treatment of common vulgaris acne in Vietnamese Patients. 2019. Open Access Macedonian Journal of Medical Sciences	Duplication of Van 2019
Sidgiddi, S., Allenby, K., Okumu, F., Gautam, A.Bioavailability, Pharmacokinetics, and Transepidermal Water Loss of Short Contact Tazarotene Lotion 0.1% Versus Tazarotene (Tazorac^R) Cream 0.1. 2019. The Journal of Clinical & Aesthetic DermatologyJ Clin Aesthet Dermatol	The paper reports 2 studies, both do not meet inclusion criteria: the first one describes a non-relevant comparison and the second one does not reported severity of acne
Simpson, N. B. B., P. E.,Forster, R. A.,Cunliffe, W. J.The effect of topically applied progesterone on sebum excretion rate. 1979. British Journal of Dermatology	No relevant data reported - pharmokinetic study
Simpson, N. B. M., K. A.5% Aluminium chloride hexahydrate and sebum excretion rate. 1982. Acta Dermato-Venereologica	Duplicate record
Singhi, M. G. B. R.Comparison of oral azithromycin pulse with daily doxycycline in the treatment of acne vulgaris. 2003. Indian journal of dermatology, venereology and leprology	No relevant study design - not RCT
Skidmore, R. K., R.,Walker, C.,Thomas, J.,Bradshaw, M.,Leyden, J.,Powala, C.,Ashley, R.Effects of subantimicrobial-dose doxycycline in the treatment of moderate acne. 2003. Archives of Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Smit, F.Minocycline versus doxycycline in the treatment of acne vulgaris. A double-blind study. 1978. Dermatologica	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Smith, E. B. P., R. S.,McCabe, J. M.,Becker, L. E.Benzoyl peroxide lotion (20%) in acne. 1980a. Cutis	Duplicate record

Reference	Reason for exclusion
Smith, J. G., Jr.,Chalker, D. K.,Wehr, R. F.The effectiveness of topical and oral tetracycline for acne. 1976. Southern Medical Journal	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Smith, M. A., Waterworth, P. M., & Curwen, M. P.A controlled trial of oral antibiotics in the treatment of acne vulgaris. 1962. British journal of dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Soldo-Belic, A. C., V.,Vujic-Podlipec, D.,Oremovic, L.,Sviben-Radovcic, Z.,Kostovic, K.,Nola, I.,Mateljic, V.Advantages of liposome-encapsulated 1% clindamycin solution versus 1% clindamycin solution in the therapy of acne vulgaris. 1999. Acta Dermatovenerologica Croatica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Spellman, M. C. P., S. H.Efficacy and safety of azelaic acid and glycolic acid combination therapy compared with tretinoin therapy for acne. 1998. Clinical therapeutics	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
St Surin-Lord, S., Schlesinger, T. E., Guenin, E.Novel tretinoin 0.05% lotion for the oncedaily treatment of moderatetosevere acne vulgaris in a preadolescent and adolescent population. 2019. Journal of Clinical and Aesthetic Dermatology	No relevant data reported - reports pooled data of 2 trials combined
Stainforth, J. M.-H., S.,Papworth-Smith, J. W.,Eady, E. A.,Cunliffe, W. J.,Norris, J. F. B.,Simpson, N. B.,Cork, M. J.A single-blind comparison of topical erythromycin/zinc lotion and oral minocycline in the treatment of acne vulgaris. 1993. Journal of Dermatological Treatment	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Stankler, L.Pustular acne vulgaris. Rotational oral antibacterial therapy for 1 year. 1979. British Journal of Clinical Practice	No relevant study design - not RCT
Stein Gold, L., D., S.,Weiss, J.,Draelos, Z. D.,Ellman, H.,Stuart, I. A.A novel topical minocycline foam for the treatment of moderate-to-severe acne vulgaris: Results of 2 randomized, double-blind, phase 3 studies. 2019. Journal of the American Academy of Dermatology	No relevant intervention - FMX101 4% is a topical minocycline foam not available in the UK
Stein Gold, L., Pariser, D. M., Guenin, E.Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate and Severe Acne Vulgaris in Females: Effect of Age on Efficacy and Tolerability. 2019. Journal of drugs in dermatology : JDD	Not obtainable
Stein Gold, L., T., J.,Cruz-Santana, A.,Papp, K.,Poulin, Y.,Schlessinger, J.,Gidner, J.,Liu, Y.,Graeber, M.A North American study of adapalene-benzoyl peroxide combination gel in the treatment of acne. 2009. Cutis	No relevant data reported - a repeat publication of Gollnick 2009
Stein Gold, L..,Werschler, W. P., & Mohawk, J.Â Adapalene/benzoyl	No relevant data reported -

Reference	Reason for exclusion
peroxide gel 0.3%/2.5%: effective acne therapy regardless of age or gender. 2017. Journal of drugs in dermatology	post hoc analysis by gender and age of Stein Gold & Weiss 2016.
Stein Gold, L.Efficacy and tolerability of a fixed combination of clindamycin phosphate (1.2%) and benzoyl peroxide (3.75%) aqueous gel in moderate and severe acne vulgaris subpopulations. 2015. Journal of Drugs in Dermatology	No relevant data reported - post hoc analysis by acne severity of Pariser 2014
Stein Gold, L.Efficacy and tolerability of fixed-combination acne treatment in adolescents. 2013. Cutis	No relevant data reported - publication from Thiboutot 2008
Stinco, G. P., F.,Valent, F.,Errichetti, E.,Di Meo, N.,Trevisan, G.,Patrone, P.Efficacy, tolerability, impact on quality of life and sebostatic activity of three topical preparations for the treatment of mild to moderate facial acne vulgaris. 2016. Giornale italiano di dermatologia e venereologia	Not in English language
Stoughton, R. B. C., R. C.,Gange, R. W.,Walter, J. F.Double-blind comparison of topical 1 percent clindamycin phosphate (Cleocin T) and oral tetracycline 500 mg/day in the treatment of acne vulgaris. 1980. Cutis	No relevant study design - not RCT
Stoughton, R. B. R., W.Topical clindamycin in the control of acne vulgaris. 1976. Cutis	No relevant article type - non-systematic review
Strauss, J. S. G., A. B.,Jones, T.,Koo, J. Y.,Leyden, J. J.,Lucky, A.,Pappas, A. A.,McLane, J.,Leach, E. E.Concomitant administration of vitamin E does not change the side effects of isotretinoin as used in acne vulgaris: a randomized trial. 2000. Journal of the American Academy of Dermatology	No relevant intervention - isotretinoin with vitamin E
Strauss, J. S., Leyden, J. J., Lucky, A. W., Lookingbill, D. P., Drake, L. A., Hanifin, J. M., Lowe, N. J., Jones, T. M., Stewart, D. M., Jarratt, M. T., Katz, I., Pariser, D. M., Pariser, R. J., Tschen, E., Chalker, D. K., Rafal, E. S., Savin, R. P., Roth, H. L., Chang, L. K., Baginski, D. J., Kempers, S., McLane, J., Eberhardt, D., Leach, E. E., Bryce, G., Hong, J.A randomized trial of the efficacy of a new micronized formulation versus a standard formulation of isotretinoin in patients with severe recalcitrant nodular acne. 2001. Journal of the American Academy of DermatologyJ Am Acad Dermatol	No relevant comparison - micronized isotretinoin vs standard isotretinoin
Stuttgen, G. I., H.,Mahrle, G.Oral vitamin A acid in treatment of dermatoses with pathologic keratinization. 1977. International Journal of Dermatology	No relevant study design - not RCT
Stuttgen, G.Oral vitamin A acid therapy. 1975. Acta Dermato-Venereologica. Supplementum	No relevant study design - not RCT
Sun, X., Qian, F., He, Y., Gu, X., Di, W.Safety and Efficacy of Combined Oral Contraceptive Ethinyl Estradiol/Drospirenone (YAZ) in Chinese Women: A Single-Arm, Open-Label, Multicenter, Post-Authorization Study. 2020. Advances in Therapy	No relevant study design - not a RCT
Sutono, T.Efficacy of Garcinia mangostana L. (mangosteen rind extract) to reduce acne severity. 2013. Medical Journal of Indonesia	No relevant intervention - extract of mangosteen rind
Swinyer, L. J. S., T. A.,Britt, M. R.Topical agents alone in acne. A blind assessment study. 1980. JAMA	No relevant intervention - suboptimal doses
Taaffe, A. C., W. J.,Cove, J.Topical erythromycin in acne - a double-blind study. 1981. British Journal of Dermatology	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Tabasum, H. A., T.,Anjum, F.,Rehman, H.The effect of Unani antiacne	No relevantstudy

Reference	Reason for exclusion
formulation (Zimade Muhasa) on acne vulgaris: A singleblind, randomized, controlled clinical trial. 2014. Journal of Pakistan Association of Dermatologists	population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Takigawa, M. T., Y.,Shimada, S.,Furukawa, F.,Noguchi, N.,Ito, T.Clinical and bacteriological evaluation of adapalene 0.1% gel plus nadifloxacin 1% cream versus adapalene 0.1% gel in patients with acne vulgaris. 2013. Journal of Dermatology	No relevant intervention - adapalene 0.1% gel plus nadifloxacin 1% cream not available in the UK
Tan, J. G., H. P. M.,Loesche, C.,Ma, Y. M.,Gold, L. S.Synergistic efficacy of adapalene 0.1%-benzoyl peroxide 2.5% in the treatment of 3855 acne vulgaris patients. 2011. Journal of Dermatological Treatment	No relevant data reported - pooled analysis of Thiboutout 2007, Stein Gold 2009, and Gollnick 2009
Tan, J. G., L. S.,Schlessinger, J.,Brodell, R.,Jones, T.,Cruz, A.,Kerrouche, N.,Jarratt, M.Short-term combination therapy and long-term relapse prevention in the treatment of severe acne vulgaris. 2012a. Journal of Drugs in Dermatology	Study design does not meet protocol eligibility criteria - combines individual patient data from 2 RCTs
Tan, J. G., L. S.,Schlessinger, J.,Brodell, R.,Jones, T.,Dhuin, J. C.,Jarratt, M.Combination of adapalene-benzoyl peroxide and oral doxycycline is efficacious in short-term therapy: Maintenance with adapalene-benzoyl peroxide prevents relapse in treatment of severe acne vulgaris. 2012b. Pediatric Dermatology	No relevant article type - conference abstract
Tang, X., Li, C., Ge, S., Chen, Z., Lu, L.Efficacy of photodynamic therapy for the treatment of inflammatory acne vulgaris: A systematic review and meta-analysis. 2020. Journal of Cosmetic DermatologyJ	Systematic review - references were checked for relevance
Tanghetti, E. A., Werschler, W. P., Lain, T., Guenin, E., Martin, G., Pillai, R.Tazarotene 0.045% Lotion for Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris: Results from Two Phase 3 Trials. 2020. Journal of drugs in dermatology : JDD	Not obtainable
Tanghetti, E. D., S.,Green, L.,Del Rosso, J.,Draelos, Z.,Leyden, J.,Shalita, A.,Glaser, D. A.,Grimes, P.,Webster, G.,Barnett, P.,Le Gall, N.Randomized comparison of the safety and efficacy of tazarotene 0.1% cream and adapalene 0.3% gel in the treatment of patients with at least moderate facial acne vulgaris. 2010. Journal of Drugs in Dermatology	No relevant data reported - subgroup analysis by sex of Draelos 2007
Tanghetti, E. H., J. C.,Oefelein, M. G.The efficacy and tolerability of dapsone 5% gel in female vs male patients with facial acne vulgaris: Gender as a clinically relevant outcome variable. 2012. Journal of Drugs in Dermatology	No relevant data reported - subgroup analysis by sex of Draelos 2007
Tanghetti, E. H., J.,Baldwin, H.,Kircik, L.,Bai, Z.,Alvandi, N.Once-Daily Topical Dapsone Gel, 7.5%: Effective for Acne Vulgaris Regardless of Baseline Lesion Count, With Superior Efficacy in Females. 2018. Journal of drugs in dermatology : JDD	No relevant data reported - post hoc analysis by sex of Stein Gold 2016
Tangjaturonrusamee, C. R., P.,Ditre, C. M.Comparison of pneumatic broadband light plus adapalene gel 0.3% versus adapalene gel 0.3% monotherapy in the treatment of mild to moderate acne. 2016. Cutis	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments

Reference	Reason for exclusion
Tanzi, E. L. A., T. S.Comparison of a 1450-nm Diode Laser and a 1320-nm Nd:YAG Laser in the Treatment of Atrophic Facial Scars: A Prospective Clinical and Histologic Study. 2004. Dermatologic Surgery	Duplicate record
Tao, S. Q. X., R. S.,Li, F.,Cao, L.,Fan, H.,Fan, Y.,Yang, L. J.Efficacy of 3.6% topical ALA-PDT for the treatment of severe acne vulgaris. 2016. European Review for Medical & Pharmacological Sciences	No relevant study design - not RCT
Taub, A. F.A comparison of intense pulsed light, combination radiofrequency and intense pulsed light, and blue light in photodynamic therapy for acne vulgaris. 2007. Journal of drugs in dermatology : JDD	No relevant data reported - number of participants assigned to each group not reported
Tay, C. H.Treatment of acne vulgaris with topical vitamin A acid. 1978. Singapore Medical Journal	No relevant study design - not RCT
Taylor, S. C. C.-B., F. E.,McMichael, A.,Downie, J. B.,Rodriguez, D. A.,Alexis, A. F.,Callender, V. D.,Alvandi, N.Efficacy, safety, and tolerability of topical dapsone gel, 7.5% for treatment of acne vulgaris by Fitzpatrick skin phototype. 2018. Journal of Drugs in Dermatology	No relevant data reported - post-hoc analysis of Eichenfeld 2016 & Stein Gold 2016 trials
Taylor, S. C.Utilizing combination therapy for ethnic skin. 2007. Cutis	No relevant data reported - subgroup analysis by skin type of Kircik 2007
Thappa, D. M. D., J.Nodulocystic acne: Oral gugulipid versus tetracycline. 1994. Journal of Dermatology	No relevant intervention - Guggulsterone
Thiboutot, D. A., D. F.,Lemay, A.,Washenik, K.,Roberts, J.,Harrison, D. D.A randomized, controlled trial of a low-dose contraceptive containing 20 mug of ethinyl estradiol and 100 mug of levonorgestrel for acne treatment. 2001. Fertility and Sterility	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Thiboutot, D. A., S.,Soto, P.Efficacy and tolerability of adapalene 0.3% gel compared to tazarotene 0.1% gel in the treatment of acne vulgaris. 2008. Journal of drugs in dermatology : JDD	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Thiboutot, D. M. K., L.,McMichael, A.,Cook-Bolden, F. E.,Tyring, S. K.,Berk, D. R.,Chang-Lin, J. E.,Lin, V.,Kaoukhov, A.Efficacy, safety, and dermal tolerability of dapsone gel, 7.5% in patients with moderate acne vulgaris: A pooled analysis of two phase 3 trials. 2016. Journal of Clinical and Aesthetic Dermatology	No relevant population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Thomas, D. R. R., S.,Smith, E. B.Comparison of topical erythromycin 1.5 percent solution versus topical clindamycin phosphate 1.0 percent solution in the treatment of acne vulgaris. 1982. Cutis	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and

Reference	Reason for exclusion
	refractory treatments
Thomsen, R. J. S., A.,Knutson, D.,Strauss, J. S.Topical clindamycin treatment of acne. Clinical, surface lipid composition, and quantitative surface microbiology response. 1980. Archives of Dermatology	No relevant intervention - topical 1% clindamycin hydrochloride hydrate not licensed in the UK
Thorneycroft, I. H. S., F. Z.,Bradshaw, K. D.,Ballagh, S. A.,Nichols, M.,Weber, M. E.Effect of low-dose oral contraceptives on androgenic markers and acne. 1999. Contraception	No relevant study population - sample includes women with and without acne, no further details reported
Thuangtong, R. T., C.,Rattanaumpawan, P.,Ditre, C. M.Comparison of salicylic acid 30% peel and pneumatic broadband light in the treatment of mild to moderately severe facial acne vulgaris. 2017. Cutis; cutaneous medicine for the practitioner	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Ting, W.Randomized, observer-blind, split-face study to compare the irritation potential of 2 topical acne formulations over a 14-day treatment period. 2012. Cutis; cutaneous medicine for the practitioner	No relevant study population - insufficient information to determine severity of acne
Toossi, P. F., M.,Malekzad, F.,Mohtasham, N.,Kimyai-Asadi, A.Subantimicrobial-dose doxycycline in the treatment of moderate facial acne. 2008. Journal of drugs in dermatology : JDD	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Trice, E. R.Treatment of acne vulgaris with Secomat -S lotion. 1966. Virginia Medical Monthly	No relevant study design - not RCT
Tschen, E. H. K., H. I.,Jones, T. M.,Monroe, E. W.,Kraus, S. J.,Connolly, M. A.,Levy, S. F.A combination benzoyl peroxide and clindamycin topical gel compared with benzoyl peroxide, clindamycin phosphate, and vehicle in the treatment of acne vulgaris. 2001. Cutis; cutaneous medicine for the practitioner	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Tuchin, V. V. G., E. A.,Bashkatov, A. N.,Simonenko, G. V.,Odoevskaya, O. D.,Altshuler, G. B.A Pilot Study of ICG Laser Therapy of Acne Vulgaris: Photodynamic and Photothermolysis Treatment. 2003. Lasers in Surgery and Medicine	No relevant data reported - sebum excretion data
Tucker, S. B. T., R.,Cochran, R.,Flannigan, S. A.Comparison of topical clindamycin phosphate, benzoyl peroxide, and a combination of the two for the treatment of acne vulgaris. 1984. British Journal of Dermatology	No relevant data - insufficient data reported
Tucker, S. B. T., T.,Cochran, R.Comparison of topical clindamycin phosphate, benzoyl peroxide and a combination of the two, for the treatment of acne vulgaris. 1990. Indian journal of dermatology, venerology and leprology	Duplicate record
Tunca, M. A., A.,Ozmen, I.,Erbil, H.Topical nadifloxacin 1% cream vs. topical erythromycin 4% gel in the treatment of mild to moderate acne. 2010. International Journal of Dermatology	No relevant intervention - topical nadifloxacin 1% cream not available in the UK

Reference	Reason for exclusion
Turan, A. S., H.,Baskan, E. B.,Turan, H.,Aydogan, K.Efficacy of topical sodium sulfacetamide in the treatment of mild and moderate acne vulgaris: a randomized, comparative study. 2012. Turkderm deri hastaliklari ve frengi arsivi	Not in English language
Tye, M. J. L., E.Acne treated with wet compresses followed by corticosteroid cream. 1968. Arizona Medicine	No relevant study design - not RCT
Tzung, T. Y. W., K. H.,Huang, M. L.Blue light phototherapy in the treatment of acne. 2004. Photodermatology Photoimmunology and Photomedicine	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Uebelhoer, N. S. B., M. A.,Dover, J. S.,Arndt, K. A.,Rohrer, T. E.Comparison of stacked pulses versus double-pass treatments of facial acne with a 1,450-nm laser. 2007. Dermatologic Surgery	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Uede, M. K., C.,Yonei, N.,Furukawa, F.,Yamamoto, Y.Persistent effects of adapalene gel after chemical peeling with glycolic acid in patients with acne vulgaris. 2013. Open dermatology journal	Participants were not selected on their complete/partial response to the first treatment
Ullah, G. N., S. M.,Bhatti, Z.,Ahmad, M.,Bangash, A. R.Comparison of oral azithromycin with oral doxycycline in the treatment of acne vulgaris. 2014. Journal of Ayub Medical College, Abbottabad : JAMC	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Ustuner, P. G., A. T.,Demirbilek, M.Clinical and bacteriological evaluation of nadifloxacin 1% cream versus erythromycin 4% gel in the treatment of mild-to-moderate facial acne vulgaris: a randomized study. 2015. Turkiye klinikleri journal of medical sciences	No relevant intervention - nadifloxacin 1% cream not available in the UK
Vali, A. F., G.,Zaghian, N.,Koosha, M.The efficacy of topical solution of 0.3% ciprofloxacin in treatment of mild to moderate acne vulgaris. 2009. Iranian Red Crescent Medical Journal	No relevant intervention - topical ciprofloxacin cream
Van der Meeren, H. L. M. V. d. S., J. G.,Stijnen, T.Dose-response relationship in isotretinoin therapy for conglobate acne. 1983. Dermatologica	Relevant outcomes only reported graphically - cannot extract useful data
Van Neste, D. T., D.,Decroix, J.Imidazoles and benzoyl peroxide: A comparative trial of two treatment schedules. 1986. Dermatologica	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
van Wayjen, R. G. v. d. E., A.Experience in the long-term treatment of patients with hirsutism and/or acne with cyproterone acetate-containing preparations: efficacy, metabolic and endocrine effects. 1995. Experimental & Clinical Endocrinology & Diabetes	No relevant study design - not RCT
Van, d. V., dMHLM,Stijnen, T.The treatment of acne conglobata with 13-cis retinoic acid (isotretinoin). 1983. Nederlands tijdschrift voor	Not in English language

Reference	Reason for exclusion
geneeskunde	
Van, T. N. D. T., L.,Nguyen Trong, H.,Chau Van, T.,Trinh Minh, T.,Thi Minh, P. P.,Dinh Huu, N.,Tran Cam, V.,Le Huyen, M.,Tran Hau, K.,Gandolfi, M.,Satolli, F.,Feliciani, C.,Tirant, M.,Vojvodic, A.,Lotti, T.Efficacy of oral isotretinoin in combination with desloratadine in the treatment of common vulgaris acne in Vietnamese Patients. 2019. Open Access Macedonian Journal of Medical Sciences	No relevant internvention - oral Desloratadine; also no relevant study population - insufficient information to determine severity of acne
Vartiainen, M. d. G., H.,Broekmeulen, C. J.Comparison of the effect on acne with a combiphasic desogestrel-containing oral contraceptive and a preparation containing cyproterone acetate. 2001. European Journal of Contraception & Reproductive Health Care	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Vasarinsh, P.Benzoyl Peroxide- Sulfur Lotions in Acne Vulgaris- A Controlled Study. 1969. Cutis; cutaneous medicine for the practitioner	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Vaswani, N. P., R. K.,Bhutani, L. K.,Ramachandran, K.Topical therapy of acne vulgaris with retinoic acid and erythromycin lotion. 1989. Indian journal of dermatology, venerology and leprology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Vaswani, N. P., R. K.Treatment of acne vulgaris with anti-androgens. 1990. Indian journal of dermatology, venerology and leprology	No relevant intervention - cimetidine
Vatanchi, M. F., G.,Siegel, D.Updates on novel research in laser and photodynamic therapy for treatment of acne vulgaris. 2017. Journal of the american academy of dermatology	Duplicate record
Venier, A. C., P.,Salvatori, S.,Varricchio, M. C.Topical treatment of acne vulgaris with clindamycin phosphate solution (double blind clinical trial). 1985. Chronica dermatologica	Not in English language
Verma, K. C. S., A. S.,Dhamija, S. K.Oral zinc sulphate therapy in acne vulgaris: a double-blind trial. 1980. Acta Dermato-Venereologica	No relevant study population - insufficient details to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Vermeulen, A. R., R.Effects of cyproterone acetate plus ethinylestradiol low dose on plasma androgens and lipids in mildly hirsute or acneic young women. 1988. Contraception	No relevant study population - sample includes people with hirsuitism or acne but no details of acne participants provided and study is not relevant for PCOS, maintenance or refractory treatments
Verschoore, M. L., A.,Wolska, H.,Jablonska, S.,Czernielewski, J.,Schaefer, H.Efficacy and safety of CD 271 alcoholic gels in the topical treatment of acne vulgaris. 1991. British Journal of Dermatology	No relevant intervention - CD 271 alcoholic gel
Verschoore, M. P., M.,Czernielewski, J.,Sorba, V.,Clucas,	No relevant study

Reference	Reason for exclusion
A.Adapalene 0.1% gel has low skin-irritation potential. 1997. Journal of the American Academy of Dermatology	population - participants did not have acne
Voravutinon, N. R., J.,Sadhwani, D.,Iyengar, S.,Alam, M.A comparative split-face study using different mild purpuric and subpurpuric fluence level of 595-nm pulsed-dye laser for treatment of moderate to severe acne vulgaris. 2016. Dermatologic Surgery	No relevant study design - not RCT
Wahab, M. A. R., M. H.,Monamie, N. S.,Jamaluddin, M.,Khondker, L.,Afroz, W.Isotretinoin versus weekly pulse dose azithromycin in the treatment of acne- A comparative study. 2008. Journal of Pakistan Association of Dermatologists	No relevant comparison - azithromycin
Walton, S. C., W. J.,Lookingbill, P.,Keczkes, K.Lack of effect of topical spironolactone on sebum excretion. 1986. British Journal of Dermatology	No relevant article type - letter to editor
Wang, A. P., Tu, P., Ji, S. Z., Wu, Y., Shen, Y., Zhu, X. J.Clinical efficacy of benzoyl peroxide gel with different concentrations in acne vulgaris. 2003. Chinese journal of dermatology	Not in English language
Wang, H. W. L., T.,Zhang, L. L.,Guo, M. X.,Stepp, H.,Yang, K.,Huang, Z.,Wang, X. L.Prospective study of topical 5-aminolevulinic acid photodynamic therapy for the treatment of moderate to severe acne vulgaris in Chinese patients. 2012. Journal of Cutaneous Medicine & Surgery	No relevant study design - not RCT
Wang, J. H. W., B.,Zheng, R. D.Effective observation on external using tretinoin cream treating common acne (Chinese). 2001. China journal of leprosy & skin diseases	Not in English language
Wang, Q. Y., D.,Liu, W.,Chen, J.,Lin, X.,Cheng, S.,Li, F.,Duan, X.Use of optical fiber imported intra-tissue photodynamic therapy for treatment of moderate to severe acne vulgaris. 2016. Medical Science Monitor	No relevant data - insufficient data reported
Wang, S. Q. C., J. T.,Flor, M. E.,Zelickson, B. D.Treatment of inflammatory facial acne with the 1,450 nm diode laser alone versus microdermabrasion plus the 1,450 nm laser: A randomized, split-face trial. 2006. Dermatologic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Wangsuwan, S., Meephansan, J.Comparative study of photodynamic therapy with riboflavin-tryptophan gel and 13% 5-aminolevulinic acid in the treatment of mild to moderate acne vulgaris. 2019. Clinical, Cosmetic and Investigational Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Wanitphakdeedecha, R. I., T.,Phothong, W.,Eimpunth, S.,Manuskiatti, W.Local and systemic effects of low-level light therapy with light-emitting diodes to improve erythema after fractional ablative skin resurfacing: a controlled study. 2019. Lasers in Medical Science	Duplicate record
Wanitphakdeedecha, R., Tavechodperathum, N., Tantrapornpong, P., Suphatsathienkul, P., Techapichetvanich, T., Eimpunth, S., Manuskiatti, W.Acne treatment efficacy of intense pulsed light photodynamic therapy with topical licochalcone A, l-carnitine, and decanediol: A spilt-face, double-blind, randomized controlled trial.	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS,

Reference	Reason for exclusion
2020. Journal of Cosmetic DermatologyJ	maintenance or refractory treatments
Waranuch, N. P., P.,Yakaew, S.,Nakyai, W.,Grandmottet, F.,Onlom, C.,Srivilai, J.,Viyoch, J.Antiacne and antiblotch activities of a formulated combination of Aloe barbadensis leaf powder, Garcinia mangostana peel extract, and Camellia sinensis leaf extract. 2019. Clinical, Cosmetic and Investigational Dermatology CCID	No relevant intervention - a combination of Aloe barbadensis leaf extract, Garcinia mangostana peel extract, and Camellia sinensis leaf extract
Warren, M. R., J.,Arbit, D.,Sevilla, C.,Flack, M.The effects on weight of a low-dose oral contraceptive in the treatment of women with moderate acne vulgaris. 2001. Fertility and sterility	No relevant article type - conference abstract
Webster, G. C., D. I.,Quiring, J.,Vogelson, C. T.,Slade, H. B.A combined analysis of 2 randomized clinical studies of tretinoin gel 0.05% for the treatment of acne. 2009. Cutis; cutaneous medicine for the practitioner	No relevant dat reported - reports pooled results of 2 trials combined
Webster, G. F. G., L.,Poulin, Y. P.,Solomon, B. A.,Loven, K.,Lee, J.A multicenter, double-blind, randomized comparison study of the efficacy and tolerability of once-daily tazarotene 0.1% gel and adapalene 0.1% gel for the treatment of facial acne vulgaris. 2002. Cutis; cutaneous medicine for the practitioner	Not obtainable
Webster, G. F.Safety and efficacy of Tretin-X compared with Retin-A in patients with mild-to-severe acne vulgaris. 2006. Skinmed	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Webster, G. R., P.,Gold, M. H.,Mraz, S.,Calvarese, B.,Chen, D.Efficacy and tolerability of a fixed combination of clindamycin phosphate (1.2%) and low concentration benzoyl peroxide (2.5%) aqueous gel in moderate or severe acne subpopulations. 2009. Journal of Drugs in Dermatology	No relevant data reported - pblication from Thiboutot 2008
Webster, G. T., D. M.,Chen, D. M.,Merikle, E.Impact of a fixed combination of clindamycin phosphate 1.2%-benzoyl peroxide 2.5% aqueous gel on health-related quality of life in moderate to severe acne vulgaris. 2010. Cutis	No relevant data reported - reports quality of life outcomes
Weiss, J. G., L. S.,Leoni, M.,Rueda, M. J.,Liu, H.,Tanghetti, E.Customized single-agent therapy management of severe inflammatory acne: A randomized, double-blind, parallel-Group, controlled study of a new treatment - Adapalene 0.3%-benzoyl peroxide 2.5% gel. 2015. Journal of Drugs in Dermatology	No relevant data reported - subgroup analysis of people with severe acne participating in Stein Gold 2016
Weiss, J. S. G., L.,Leoni, M.,Rueda, M. J.,Liu, H.,Tanghetti, E.Customized Single-agent Therapy Management of Severe Inflammatory Acne: A Randomized, Double-blind, Parallel-group, Controlled Study of a New Treatment--Adapalene 0.3%-Benzoyl Peroxide 2.5% Gel. 2015. Journal of Drugs in Dermatology: JDD	Duplicate record
Weissmann, A. W., A.,Plewig, G.Reduction of bacterial skin flora during oral treatment of severe acne with 13-cis retinoic acid. 1981. Archives of Dermatological Research	No relevant study design - not RCT
Weltert, Y. C., S.,Gibaud, C.,Courau, S.,Pechenart, P.,Sirvent, A.,Girard, F.Double-blind clinical assessment of the efficacy of a 4% nicotinamide gel (Exfoliac NC Gel) versus a 4% erythromycin gel in the treatment of moderate acne with a predominant inflammatory component. [French, English]. 2004. Nouvelles Dermatologiques	Not in English language
Wen, X. L., Y.,Hamblin, M. R.Photodynamic therapy in dermatology beyond non-melanoma cancer: An update. 2017. Photodiagnosis and	Duplicate record

Reference	Reason for exclusion
Photodynamic Therapy	
Wexler, L.Two controlled studies of a topical steroid preparation in the treatment of acne vulgaris. 1968. Applied Therapeutics	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Wiegell, S. R. W., H. C.Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid versus methyl aminolevulinate. 2006a. Journal of the American Academy of Dermatology	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Wilhelm, K. P. W., D.,Neumeister, C.,Zsolt, I.,Schwantes, U.Lack of irritative potential of nadifloxacin 1% when combined with other topical anti-acne agents. 2012. Clinical and Experimental Dermatology	No relevant study population - participants did not have acne and study is not relevant for PCOS, maintenance or refractory treatments
Wilkinson, R. D. A., J. E.,Murray, J. J.,Craig, G. E.Benzoyl peroxide and sulfur: foundation for acne management. 1966. Canadian Medical Association Journal	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Winkler, U. H. F., H.,Mulders, J. A.Cycle control, quality of life and acne with two low-dose oral contraceptives containing 20 microg ethinylestradiol. 2004a. Contraception	Duplicate record
Winkler, U. H. F., H.,Mulders, JapaCycle control, quality of life and acne with two low-dose oral contraceptives containing 20 mug ethinylestradiol. 2004b. Contraception	No relevant study population - participants did not have acne
Wishart, J. M.An open study of Triphasil and Diane 50 in the treatment of acne. 1991. The Australasian journal of dermatology	No relevant population - insufficient information reported about acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Witkowski, J. A. P., L. C.Chlorhydroxyquin-Benzoyl Peroxide Lotion in the Treatment of Acne - An Objective Evaluation. 1969. Cutis; cutaneous medicine for the practitioner	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Wolf, J. E., Jr.Safety and tolerability in the MORE trial. 2006. Cutis	No relevant study design - not RCT
Wong, R. C. K., S.,Heezen, J. L.Oral ibuprofen and tetracycline for the treatment of acne vulgaris. 1984. Journal of the American Academy of Dermatology	No relevant comparison
Woolery-Lloyd, H. B., L.,Ikeno, H.Sodium L-ascorbyl-2-phosphate 5% lotion for the treatment of acne vulgaris: a randomized, double-blind, controlled trial. 2010. NA	No relevant study population - sample includes people with mild to severe acne and study

Reference	Reason for exclusion
	is not relevant for PCOS, maintenance or refractory treatments
Worret, I. A., W.,Zahradnik, H. P.,Andreas, J. O.,Binder, N.Acne resolution rates: Results of a single-blind, randomized, controlled, parallel phase III trial with EE/CMA (Belara) and EE/LNG (Microgynon). 2001. Dermatology	No relevant data reported
Xia, J. H., G.,Hu, D.,Geng, S.,Zeng, W.Concomitant use of 1,550-nm nonablative fractional laser with low-dose isotretinoin for the treatment of acne vulgaris in asian patients: A randomized split-face controlled study. 2018. Dermatologic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Xing,Fire needle therapy for moderate-severe acne: A PRISMA systematic review and meta-analysis of randomized controlled trials. 2019. NA	No relevant intervention - systematic review about fire needle therapy
Xu, H. L.Supplemented Raising and Sinking powder for treating ninety cases with acne due to blood heat stagnation. 2015b. Henan traditional chinese medicine [henan zhong yi]	No relevant intervention - supplemented raising and sinking powder combined with isotretinoin erythromycin gel
Xu,Supplemented Raising and Sinking powder for treating ninety cases with acne due to blood heat stagnation. 2015a. NA	Duplicate record
Yang, G. L. Z., M.,Wang, J. M.,He, C. F.,Luo, Y.,Liu, H. Y.,Gao, J.,Long, C. Q.,Bai, J. R.Short-term clinical effects of photodynamic therapy with topical 5-aminolevulinic acid for facial acne conglobata: an open, prospective, parallel-arm trial. 2013. Photodermatology, Photoimmunology & Photomedicine	No relevant study design - not RCT
Yang, Z., Zhang, Y., Lazic Mosler, E., Hu, J., Li, H., Zhang, Y., Liu, J., Zhang, Q.Topical benzoyl peroxide for acne. 2020. Cochrane Database of Systematic Reviews	Systematic review - references were checked for relevance
Yeung, C. K. S., S. Y.,Bjerring, P.,Yu, C. S.,Kono, T.,Chan, H. H.A comparative study of intense pulsed light alone and its combination with photodynamic therapy for the treatment of facial acne in Asian skin. 2007. Lasers in Surgery and Medicine	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Yilmaz, O. S., N.,Yuksel, E. P.,Aydin, F.,Ozden, M. G.,Canturk, T.,Turanli, A.Evaluation of 532-nm KTP laser treatment efficacy on acne vulgaris with once and twice weekly applications. 2011. Journal of Cosmetic & Laser Therapy	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Yong, C. C.Benzoyl peroxide gel therapy in acne in Singapore. 1979. International Journal of Dermatology	No relevant study population - sample includes 11% people with 11% acne
Yoon, J. H. P., E. J.,Kwon, I. H.,Kim, C. W.,Lee, G. S.,Hann, S.	No relevant intervention -

Reference	Reason for exclusion
K.,Kim, K. H.,Kim, K. J.Concomitant use of an infrared fractional laser with low-dose isotretinoin for the treatment of acne and acne scars. 2014. Journal of dermatological treatment	laser treatment for acne scarring
Yoon, J. Y. K., H. H.,Min, S. U.,Thiboutot, D. M.,Suh, D. H.Epigallocatechin-3-gallate improves acne in humans by modulating intracellular molecular targets and inhibiting P. acnes. 2013. Journal of Investigative Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Yu, Z. S., J.,Lew-Kaya, D.,Walker, P.,Yu, D.,Tang-Liu, D. D.Pharmacokinetics of tazarotene cream 0.1% after a single dose and after repeat topical applications at clinical or exaggerated application rates in patients with acne vulgaris or photodamaged skin. 2003. Clinical Pharmacokinetics	No relevant study population - sample includes people with acne or photodamage - relevant outcomes not reported separately
Zachariae, H.Topical vitamin-A-acid in acne. 1980. Acta dermato-venereologica	No relevant study design - not RCT
Zander, E. W., S.Treatment of acne vulgaris with salicylic acid pads. 1992. Clinical Therapeutics	Duplicate record
Zarate, A. M., V. B.,Greenblatt, R. B.Effect of an antiandrogen, 17-alpha-methyl-B-nortestosterone, on acne and hirsutism. 1966. Journal of Clinical Endocrinology & Metabolism	No relevant study design - not RCT
Zeichner, J. A. H., M.,Linkner, R. V.,Wong, V.Efficacy and safety of tretinoin 0.025%/clindamycin phosphate 1.2% gel in combination with benzoyl peroxide 6% cleansing cloths for the treatment of facial acne vulgaris. 2013. Journal of Drugs in Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Zeichner, J. A. P., R. V.,Haddican, M.,Wong, V.Efficacy and safety of a ceramide containing moisturizer followed by fixed-dose clindamycin phosphate 1.2%/benzoyl peroxide 2.5% gel in the morning in combination with a ceramide containing moisturizer followed by tretinoin 0.05% gel in the evening for the treatment of facial acne vulgaris. 2012. Journal of Drugs in Dermatology: JDD	No relevant study design - not RCT
Zeichner, J. A., Harper, J. C., Roberts, W. E., Guenin, E., Bhatt, V., Pillai, R.Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris: assessment of safety and tolerability in subgroups. 2019. Journal of Clinical and Aesthetic Dermatology	Not obtainable
Zeichner, J. A.The Efficacy and Tolerability of a Fixed Combination Clindamycin (1.2%) and Benzoyl Peroxide (3.75%) Aqueous Gel in Adult Female Patients with Facial Acne Vulgaris. 2015. The Journal of Clinical & Aesthetic Dermatology	Reports post hoc analysis of >=25 years old for Pariser 2014
Zeichner, J.Strategies to minimize irritation and potential iatrogenic post-inflammatory pigmentation when treating acne patients with skin of color. 2011. Journal of Drugs in Dermatology: JDD	Duplicate record
Zeng, R., Liu, Y., Zhao, W., Yang, Y., Wu, Q., Li, M., Lin, T.A split-face comparison of a fractional microneedle radiofrequency device and fractional radiofrequency therapy for moderate-to-severe acne vulgaris. 2020. Journal of Cosmetic Dermatology.	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and

Reference	Reason for exclusion
	refractory treatments
Zeng, X. L., W. L.,Zhao, T.Effects of Chinese medical facial mask comprehensive therapy in treating acne vulgaris. 2012b. Zhongguo zhong xi yi jie he za zhi zhongguo zhongxiyi jiehe zazhi = chinese journal of integrated traditional and western medicine	Duplicate record
Zeng,Effects of Chinese medical facial mask comprehensive therapy in treating acne vulgaris. 2012a. NA	Not in English language
Zhang, J., Zhang, X., He, Y., Wu, X., Huang, J., Huang, H., Lu, C.Photodynamic therapy for severe facial acne vulgaris with 5% 5-aminolevulinic acid vs 10% 5-aminolevulinic acid: A split-face randomized controlled study. 2020. Journal of Cosmetic DermatologyJ	Duplicate publication
Zhang, X. M.Clinical observations on the efficacy of autohemotherapy plus pricking-cupping bloodletting in treating common acne. 2015. Shanghai journal of acupuncture and moxibustion [shang hai zhen jiu za zhi]	Not in English language
Zhou, B. R. Z., T.,Bin Jameel, A. A.,Xu, Y.,Guo, S. L.,Wang, Y.,Permatasari, F.,Luo, D.The efficacy of conditioned media of adipose-derived stem cells combined with ablative carbon dioxide fractional resurfacing for atrophic acne scars and skin rejuvenation. 2016b. Journal of Cosmetic and Laser Therapy	No relevant study population - sample includes people with acne scars
Zhou, L.Pipa Qingfei Decoction combined with External Application of Acne Tincture in Treating Acne for 120 Cases. 2016c. Chinese medicine modern distance education of china [zhong guo zhong yi yao xian dai yuan cheng jiao yu]	Duplicate record
Zhou, Y. Q. Y., R. J.The Curative Effect Observation of Tretinoin Capsule Combined with Tretinoin Cream in Treating Acne Vulgaris (Chinese). 2000. Chinese journal of dermatovenereology	Not in English language
Zhou,Pipa Qingfei Decoction combined with External Application of Acne Tincture in Treating Acne for 120 Cases. 2016a. NA	Not obtainable
Zhu, X. J. T., P.,Zhen, J.,Duan, Y. Q.Adapalene gel 0.1%: effective and well tolerated in the topical treatment of acne vulgaris in Chinese patients. 2001. Cutis; cutaneous medicine for the practitioner	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Zouboulis, C. C. F., T. C.,Wohlrab, J.,Barnard, J.,Alio, A. B.Study of the efficacy, tolerability, and safety of 2 fixed-dose combination gels in the management of acne Vulgaris. 2009. Cutis	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments

1 *PCOS: polycystic ovary syndrome; RCT: randomised controlled trial*

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3 **Economic studies and studies reporting utility data**

4 **Table 25: Excluded economic studies and reasons for their exclusion**

Economic studies	Reason for exclusion

Economic studies	Reason for exclusion
Borgonjen RJ, de Lange JA, van de Kerkhof PCM. Guideline-based clinical decision support in acne patients receiving isotretinoin: improving adherence and cost-effectiveness. J Eur Acad Dermatol Venereol. 2017; 31(10): ve440-e442	Intervention outside scope (clinical decision support)
Bossuyt L, Bosschaert J, Richert B, Cromphaut P, Mitchell T, Al Abadie M, Henry I, Bewley A, Poyner T, Mann N, Czernielewski J. Lymecycline in the treatment of acne: an efficacious, safe and cost-effective alternative to minocycline. Eur J Dermatol 2003; 13(2):130-5.	Only intervention costs (drug acquisition) considered
Czilli T, Tan J, Knezevic S, Peters C. Cost of Medications Recommended by Canadian Acne Clinical Practice Guidelines. J Cutan Med Surg. 2016; 20(6): 542-545.	Only intervention costs (drug acquisition) considered
Haddock ES, Eichenfield LF. High-dose isotretinoin: Bigger dents in wallets? J Am Acad Dermatol. 2016 Aug;75(2):e75-6. EXTRA	Letter
Hansen, L. A., Vermeulen, L. C., Bland, S., & Wetterneck, T. B. (2007). Guideline for Low-Cost Antimicrobial Use in the Outpatient Setting. American Journal of Medicine, 120(4), 295-302.	Not an economic evaluation - identification of drugs with low acquisition cost that are effective
Joish VN, Boklage S, Lynen R, Schmidt A, Lin J. Use of drospirenone/ ethinyl estradiol (DRSP/EE) among women with acne reduces acne treatment-related resources. J Med Econ. 2011; 14(6): 681-9.	Retrospective analysis of administrative data
Lee YH, Liu G, Thiboutot DM, Leslie DL, Kirby JS. A retrospective analysis of the duration of oral antibiotic therapy for the treatment of acne among adolescents: investigating practice gaps and potential cost-savings. J Am Acad Dermatol. 2014; 71(1): 70-6.	Retrospective analysis of administrative data
Leyden JJ, Tanghetti EA, Miller B, Ung M, Berson D, Lee J. Once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.1% microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. Cutis 2002; 69(2 Suppl):12-9.	Only intervention costs (drug acquisition) considered
Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, Williams HC. Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne. Health Technol Assess 2005; 9(1)	Average CE ratios reported, no incremental analysis and not possible to estimate ICERs as costs per intervention not reported
Ozolins M, Eady EA, Avery AJ, Cunliffe WJ, Po AL, O'Neill C, Simpson NB, Walters CE, Carnegie E, Lewis JB, Dada J, Haynes M, Williams K, Williams HC. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. Lancet 2004; 364(9452): 2188-95.	Average CE ratios reported, no incremental analysis and not possible to estimate ICERs as costs per intervention not reported
Penna P, Meckfessel MH, Preston N. Fixed-Dose Combination Gel of Adapalene and Benzoyl Peroxide plus Doxycycline 100 mg versus Oral Isotretinoin for the Treatment of Severe Acne: Efficacy and Cost Analysis. Am Health Drug Benefits. 2014; 7(1):37-45.	Only drug acquisition costs considered; efficacy based on naïve synthesis of RCT arm data
Rosamilia LL. Economic stewardship in acne management. Cutis. 2018; 102(1): 8-9.	Not an economic evaluation
Rubin CB, Lipoff JB. Primary Nonadherence in Acne Treatment: The Importance of Cost Consciousness. JAMA Dermatol. 2015; 151(10):1144-5.	Letter - not an economic evaluation
Straight CE, Lee YH, Liu G, Kirby JS (2015). Duration of oral antibiotic therapy for the treatment of adult acne: a	Retrospective analysis of administrative data

Economic studies	Reason for exclusion
retrospective analysis investigating adherence to guideline recommendations and opportunities for cost-savings. Journal of the American Academy of Dermatology, 72(5), 822-827.	
Tassavor M, Payette MJ. Estimated cost efficacy of U.S. Food and Drug Administration-approved treatments for acne. Dermatol Ther. 2019; 32(1): e12765	Letter - description of costs associated with different pharmacological interventions (drug + lab testing + clinician visit costs)
Webster GF, Guenther L, Poulin YP, Solomon BA, Loven K, Lee J. A multicenter, double-blind, randomized comparison study of the efficacy and tolerability of once-daily tazarotene 0.1% gel and adapalene 0.1% gel for the treatment of facial acne vulgaris. Cutis. 2002 Feb;69(2 Suppl):4-11.	Only intervention costs (drug acquisition) considered
Yuwnate AH, Chandane RD, Sah RK, et al. Efficacy and cost-effective analysis of benzyl benzoate, permethrin, and ivermectin in the treatment of scabies and azithromycin versus doxycycline in the treatment of acne vulgaris. Natl J Physiol Pharm Pharmacol. 2019; 9(10): 977-982	Economic evaluation conducted in India
Zeitany AE, Bowers EV, Morrell DS. High-dose isotretinoin has lower impact on wallets: A cost analysis of dosing approaches. J Am Acad Dermatol. 2016; 74(1):174-6.	Letter; cost analysis using data based on a letter reporting a retrospective analysis

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Studies reporting utility data	Reason for exclusion
Afsar FS, Seremet S, Demirlendi Duran H, Karaca S, Mumcu Sonmez N. Sexual quality of life in female patients with acne. Psychol Health Med. 2020; 25(2):171-178.	No utility data for acne health states
Altunay IK, Özkur E, Dalgard FJ, et al. Psychosocial Aspects of Adult Acne: Data from 13 European Countries. Acta Derm Venereol. 2020 Feb 5;100(4):adv00051.	No utility data reported
Balkrishnan R, Kulkarni AS, Cayce K, Feldman SR. Predictors of healthcare outcomes and costs related to medication use in patients with acne in the United States. Cutis. 2006 Apr;77(4): 251-5.	No utility data reported
Dreno B, Bordet C, Seite S, Taieb C, 'Registre Acné' Dermatologists. Acne relapses: impact on quality of life and productivity. J Eur Acad Dermatol Venereol. 2019; 33(5): 937-43.	No utility data reported
Seidler AM, Bayoumi AM, Goldstein MK, Cruz PD Jr, Chen SC. Willingness to pay in dermatology: assessment of the burden of skin diseases. J Invest Dermatol. 2012; 132(7):1785-90.	Utility data obtained from people valuing their own health state
VanBeek MJ. Integrating patient preferences with health utilities: a variation on health-related quality of life. Arch Dermatol. 2008; 144(8): 1037-41.	Editorial - no utility data reported

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Appendix L – Research recommendations

Research recommendations for review question: For people with moderate to severe acne vulgaris what are the most effective treatment options?

Research question - reduced dose oral isotretinoin

What is the efficacy of reduced dose oral isotretinoin in the management of acne vulgaris?

Why this is important

Oral isotretinoin is prescribed by consultant dermatologist-led team for severe forms of acne resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy. The daily dose typically ranges between 0.5mg to 1mg/kg, however dosage adjustments may be required for people with severe intolerances or whom are at higher risk of developing serious adverse effects. There is limited high-quality data on the efficacy and optimum treatment duration of reduced (less than 0.5mg/kg) daily dose isotretinoin in acne. Furthermore, there have been reports of the successful use of reduced daily dose isotretinoin, including weekly (mini) or bi-weekly (micro) dosage regime as maintenance therapy in people with recurrent relapse despite adequate response to multiple courses of isotretinoin. The evidence for reduced dose isotretinoin as maintenance therapy have been limited to case series and small cohort studies.

Further research will help to establish if

- reduced daily dose of oral isotretinoin is effective in the treatment of acne vulgaris
- reduced dose isotretinoin regime is effective as maintenance therapy; and
- the optimum duration of treatment.

Table 26: Research recommendation rationale

Research question	What is the efficacy of reduced dose oral isotretinoin in the management of acne vulgaris?
Why is this needed	
Importance to 'patients' or the population	The daily dose of isotretinoin prescribed usually ranges between 0.5mg – 1mg/kg. For some people, the dosage adjustment to the maximum tolerated dose as the risk of certain adverse effects are dose dependent. There is limited high-quality data on the effectiveness of reduced daily dose of isotretinoin for treating acne and the optimum duration of treatment. In people with recurrent acne relapse despite adequate response to multiple courses of isotretinoin, reduced dose isotretinoin regime may be an attractive option. However, evidence for reduced dose isotretinoin as maintenance therapy are limited to case series and small cohort studies.
Relevance to NICE guidance	There was limited evidence for the use of oral isotretinoin at a reduced daily dose in acne for the committee to make a strong recommendation. There was a lack of data on the use of low dose isotretinoin in acne maintenance therapy for any recommendations to be made. Therefore, research investigating the efficacy and safety of reduced dose oral isotretinoin is warranted.
Relevance to the NHS	Acne vulgaris, which is the eighth most prevalent disease globally, affects the majority of teenagers and young adults and is common in the UK.

Research question	What is the efficacy of reduced dose oral isotretinoin in the management of acne vulgaris?
	Severe intolerance, significant adverse effects are dose dependent and therefore reduced dose oral isotretinoin may offer a safer and effective alternative to standard dose oral isotretinoin. For people with recurrent relapsing acne, treatment options are currently limited and reduced daily dose including mini and micro dose regimes may be a suitable and effective option as maintenance treatment.
National priorities	• The Medicines and Healthcare Products Regulatory Agency (MHRA) in 2020 are in the process of conducting an in-depth review of psychiatric and sexual adverse effects of oral isotretinoin with the aim to reduce risk of these adverse effects. As many isotretinoin associated adverse effects are dose related, there is a clear benefit of investigating whether reduced dose oral isotretinoin is safe and effective. • Reducing antibiotic prescribing in order to prevent antimicrobial resistance is a national priority. It would be helpful to determine whether reduced dose oral isotretinoin would be an effective and safe alternative to repeated courses of oral and/or topical antibiotics in the treatment of acne and as maintenance therapy.
Current evidence base	Limited research has been conducted on this area and therefore additional, high-quality studies are required.
Equality	Not applicable
Feasibility	People receiving oral isotretinoin would need to be provided with adequate detailed information about the potential adverse effects of isotretinoin and participants in studies investigating reduced dose oral isotretinoin would need to be monitored for these adverse effects.
Other comments	Not applicable

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2 **Table 27: Research recommendation characteristics table**

Criterion	Explanation
Population	People with: • severe forms of acne resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy • refractory acne vulgaris despite previous treatment courses with standard daily dose oral isotretinoin.
Intervention	Reduced dose oral isotretinoin as: • reduced daily dose (less than 0.5mg/kg) • reduced dose regime (mini or micro)
Comparator	• People prescribed standard daily dose of isotretinoin • People prescribed first-line treatment option that includes an oral antibiotic • People on topical maintenance treatment
Outcomes	• Change in severity of acne using a validated scoring system • Patient reported outcomes
Study design	Randomised controlled trial
Timeframe	• 6 months (intervention) and 12 months (follow-up) for treatment study

Criterion	Explanation
	• 12 months (intervention) and 12 months (follow-up) for maintenance study
Additional information	Not applicable

Research question - physical modalities (excluding chemical peels)

What is the effectiveness of physical modalities, (such as light devices) in the treatment of acne vulgaris orpersistent acne vulgaris-related scarring?

Why this is important

Physical treatments for acne are popular with people because they have the benefit of treating a local area without systemic effects. They can be used in people with co-morbidities or side effects where other treatments are unsuitable. They are currently available in the private sector but there is no standardisation of treatment modalities or duration. Many different physical therapies have been described for acne including:

- Comedone extraction
- Phototherapy – including UVB, intense pulsed light, blue and red light
- Photochemical therapy (e.g. photodynamic therapy)
- Laser
- Photopneumatic therapy (e.g. intense pulsed light + vacuum)
- Photothermal therapy (eg gold nanoparticles +light or laser)

Physical treatments are also used for acne scarring. These include:

- Punch excision
- CO2 laser
- Dermabrasion
- Radiofrequency (e.g. fractional microneedling, bipolar)

Further research is required to determine the most effective physical treatments for acne and acne scarring. This could open the way to wider availability in the NHS.

Table 28: Research recommendation rationale

Research question	What is the effectiveness of physical modalities (such as light devices) in the treatment of acne vulgaris or persistent acne vulgaris-related scarring?
Why is this needed	
Importance to 'patients' or the population	Physical treatments for acne are popular with people because they have the benefit of treating a local area without systemic effects. They can be used in people with co-morbidities or side effects where other treatments are unsuitable. There is evidence from small studies that physical therapies including various light sources with or without addition of chemical or physical photosensitiser may be effective in all grades of acne. There is also some evidence to support CO2 laser treatment for acne scarring. However, the studies are too small or of insufficient quality to allow recommendations to be made.
Relevance to NICE guidance	Currently physical treatments for acne vulgaris cannot be recommended. Weak recommendation can be made for CO2 laser for acne scarring, but stronger evidence is required to allow a stronger recommendation. which would lead to wider availability on NHS.

Research question	What is the effectiveness of physical modalities (such as light devices) in the treatment of acne vulgaris or persistent acne vulgaris-related scarring?
Relevance to the NHS	Acne vulgaris is the most common skin condition affecting the majority of teenagers and young adults. Acne scarring leads to lifelong psychological distress for some people. Physical treatments for acne could provide an alternative for people unwilling or unable to use other treatment modalities. With more evidence of effectiveness and cost effectiveness these treatments may become available on the NHS. Physical treatments for acne scarring may benefit the NHS by reducing psychological morbidity.
National priorities	There are 2 national priorities, one is to improve young people's mental health and another is to reduce antibiotic prescribing to prevent resistance. • Improving the mental health of young people is a national priority. Improving acne can have a positive impact on mental health. Rates of depression and suicide are increasing in the under 25-year-old age group, especially amongst men 20-25 years old. (suicides in the UK 2019 ons.gov.uk). In 2018 the government produced a paper 'Transforming children's and young people's mental health provision', including improving services for those 16-25 years old. This aligns with a need to understand support required for young people with acne vulgaris https://www.gov.uk/government/consultations/transforming-children-and-young-peoples-mental-health-provision-a-green-paper/quick-read-transforming-children-and-young-peoples-mental-health-provision • Acne has traditionally been treated with long courses of antibiotics. If any particular type of physical treatment could be identified as having a positive impact on acne vulgaris then it may lead to a decreased need for antibiotics. Antibiotic resistance is rising in the UK and the government wants to optimise antibiotic prescribing to prevent the development of superbugs. Keeping people well informed would therefore help to address this priority (Tackling antimicrobial resistance 2019–2024 The UK's five-year national action plan Published 24 January 2019. HM Government) https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784894/UK_AMR_5_year_national_action_plan.pdf
Current evidence base	It is hard to draw conclusions from the current evidence. There are a lack of existing randomised controlled trials in physical treatments for acne and acne scarring, and those which have been done have been variable quality on small numbers of participants.
Equality	Access to any recommended physical treatments for acne or acne scarring currently differs across the country and according to socioeconomic group. They are mainly available in the private sector.
Feasibility	Physical treatments need to be supervised, even if they are delivered at home. There would be significant NHS costs associated with setting up provision for physical treatments, but this may be offset by benefits. A time commitment from participants would be required.
Other comments	Not applicable

Table 29: Research recommendation characteristics table - (a) relates to acne management and (b) persistent acne vulgaris-related scarring management

Criterion	Explanation
Population	a) Adults with acne vulgaris. b) Adults with persistent acne vulgaris-related scarring
Intervention	a) any physical intervention (excluding chemical peels) for acne, for example: • A range of light therapies b) any physical intervention for acne scarring, for example • CO2 laser single or multiple treatments
Comparison	a) no treatment or another active treatment. b) no treatment for acne scarring
Outcome	a) Participant reported improvement, clinician reported improvement in lesion count b) Participant reported improvement, clinician reported improvement in scar appearance a) Recurrence a&b) Side effects: participant and clinician reported, including pigmentary changes and scarring
Study design	Randomised controlled trial
Timeframe	a) • 3-6 months (intervention) • 6 month (follow-up) b) • Intervention period • 6 and 12 month follow up
Additional information	Ideally longer term follow-up data collection would also be useful.

Research question - chemical peels

What is the effectiveness of chemical peels in the treatment of acne vulgaris or persistent acne vulgaris-related scarringacne?

Why this is important

Chemical peels are used to remove the surface of the skin. Peels may be 'superficial' for treatment of acne vulgaris, removing the dead layer of skin, or 'deeper' for atrophic scar management. They are usually applied repeatedly as a course of treatment. Chemical peels are currently not used as standard treatment in the NHS but are available to buy by the public and can be provided by private aesthetic practitioners. The use of chemical peels has potential to change acne and acne scarring management, as an alternative to those who cannot use, tolerate, or are resistant, to other treatments. Therefore, further research is needed to establish its effectiveness.

Table 30: Research recommendation rationale

Research question	What is the effectiveness of chemical peels in the treatment of acne vulgaris or persistent acne vulgaris-related scarringacne?

Research question	What is the effectiveness of chemical peels in the treatment of acne vulgaris or persistent acne vulgaris-related scarringacne?
Why is this needed	
Importance to 'patients' or the population	Chemical peels have the potential to be used as an alternative for people who cannot use, tolerate, or are resistant, to other treatments but they are not currently available in the NHS.
Relevance to NICE guidance	Chemical peels are currently not routinely offered as a treatment of acne vulgaris or acne associated scarring in the NHS and there is insufficient evidence to make a strong recommendation.
Relevance to the NHS	Acne vulgaris is the most common skin condition affecting the majority of teenagers and young adults. Acne scarring leads to lifelong psychological distress for some people. Chemical peels for acne could provide an alternative for people unwilling or unable to use other treatment modalities. With more evidence of effectiveness and cost effectiveness these treatments may become available on the NHS. Chemical peels for acne scarring may benefit the NHS by reducing psychological morbidity.
National priorities	• Acne has traditionally been treated with long courses of antibiotics. If chemical peels are shown to be effective in the management of acne vulgaris then it may lead to a decreased need for antibiotics. Antibiotic resistance is rising in the UK and the government wants to optimise antibiotic prescribing to prevent the development of superbugs. Keeping people well informed would therefore help to address this priority (Tackling antimicrobial resistance 2019–2024 The UK's five-year national action plan Published 24 January 2019. HM Government) https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784894/UK_AMR_5_year_national_action_plan.pdf • There are safety concerns about the use of oral retinoids (https://www.gov.uk/government/publications/isotretinoin-for-severe-acne-uses-and-effects) so provision of alternative therapy would be welcome if safe and effective. • Improving the mental health of young people is a national priority. If chemical peels are safe and effective to improve acne it may help improve self-esteem and confidence. Rates of depression and suicide are increasing in the under 25-year-old age group, especially amongst men 20-25 years old. (suicides in the UK 2019 ons.gov.uk). In 2018 the government produced a paper 'Transforming children's and young people's mental health provision', including improving services for those 16-25 years old. More effective acne treatment can have a positive impact on mental wellbeing and therefore addresses this priority. https://www.gov.uk/government/consultations/transforming-children-and-young-peoples-mental-health-provision-a-green-paper/quick-read-transforming-children-and-young-peoples-mental-health-provision
Current evidence base	There was no evidence for the use of chemical peels, either alone or combined, in moderate to severe acne treatment. There was some evidence that chemical peels may be effective in the treatment of mild to moderate acne. However, there was a low number of studies with small sample size. None of the studies compared effectiveness of chemical peels against placebo. The evidence base for chemical peels in treatment of acne associated scarring was low to very low quality with small sample

Research question	What is the effectiveness of chemical peels in the treatment of acne vulgaris or persistent acne vulgaris-related scarringacne?
	size and limited follow-up time.
Equality	None specified
Feasibility	This research is feasible
Other comments	Not applicable

Table 31: Research recommendation characteristics table – (a) relates to acne management and (b) persistent acne vulgaris-related scarring management

Criterion	Explanation
Population	a) Adults with acne vulgaris. b) Adults with persistent acne vulgaris-related scarring
Intervention	a) Chemical peels for the treatment acne b) Chemical peels for the treatment of acne associated scarring
Comparison	Any other peel Any other treatment Placebo
Outcome	a) Patient reported improvement, clinician reported improvement in lesion count b) Patient reported improvement, clinician reported improvement in scar appearance a) Recurrence a&b) Side effects: patient and clinician reported, including pigmentary changes and scarring
Study design	Randomised control trial or split-face trial
Timeframe	Likely treatment over 3 months with follow up to 3 years
Additional information	Not applicable

Appendix M – Network Meta-analysis report from the NICE Guidelines Technical Support Unit (TSU)

Network meta-analysis report for review question: For people with moderate to severe acne vulgaris what are the most effective treatment options?

Prepared by: NICE TSU, Bristol (Caitlin Daly and Nicky J. Welton)

Introduction

The purpose of this analysis was to estimate the comparative effectiveness of various interventions for treating people with moderate to severe acne.

The outcomes included in this analysis were efficacy, discontinuation for any reason, and discontinuation due to side effects. Risk of scarring was considered, but there was insufficient evidence to conduct a network meta-analysis (NMA).

Methods

Inclusion of Split-Face Trials

Split-face randomised controlled trials (RCTs) were eligible for inclusion in the efficacy analysis if they provided data on the difference in percentage change from baseline acne lesion counts and its corresponding standard error, which appropriately accounted for within-patient correlation.

Split-face RCTs were not eligible for the discontinuation for any reason outcome, as the discontinuation results could not be attributed to a particular treatment.

Split-face RCTs (Horfelt 2006, Hong 2013, Dreno 2017) were eligible for the discontinuation due to side effects outcome. However, this required the estimation of additional parameters to account for censoring, and there were insufficient data to estimate this. Consequently, split-face RCTs were not included in the discontinuation due to side effects analysis.

Efficacy: Intention to Treat (ITT) vs. Completers Data

In the efficacy analysis, summary data from an ITT analysis were prioritised over a completer analysis within RCTs. If ITT data were available the sample size of each treatment arm k of trial i, $n_{i,k}$ was the number randomised to arm k, but if ITT data were not available, the number of completers was used as the sample size for each arm in the analysis.

Prioritization of Efficacy Data

Let $x_{j,i,k}$ and $y_{j,i,k}$ be the lesion counts at baseline and follow-up, respectively, for individual j, treatment arm k of trial i. Let $p_{j,i,k} = \frac{(x_{j,i,k} - y_{j,i,k})}{x_{j,i,k}} = 1 - \frac{y_{j,i,k}}{x_{j,i,k}}$ be the proportionate reduction in lesion counts. To be included in the analysis of efficacy data, parallel RCTs had to provide enough data to calculate one of the following prioritised sets of summary count data:

a. The mean percent change from baseline (pCFB) count, $\overline{P}_{i,k} = \frac{1}{n_{i,k}} \sum_{j=1}^{n_{i,k}} p_{j,i,k}$, and its standard error, $se_{\overline{P}_{i,k}}$, for each treatment arm k,

   OR

the mean difference in percent change from baseline count between treatment arms 1 and k, $MD_{\bar{P}_{i,k}} = \bar{P}_{i,k} - \bar{P}_{i,1}$, and its standard error, $se\left(MD_{\bar{P}_{i,k}}\right)$. Trials with more than 2 arms also needed to provide a measure of the covariance between the relative effects, $Cov\left(MD_{\bar{P}_{i,j}}, MD_{\bar{P}_{i,k}}\right), j \neq k$.

b. The mean baseline count, $\bar{X}_{i,k} = \frac{1}{n_{i,k}} \sum_{j=1}^{n_{i,k}} x_{j,i,k}$, the mean change from baseline (CFB), $\bar{C}_{i,k} = \frac{1}{n_{i,k}} \sum_{j=1}^{n_{i,k}} \left(x_{j,i,k} - y_{j,i,k}\right)$, and their corresponding standard errors, $se_{\bar{X}_{i,k}}, se_{\bar{C}_{i,k}}$, respectively, for each treatment arm k.

c. The mean baseline count, $\bar{X}_{i,k}$, the mean count at follow-up, $\bar{Y}_{i,k} = \frac{1}{n_{i,k}} \sum_{j=1}^{n_{i,k}} y_{j,i,k}$, their corresponding standard errors, $se_{\bar{X}_{i,k}}, se_{\bar{Y}_{i,k}}$, respectively, for each treatment arm k, and the correlation between the baseline and follow-up means, ρ.

An exception to the above prioritised list was made if a trial reported inflammatory and non-inflammatory counts, in which case (b) and (c) were prioritised to enable inclusion of the combined inflammatory and non-inflammatory counts, see 'Efficacy: combining lesion counts'.

As mentioned earlier, split-face trials had to provide enough data to calculate the mean difference in pCFB count between treatment arms 1 and k, $MD_{\bar{P}_{i,k}}$, where the standard error, $se\left(MD_{\bar{P}_{i,k}}\right)$, had accounted for within-patient variability.

Each trial included in the analysis contributed data on one of the following prioritised lesion types, where lesions at the top of the list were preferred:

i. Total lesion count
ii. Inflammatory count
iii. Pustule count
iv. Papule count
v. Nodule count
vi. Cyst count
vii. Non-inflammatory count

Trials that only reported efficacy measures based on a scale, rather than lesion counts, were also considered. To include these data in the analysis of efficacy counts, we required reliable evidence from trials reporting summary data on both lesion counts and validated scales to model the relationship between the two. However, there were insufficient data to model this relationship, and so no studies reporting efficacy measures based on a scale were included.

Efficacy: Combining Lesion Counts

Where RCTs did not report total lesion counts, but reported counts for multiple types of lesions, an effort was made to try to combine these counts across lesion types. For example, adding a sub- script l for lesion type to all notation and using a superscript $total$ to indicate the summary for total lesion counts, summaries for total lesion counts can be obtained from sub-types at baseline:

$$\bar{X}_{i,k}^{total} = \sum_{l=1}^{n_{types}} \bar{X}_{i,k,l}$$

$$\left(se_{\bar{X}_{i,k}}^{total}\right)^2 = \sqrt{\sum_{l=1}^{n_{types}} \left(se_{\bar{X}_{i,k,l}}^2\right) + 2\sum_{l \neq m} \text{cov}(\bar{X}_{i,k,l}, \bar{X}_{i,k,m})}$$

The same approach was used to obtain mean change from baseline, $\bar{C}_{i,k}^{total}$, and follow-up, $\bar{Y}_{i,k}^{total}$, for total lesion counts by combining summaries for sub-types.

In all cases, assumptions about the correlation between the outcomes on the different lesions were required to properly estimate the standard errors. No RCT included in the analysis reported this, and no other reliable source of evidence in the literature was found. As such, we derived the correlations between lesion counts in trials reporting the SDs for each lesion type and the SD for their total. This was possible for inflammatory and non-inflammatory counts, where the correlation may be calculated as (Casella 2002):

$$\rho = \frac{\left(sd^{total}\right)^2 - \left(sd^{\text{inflammatory}}\right)^2 - \left(sd^{\text{non-inflammatory}}\right)^2}{2sd^{\text{inflammatory}}sd^{\text{non-inflammatory}}} .$$

We observed a wide variation of correlations across studies reporting baseline counts. We preferred the correlation values between CFB counts from two large studies (Feldman 2013 study 301 and 302). The average of the correlations between the inflammatory and non-inflammatory baseline counts was 0.3957, and this value was assumed for baseline, follow-up and CFB counts.

Efficacy Data Imputation

Some RCTs reported the median baseline, follow-up, CFB, or pCFB counts, rather than the mean. In these trials, we assumed that the counts were normally distributed such that the mean count was approximately equal to the median count.

Where a trial did not directly report information to calculate the standard error of the mean outcome (baseline, follow-up, CFB, or pCFB counts) the standard deviations (SDs), $sd_{i,k}$, were derived based on other information reported in the trial as described below and standard errors obtained as $se_{i,k} = sd_{i,k} \Big/ \sqrt{n_{i,k}}$.

Imputing SDs based on Interquartile Range (IQR)

(for RCT Nicklas 2019)

Let $IQR_{i,k}$ represent the interquartile range, i.e., the difference between the first and third quartile lesion counts, in treatment arm k . Then, assuming that the counts are normally distributed (Wiebe 2006),

$$sd_{i,k} \approx \frac{IQR_{i,k}}{1.35} .$$

Imputing SDs based on Range

(for RCT Gruber 1998 - see 'Additional derivations')

Let $\min_{i,k}, \max_{i,k}$ represent the minimum and maximum lesion counts, respectively, in treatment arm k. Then, assuming that the counts are normally distributed (Wiebe 2006),

$$sd_{i,k} \approx \frac{\max_{i,k} - \min_{i,k}}{4}.$$

Imputing SDs based on Confidence Interval Limits

If a RCT reported the $100(1-\alpha)\%$ confidence interval (CI) limits for arm-level summaries or a mean difference, the standard error would be derived as

$$se_{i,k} = \frac{\text{upper limit}_{i,k} - \text{lower limit}_{i,k}}{2z_{1-\alpha/2}},\ se(MD_{i,k}) = \frac{\text{upper limit}_{i,k} - \text{lower limit}_{i,k}}{2z_{1-\alpha/2}}.$$

where $z_{1-\alpha/2}$ is the $1-\alpha/2$ quantile of the standard normal distribution. When a CI corresponded to a MD, the SDs of both treatment groups were assumed to be equal and were imputed from the standard error of the mean difference,

$$sd_{i,1} = sd_{i,k} = \frac{se(MD_{i,k})}{\sqrt{\frac{1}{n_{i,1}} + \frac{1}{n_{i,k}}}}.$$

If a RCT (Stein Gold 2008) only reported one of the $100(1-\alpha)\%$ CI limits for arm-level summaries or a mean difference, the standard error was derived as

$$se_{i,k} = \frac{|\text{mean} - \text{limit}_{i,k}|}{z_{1-\alpha/2}},\ se(MD_{i,k}) = \frac{|MD_{i,k} - \text{limit}_{i,k}|}{z_{1-\alpha/2}}.$$

Imputing SDs based on p-values

If an exact p-value was reported, then the SD is inferred exactly. If an RCT reported a p-value in the form of "<0.05", then SDs were imputed assuming a p-value = 0.05 (or the upper limit of the specified range). This is a conservative approach as this provides an upper limit for the SD. If an RCT reported a p-value as "significant", but did not state the significance level, a p-value of 0.05 was assumed. If an RCT reported a p-value as "non-significant" or in the form of ">0.05", then no p-value was assumed, and thus a SD could not be imputed.

P-values corresponding to between-group comparisons

[for RCTs: Thiboutot 2002 (geometric means), Dobson 1980, Peck 1982, Gruber 1998, Zouboulis 2000, Gollnick 2001, Cunliffe 2003, Dubertret 2003, Pariser 2005, Thiboutot 2005, Stewart 2006, Tanghetti 2006, Kircik 2007, Tanghetti 2007, Ansarin 2008, Eichenfield, Jarratt et al. 2010 (Study 1), Eichenfield, Jarratt et al. 2010 (Study 2), Stein Gold 2010, Dreno 2011, Tanghetti 2011, Thiboutot 2008/Eichenfield 2012, Tan 2014, Pariser 2014/Cook Bolden 2015/Zeichner 2015, Stein Gold 2016, Xu 2017, Moore 2018 (study SC1401), Moore 2018 (study SC1402), Tan 2019 - PERFECT 1 study, Tan 2019 - PERFECT 2 study, Tanghetti 2019, Tyring 2018/Eichenfield 2019, Dogra 2020]

Where an RCT only provided information on uncertainty in the form of p-values corresponding to hypothesis tests of mean differences, $MD_{i,k}$, the corresponding standard errors for parallel RCTs were derived as

$$se\left(MD_{i,k}\right) = \frac{\left|MD_{i,k}\right|}{t^{-1}\left(\text{p-value}_{i,k}, df = n_{i,1} + n_{i,k} - 2\right)},$$

where $t^{-1}\left(\cdot, df\right)$ is the the inverse quantile of a t distribution with df degrees of freedom. This imputation assumes p-values correspond to a one-sided t-test (Wiebe 2006, Altman 2011). The SDs were assumed to be equal across treatment arms, giving

$$sd_{i,1} = sd_{i,k} = \frac{se\left(MD_{i,k}\right)}{\sqrt{\frac{1}{n_{i,1}} + \frac{1}{n_{i,k}}}}.$$

The above approach was used to impute the standard deviation of the reference treatment in two RCTs (Eichenfield 2010 Study 1, Eichenfield 2010 Study 2) for the baseline model used in the economic analysis (see Appendix J). In multi-arm trials, all possible SDs were imputed from the reported p-values and an average of the imputed SDs across arms was used as the imputed SD for each arm in the analysis.

In split-face RCTs (Horfelt 2006, Tanghetti 2008, Hong 2013, Zhang 2019) we only needed to derive the standard error of the mean difference in percentage change from baseline counts, as this was what was required for the analysis. Again, the p-values were assumed to correspond to a one-sided t-test:

$$se\left(MD_{\bar{P}_i}\right) = \frac{\left|MD_{\bar{P}_i}\right|}{t^{-1}\left(\text{p-value}_i, df = n_i - 1\right)}.$$

Imputing Follow-up and pCFB SDs based on Baseline SDs

Two RCTs (Parsad 2001, see 'Efficacy: Combining Lesion Counts', Dhawan 2013) reported mean pCFB counts, but the only measure of uncertainty reported in the trial were the SDs of the baseline counts. To impute the pCFB SDs a weighted linear regression model was fitted to data from RCTs that reported both baseline SDs and pCFB SDs, regardless of the type of lesion count. The weights for each arm k in study i were calculated as $w_{i,k} = \frac{n_{i,k}}{\sum_i \sum_k n_{i,k}}$.

This gave the following regression equation ($R^2 = 0.22$) from which the pCFB SDs were imputed:

$$sd_{P_{i,k}} = -0.4770 sd_{X_{i,k}} + 44.0696$$

for each treatment arm k.

Similarly, another RCT (Webster 2014) reported mean baseline and CFB counts, but the only measure of uncertainty reported in that trial were the SDs of CFB counts. The baseline SDs were imputed using a weighted linear regression model, fitted to data from RCTs that reported both baseline SDs and follow-up SDs, regardless of the type of lesion count. The weights for each arm k in study i were calculated as $w_{i,k} = \frac{n_{i,k}}{\sum_i \sum_k n_{i,k}}$. This gave the following regression equation ($R^2 = 0.80$) from which the baseline SDs were imputed:

$$sd_{B_{i,k}} = 0.70959 sd_{C_{i,k}} + 3.62209$$

for each treatment arm k.

Imputing Correlation between Baseline and Follow-up Counts

None of the RCTs reporting mean baseline and follow-up counts reported the correlation between the baseline and follow-up counts. Instead, this was imputed in all trials by calculating the correlation between the baseline and follow-up counts in three RCTs that reported all of the SDs for baseline, follow-up and CFB counts:

$$\rho = \frac{sd_{B_{i,k}}^2 + sd_{F_{i,k}}^2 - sd_{C_{i,k}}^2}{2sd_{B_{i,k}} sd_{F_{i,k}}}.$$

These RCTs only reported the SDs for total lesion types and the median correlation was 0.45.

Additional Derivations

In one 2-arm RCT (Gruber 1998) the range of the mean difference in CFB counts for both groups, as well as a corresponding p-value was reported. The SDs corresponding to these two sources of uncertainty were derived, and the average of the SDs was imputed as the SD for all arms, assuming they were equal.

In one 3-arm RCT (Dubertret 2003) the confidence interval of one of the mean differences, as well as a p-value for another mean difference was reported. The SDs corresponding to these two sources of uncertainty were derived, and the average of the SDs was imputed as the SD for all arms, assuming they were equal.

In one 3-arm RCT (Strauss 1984) the mean baseline and follow-up counts were reported, only p-values corresponding to the within group changes from baseline were reported. In these cases, the standard deviation of the mean CFB counts was first calculated:

$$sd_{C_{i,k}} = \frac{\bar{C}_{i,k}}{\frac{1}{\sqrt{n_i}} t^{-1}\left(p-value, df = n_{i,k}-1\right)}.$$

The SDs of the baseline counts were then imputed, assuming the baseline and follow-up SDs were equal,

$$sd_{X_{i,k}} = sd_{Y_{ik}} = \frac{sd_{C_{i,k}}}{\sqrt{2(1-\rho)}}$$

where ρ was the assumed correlation between the baseline and follow-up counts.

In one split-face RCT (Zhang 2017) the SE of the MD was derived from the reported t-statistic, t_i, corresponding to a t-test of the MD:

$$se\left(MD_{\bar{P}_i}\right) = \frac{\left|MD_{\bar{P}_i}\right|}{t_i}.$$

In one 4-arm RCT (Thiboutot 2002) the geometric means of the pCFB counts for all arms, $\bar{P}_{geo_{i,k}}$, along with a p-value corresponding to the mean difference of the log pCFB counts in two arms were reported. The SDs of the log pCFB counts in these arms, $sd_{\log(P_{i,k})}$, were

assumed to be equal and derived based on the mean difference of the log pCFB counts in two arms for which a p-value, $\text{p-value}_{i,1k}$, was reported:

$$se\left(MD_{\overline{\log(P_{i,1k})}}\right) = \frac{\log\left(\bar{P}_{geo_{i,k}}\right) - \log\left(\bar{P}_{geo_{i,1}}\right)}{t^{-1}\left(\text{p-value}_{i,1k}, df = n_{i,1} + n_{i,k} - 2\right)},$$

$$sd_{\log(P_{i,1})} = sd_{\log(P_{i,2})} = sd_{\log(P_{i,3})} = sd_{\log(P_{i,4})} = \frac{se\left(MD_{\log(\bar{P}_{i,k})}\right)}{\sqrt{\frac{1}{n_{i,1}} + \frac{1}{n_{i,k}}}}.$$

The standard error of all pairwise mean differences of the log pCFB counts were calculated as

$$se\left(MD_{\overline{\log(P_{i,jk})}}\right) = \sqrt{\frac{sd^2_{\log(P_{i,j})}}{n_{i,j}} + \frac{sd^2_{\log(P_{i,k})}}{n_{i,k}}}.$$

The mean differences of the log pCFB counts and their corresponding standard errors were converted to the raw pCFB scale based on Method 3 of Higgins 2008:

$$MD_{\bar{P}_{i,jk}} = MD_{\overline{\log(P_{i,jk})}}\bar{\bar{P}}_{geo_{i,jk}},\ se\left(MD_{\bar{P}_{i,jk}}\right) = se\left(MD_{\overline{\log(P_{i,jk})}}\right)\bar{\bar{P}}_{geo_{i,jk}}$$

where $\bar{\bar{P}}_{geo_{i,jk}}$ is the geometric mean of geometric means $\bar{P}_{geo_{i,j}}, \bar{P}_{geo_{i,k}}$. The mean differences relative to arm 1, $MD_{\bar{P}_{i,1k}}$, along with their standard errors, were inputted into the analysis. The covariance between the relative effects $MD_{\bar{P}_{i,12}}, MD_{\bar{P}_{i,13}}$ was calculated as (Franccini 2012)

$$Cov\left(MD_{\bar{P}_{i,12}}, MD_{\bar{P}_{i,13}}\right) = \frac{\left(se\left(MD_{\bar{P}_{i,12}}\right)\right)^2 + \left(se\left(MD_{\bar{P}_{i,13}}\right)\right)^2 - \left(se\left(MD_{\bar{P}_{i,23}}\right)\right)^2}{2}.$$

Similarly, the covariance between the relative effects $MD_{\bar{P}_{i,13}}, MD_{\bar{P}_{i,14}}$ $Cov\left(MD_{\bar{P}_{i,13}}, MD_{\bar{P}_{i,14}}\right)$, was calculated. Since the covariance of the relative effects $MD_{\bar{P}_{i,12}}, MD_{\bar{P}_{i,13}}, MD_{\bar{P}_{i,14}}$ is equal to $se^2_{\bar{P}_{i,1}}$ (Franchini 2012), this was imputed as

$$se^2_{\bar{P}_{i,1}} = \frac{Cov\left(MD_{\bar{P}_{i,12}}, MD_{\bar{P}_{i,13}}\right) + Cov\left(MD_{\bar{P}_{i,13}}, MD_{\bar{P}_{i,14}}\right)}{2}$$

and inputted into the analysis.

Network meta-analysis

In order to take all trial information into consideration network meta-analyses (NMA) were conducted. NMA is a generalisation of standard pairwise meta-analysis for A versus B trials, to data structures that include, for example, A versus B, B versus C, and A versus C trials (Lu 2004, Caldwell 2005, Dias 2013a). A basic assumption of NMA methods is that direct and indirect evidence estimate the same parameter, that is, the relative effect between A and B measured directly from an A versus B trial, is the same as the relative effect between A

and B estimated indirectly from A versus C and B versus C trials. NMA techniques strengthen inference concerning the relative effect of two treatments by including both direct and indirect comparisons between treatments, and, at the same time, allow simultaneous inference on all treatments while respecting randomisation (Lu 2004; Caldwell 2005).

Simultaneous inference on the relative effects of all treatments is possible whenever treatments are part of a single "network of evidence", that is, every treatment is linked to at least one of the other treatments under assessment. The correlation between the random effects of multi-arm trials (i.e. those with more than 2 arms) in the network is taken into account in the analysis (Dias 2013a). In a NMA, we assume that intervention A is similar (in dose, administration etc.) when it appears in the A versus B and A versus C studies and also that the participants included in each trial are similar in terms of characteristics that may modify relative treatment effects (Dias 2018).

A Bayesian framework was used to estimate all parameters, using Markov chain Monte Carlo simulation methods implemented in OpenBUGS 3.2.3 for efficacy and WinBUGS 1.4.3 for both discontinuation outcomes (Lunn 2000 & 2013). Codes for all outcomes are provided in supplement 7. Data used in every analysis described in this appendix are provided in supplement 8.

Efficacy

The mean pCFB counts were assumed to have a normal likelihood:

$$\bar{P}_{i,k} \sim N\left(\theta_{i,k}, se^2_{\bar{P},i,k}\right)$$

where $\theta_{i,k}$ is the proportional change from baseline.

In RCTs reporting mean baseline and CFB counts, we assumed that the baseline counts were not correlated with the CFB counts, and thus the likelihoods were

$$\begin{aligned} \bar{X}_{i,k} &\sim N(\mu_{X_{i,k}}, se^2_{\bar{X}_{i,k}}) \\ \bar{C}_{i,k} &\sim N\left(\theta_{i,k}\mu_{X_{i,k}}, se^2_{\bar{C}_{i,k}}\right). \end{aligned}$$

where $\mu_{X_{i,k}}$ is the mean CFB count in study i arm k.

In RCTs reporting mean baseline and follow-up counts, noting that the baseline and follow-up means are correlated, a bivariate normal likelihood was given for this data:

$$\begin{pmatrix} \bar{X}_{i,k} \\ \bar{Y}_{i,k} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{\bar{X}_{i,k}} \\ \mu_{\bar{X}_{i,k}}(1-\theta_{i,k}) \end{pmatrix}, \begin{pmatrix} se^2_{\bar{X}_{i,k}} & \rho se_{\bar{X}_{i,k}} se_{\bar{Y}_{i,k}} \\ \rho se_{\bar{X}_{i,k}} se_{\bar{Y}_{i,k}} & se^2_{\bar{Y}_{i,k}} \end{pmatrix}\right).$$

The treatments were assumed to act additively on the proportional change from baseline, $\theta_{i,k}$, so the NMA model is given directly to $\theta_{i,k}$:

$$\theta_{i,k} = \mu_i + \delta_{i,k}$$

where μ_i are the trial-specific baseline effects and $\delta_{i,k}$ are the trial-specific treatment effects, measuring the difference in the mean proportionate reduction in lesion counts, where positive values represent a reduction in counts, and negative values represent an increase in counts. These differences were modelled as fixed effects:

$$\delta_{i,k} = d_{t_{i,k}} - d_{t_{i,1}}$$

or random effects:

$$\delta_{i,k} \sim Normal\left(d_{t_{i,k}} - d_{t_{i,1}}, \tau^2\right)$$

where d_k are the basic parameters measuring the difference in mean proportionate reduction in lesion counts for treatment k vs. treatment 1, such that $d_1 = 0$, and τ is the between-study SD.

Non-informative Normal(0, 100^2) priors were assigned to the trial-specific baseline effects, as well as the mean lesion counts at baseline, while a Uniform(0, 25) prior was assigned to the between-study standard deviation in the random effects models (Dias 2011a), and was sufficiently wide so that the posterior distribution was not constrained. The treatment effects were informed by class effects, see 'Class effect models'. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic and was satisfactory by 60,000 simulations for both outcomes (Gelman 1992, Brooks 1998). A further simulation sample of 120,000 iterations post-convergence was obtained on which all reported results were based.

Supplement 9 provides the list of studies included in the efficacy NMA of treatments for people with moderate to severe acne with details on the types of efficacy data used, and the list of studies excluded from the efficacy NMA, although they reported efficacy data, with reasons for exclusion.

Discontinuation for any Reason or due to Side Effects

RCTs with zero or 100% events in all arms were excluded from the analyses of both discontinuation outcomes because these studies provide no evidence on relative effects (Dias 2011a). For studies with zero or 100% events in at least one, but not all arms, we planned to analyse the data without continuity corrections where computationally possible. Where this was not possible, we used a continuity correction where we added 0.5 to both the number of events and the number of non-events, which has been shown to perform well when there is an approximate 1:1 randomisation ratio across intervention arms (Sweeting 2004).

The number of participants who discontinued for any reason out of the total randomised to arm k were modelled with a binomial likelihood and logit link (Dias 2011a & 2018). Similarly, the number of participants who discontinued due to side effects out of the total randomised to arm k were modelled with a binomial likelihood and logit link (Dias 2011a & 2018).

For both outcomes, non-informative Normal(0, 100^2) priors were assigned to the trial-specific baseline effects, while a Uniform(0, 5) prior was assigned to the between-study standard deviation in the random effects models (Dias 2011a). The treatment effects were informed by class effects, see 'Class effect models'. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic and was satisfactory by 60,000 simulations for both outcomes (Gelman 1992, Brooks 1998). A further simulation sample of 120,000 iterations post-convergence was obtained on which all reported results were based.

Class Effect Models

Classes of treatments are groups of interventions which are thought to have similar modes of action (Dias 2108). Class models (Dias 2018) were used so that strength could be borrowed across treatments in the same class and to connect disconnected networks.

For all outcomes, both fixed and random class effects models were fitted. The random class effects model assumes that the relative effects of treatments within a class are

exchangeable. That is, that the effects of treatments in a class are distributed around a common class mean, m_{D_k}, with a within-class variance, τ_k^2,

$$d_k \sim Normal\left(m_{D_k}, \tau_k^2\right)$$

where D_k identifies the class that treatment k belongs to. Treatment effects are shrunk towards a class mean and can borrow strength from other elements of the class.

Where there were less than 5 treatments within a class, the relative treatment effects were assumed to come from a normal distribution with a class mean and variance being borrowed from another similar class in the model, where possible. The following variance sharing rules were used:

- Treatments within classes that only differed by duration or a zinc acetate dihydrate add-on shared a within-class variance:
  - Efficacy: benzoyl peroxide [topical], lincosamide [topical], retinoid - total cumul dose < 120mg/kg (single course) [oral], benzoyl peroxide [topical] + lincosamide [topical], benzoyl peroxide [topical] + macrolide [topical]
  - Discontinuation for any reason: lincosamide [topical], retinoid - total cumul dose < 120mg/kg (single course) [oral], co-cyprindiol [oral], benzoyl peroxide [topical] + macrolide [topical]
- Efficacy:
  - Retinoid [topical], lincosamide [topical] + retinoid [topical], and benzoyl peroxide [topical] + lincosamide [topical] + retinoid [topical] shared a within-class variance
  - Photochemical + photothermal therapy, and photodynamic therapy shared a within-class variance
  - Tetracycline [oral], retinoid [topical] + tetracycline [oral], and benzoyl peroxide [topical] + retinoid [topical] + tetracycline [oral] shared a within-class variance
- Discontinuation for any reason:
  - Retinoid [topical], photodynamic therapy, and benzoyl peroxide [topical] + lincosamide [topical] + retinoid [topical] shared a within-class variance
  - Tetracycline [oral], retinoid [topical] + tetracycline [oral], and benzoyl peroxide [topical] + retinoid [topical] + tetracycline [oral] shared a within-class variance
- Discontinuation due to side effects:
  - Lincosamide [topical], retinoid [topical], photodynamic therapy, and lincosamide [topical] + retinoid [topical] shared a within-class variance
  - Tetracycline [oral], retinoid [topical] + tetracycline [oral], and benzoyl peroxide [topical] + retinoid [topical] + tetracycline [oral] shared a within-class variance

The fixed class effects model assumes treatments within a class D_k have identical relative effects,

$$d_k = m_{D_k}.$$

Non-informative Normal(0, 100^2) priors were assigned to the class mean effects, as well as the effects of treatments not belonging to a class, while Uniform(0, 50) and Uniform(0, 5) priors were assigned to the within-class SDs in the random class effects models for efficacy and the discontinuation outcomes, respectively (Dias 2011a).

Two scenarios were considered: one where the different types of placebo within the placebo class were assumed to have exchangeable effects and one where they were assumed to have identical effects, regardless of the assumptions made for the other classes.

Note that evidence on treatments which were not licensed in the UK, but belonged to a class considered in the network, was initially included in the analyses to help estimate the class effects. However, because fixed class effects models were selected (as described in Results), this evidence was removed so that the resulting estimates were driven by treatments available in the UK.

Model Critique

When considering models for NMA, there are several aspects of the data that will impact the choice of parameters included in the model. Two important assumptions must be made in NMA regarding heterogeneity and consistency. Heterogeneity concerns the differences in treatment effects between trials within each treatment contrast, while consistency concerns the differences between the direct and indirect evidence informing the treatment contrasts (Dias 2011b & 2013b). A further assumption made in the analyses of the efficacy and discontinuation outcomes concerned the within-class variability, where the treatment effects within a class may be assumed to be identical or exchangeable.

Several models were considered for the base-case analyses, all of which assumed consistency:

1) **Fixed study, fixed class effects** model. This is the simplest model available to estimate the treatment effects, where treatments within classes are assumed to have identical effects and there is no heterogeneity between trials estimating the same treatment effects.
2) **Random study, fixed class effects** model. Treatments within classes are assumed to have identical effects, but any beyond chance differences between trial-specific estimates of the same treatment contrasts are captured by the between-study SD.
3) **Fixed study, random class effects** model. Treatments within classes are assumed to have exchangeable effects and there is no heterogeneity between trials estimating the same treatment effects.
    a. The effects of different types of placebo were assumed to be identical.
    b. The effects of different types of placebo were assumed to be exchangeable.
4) **Random study, random class effects** model. Treatments within classes are assumed to have exchangeable effects and any beyond chance differences between trial-specific estimates of the same treatment contrasts are captured by the between-study SD.
    a. The effects of different types of placebo were assumed to be identical.
    b. The effects of different types of placebo were assumed to be exchangeable

When critiquing NMA models, it is good practice to assess and compare the fit of both fixed and random effects models, as differences may provide evidence of potential between-study heterogeneity. The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess the goodness of fit of each model (Spiegelhalter 2002). Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study arm contributes 1 data point) (Spiegelhalter 2002).

In addition to comparing how well the models fit the data using the posterior mean of the residual deviance, models were compared using the deviance information criterion (DIC). This is equal to the sum of the posterior mean deviance and the effective number of parameters, and thus penalizes model fit with model complexity (Spiegelhalter 2002). Lower values are preferred and typically differences of at least 3 points are considered meaningful (Spiegelhalter 2002).

Inconsistency Checks

Inconsistency was assessed by comparing the chosen base-case model assuming consistency to an "inconsistency", or unrelated mean effects, model (Dias 2011b & 2013b). The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. Note that inconsistency can only be assessed when there are closed loops of direct evidence on 3 treatments that are informed by at least 3 distinct trials (van Valkenhoef 2016). The consistency and inconsistency models were compared based on their posterior residual deviance and DIC. Where the base-case model assumed random study effects, if the inconsistency model has smaller heterogeneity (measured by the posterior median between-study SD) compared to the consistency model, then this indicates potential inconsistency in the data.

To visually assess if specific data-points are contributing to inconsistency, we plotted contributions to the posterior mean residual deviance for each data-point for the inconsistency model versus the consistency model. Points lying below the line of equality indicate data-points contributing to inconsistency.

We performed further checks for evidence of inconsistency through node-splitting both at the class-level and at the intervention level using the R2OpenBUGS package in R (Sturtz 2005) (see code in supplement 4). This method permits the direct and indirect evidence contributing to an estimate of a relative effect to be split and compared (Dias 2010a, van Valkenhoef 2016). Note that there were a small number of instances where a multi-arm trial contained the node of interest twice. In these situations, one arm was randomly removed in order to approximate the direct and indirect estimates.

Subgroup and Sensitivity Analyses

Female and Male networks

When evidence on treatments that were only appropriate for females (e.g., co-cyprindiol [oral], combined oral contraceptives [oral]) indirectly contributed to other comparisons in the network, a separate analysis was conducted for males based on a sub-network with female only treatments removed. If the evidence on female only treatments did not indirectly inform other comparisons, then no re-analysis of the NMA was necessary and the treatment rankings for males was based on the subset treatments appropriate for males.

Bias-Adjustment Models

To assess and explain the presence of bias in the included evidence, models which adjusted for bias were fitted (Dias 2018). For each domain on the Cochrane Risk of Bias Tool (version 2) that had sufficient variability in the ratings, bias adjustment models were fitted to downweight trials at high or unclear risk of bias (Welton 2009, Dias 2010b):

$$\theta_{i,k} = \mu_i + \left(\delta_{i,k} + \beta_{i,k} x_{i,k} bias_{i,j}\right)$$

where $\beta_{i,k}$ is trial-specific bias of the treatment in arm k relative to the treatment in arm 1,

$$x_{i,k} = \begin{cases} -1 & \text{if } k \text{ vs. 1 is an active vs. inactive comparison} \\ 0 & \text{if } k \text{ vs. 1 is an active vs. active or inactive vs. active comparison} \\ 1 & \text{if } k \text{ vs. 1 is an inactive vs. active comparison} \end{cases},$$

and

$$bias_{i,j} = \begin{cases} 1 & \text{if study } i \text{ is at high or unclear risk of bias on domain } j \\ 0 & \text{otherwise} \end{cases} .$$

In addition, small study bias was also investigated (Dias 2018, Moreno 2009a & 2009b),

$$\theta_{i,k} = \mu_i + \left(\delta_{i,k} + \beta_{i,k} x_{i,k} \Big/ \sqrt{N_i} \right)$$

where N_i is the number of patients in trial i, or number of observations in the case of a split-face trial.

Age-adjusted analyses

A meta-regression adjusting for age was planned if at least 90% of the included trials for the efficacy outcome reported enough information on age to determine the proportion of participants less than ≤25 years of age and those >25 years of age. In studies reporting efficacy, 82.2% of the studies reported sufficient age data, and since the inclusion criteria was not met for the primary efficacy outcome, the age-adjusted analyses were not carried out.

Results

Efficacy

Initially this analysis was carried out on 65 trials of 31 classes and 65 interventions of varying durations which may or may not have been licensed in the UK, where the unlicensed interventions (e.g. tretinoin alone) were included to help the estimation of the class effects. However, because there was not enough evidence to inform the within-class variability, and the random study effects, fixed class effect model provided adequate fit (Table 32), the analysis was re-run with the non-UK licensed interventions being removed, where 56 trials of 27 classes and 56 interventions were included (

Figure 16, Figure 17, Table 33). The random study effects, fixed class effects model was selected as the base-case model, as the posterior residual deviance indicated adequate model fit, the DICs suggested this model was preferred, and there was not enough evidence to inform the within-class variability (Table 34).

Table 32: Model fit statistics for efficacy with non-UK licensed interventions included

Model	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[a]	DIC[b]
FE, fixed class	---	229.3	1028.0
RE, fixed class	**6.58 (4.12, 9.67)**	**164.7**	**989.0**
FE, random class (placebos coded the same)	---	177.9	991.3
FE, random class (placebos coded separately)	---	176.2	990.3
RE, random class (placebos coded the same)	3.95 (0.55, 7.25)	162.3	986.0
RE, random class (placebos coded separately)	3.79 (0.57, 7.00)	161.6	985.4

Abbreviations: CrI, credible interval; DIC, deviance information criteria; FE, fixed study effects; RE, random study effects; SD, standard deviation; UME, unrelated mean effects

[a] *Posterior mean residual deviance compared to 157 total data points*

[b] *Lower values of DIC preferred*

Figure 16: Network diagram of direct evidence between classes included in efficacy analysis. The width of the lines is proportional to the number of studies making the comparisons, while the size of the nodes is proportional to the number of observations on a particular class.

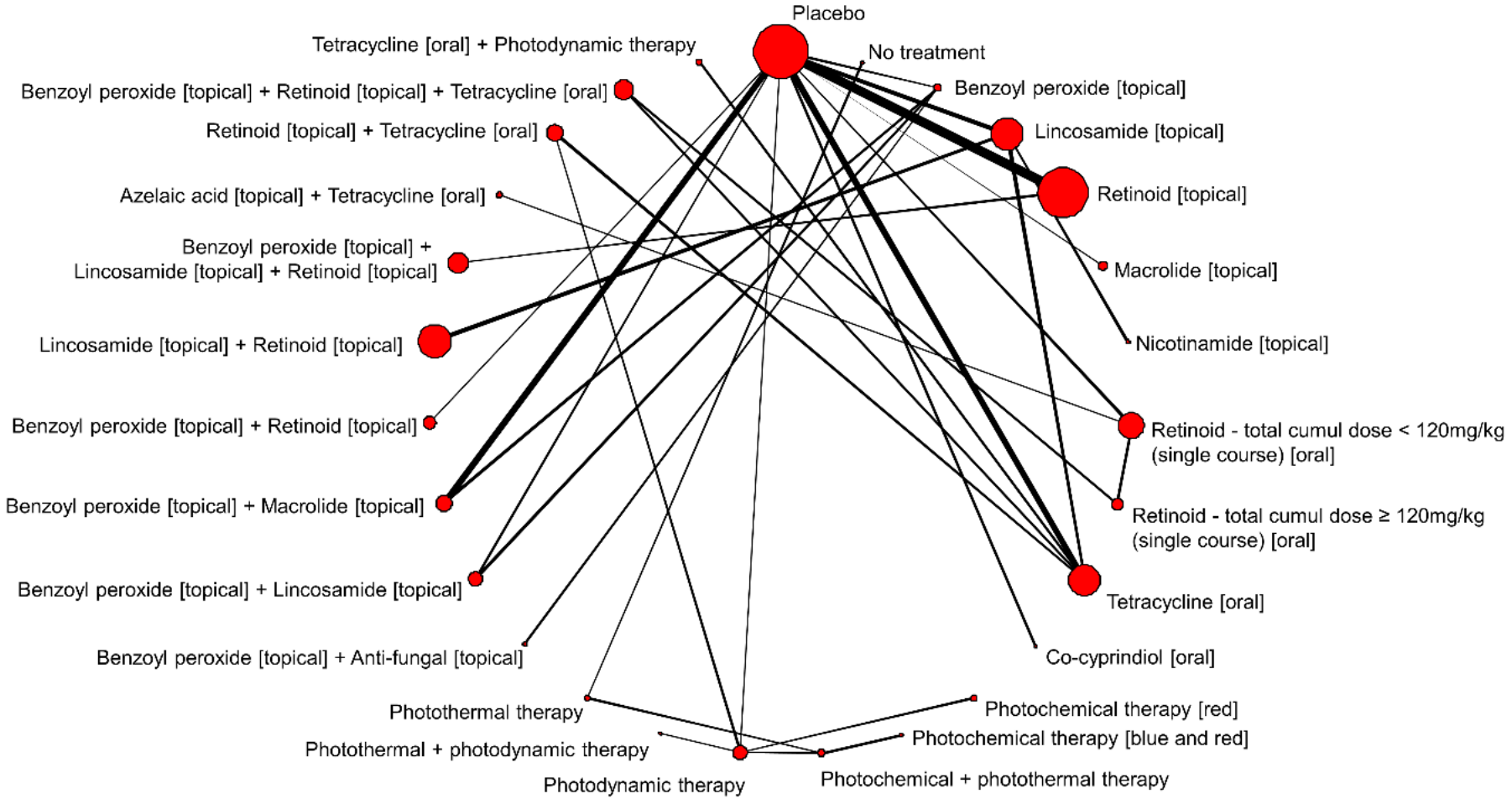


Figure 17: Network diagram of direct evidence between interventions included in efficacy analysis. The width of the lines is proportional to the number of studies making the comparisons, while the size of the nodes is proportional to the number of observations on a particular intervention.

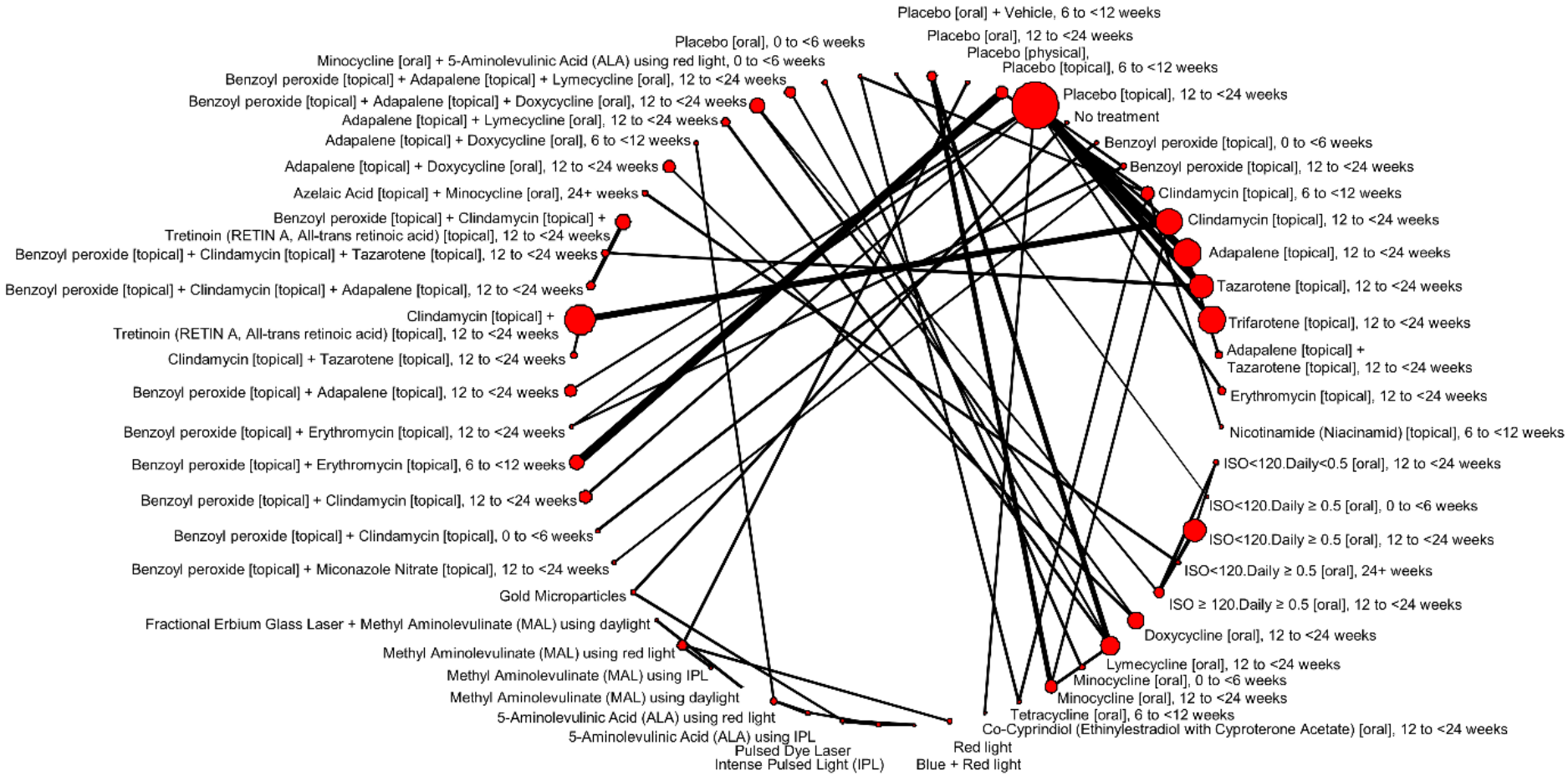


Table 33: Number of observations for each class, intervention and duration in efficacy analysis

Class	n	Treatment	n	Duration	n
Placebo	4122	Placebo [oral]	162	0 to <6 weeks	17
				12 to <24 weeks	145
		Placebo [oral] + Vehicle	29	6 to <12 weeks	29
		Placebo [physical]	30		30
		Placebo [topical]	3901	6 to <12 weeks	276
				12 to <24 weeks	3625
No treatment	25	No treatment	25		25
Benzoyl peroxide [topical]	80	Benzoyl peroxide [topical]	80	0 to <6 weeks	23
				12 to <24 weeks	57
Lincosamide [topical]	1479	Clindamycin [topical]	1479	6 to <12 weeks	164
				12 to <24 weeks	1315
Retinoid [topical]	3570	Adapalene [topical]	1309	12 to <24 weeks	1309
		Tazarotene [topical]	947	12 to <24 weeks	947
		Trifarotene [topical]	1214	12 to <24 weeks	1214
		Adapalene [topical] followed by Tazarotene [topical]	100	12 to <24 weeks	100
Macrolide [topical]	109	Erythromycin [topical]	109	12 to <24 weeks	109
Nicotinamide [topical]	29	Nicotinamide (Niacinamid) [topical]	29	6 to <12 weeks	29
Retinoid - total cumulative dose < 120mg/kg (single course) [oral]	938	Isotretinoin<120.Daily<0.5 [oral]	46	12 to <24 weeks	46
		Isotretinoin<120.Daily≥0.5 [oral]	892	0 to <6 weeks	16
				12 to <24 weeks	841
				24+ weeks	35
Retinoid - total cumulative dose ≥ 120mg/kg (single course) [oral]	182	Isotretinoin≥120.Daily≥0.5 [oral]	182	12 to <24 weeks	182
Tetracycline [oral]	1386	Doxycycline [oral]	456	12 to <24 weeks	456
		Lymecycline [oral]	595	12 to <24 weeks	595
		Minocycline [oral]	306	0 to <6 weeks	47

				12 to <24 weeks	259
		Tetracycline [oral]	29	6 to <12 weeks	29
Co-cyprindiol [oral]	12	Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	12	12 to <24 weeks	12
Photochemical therapy [red]	53	Red light	53		53
Photochemical therapy [blue and red]	15	Blue + Red light	15		15
Photochemical + photothermal therapy	71	Intense Pulsed Light (IPL)	35		35
		Pulsed Dye Laser	36		36
Photodynamic therapy	298	5-Aminolevulinic Acid (ALA) using IPL	33		33
		5-Aminolevulinic Acid (ALA) using red light	81		81
		Methyl Aminolevulinate (MAL) using daylight	14		14
		Methyl Aminolevulinate (MAL) using IPL	20		20
		Methyl Aminolevulinate (MAL) using red light	150		150
Photothermal + photodynamic therapy	14	Fractional Erbium Glass Laser + Methyl Aminolevulinate (MAL) using daylight	14		14
Photothermal therapy	46	Gold Microparticles	46		46
Benzoyl peroxide [topical] + Anti-fungal [topical]	25	Benzoyl peroxide [topical] + Miconazole Nitrate [topical]	25	12 to <24 weeks	25
Benzoyl peroxide [topical] + Lincosamide [topical]	276	Benzoyl peroxide [topical] + Clindamycin [topical]	276	0 to <6 weeks	23
				12 to <24 weeks	253
Benzoyl peroxide [topical] + Macrolide [topical]	365	Benzoyl peroxide [topical] + Erythromycin [topical]	365	6 to <12 weeks	337
				12 to <24 weeks	28
Benzoyl peroxide [topical] + Retinoid [topical]	217	Benzoyl peroxide [topical] + Adapalene [topical]	217	12 to <24 weeks	217
Lincosamide [topical] + Retinoid [topical]	1548	Clindamycin [topical] + Tazarotene [topical]	75	12 to <24 weeks	75
		Clindamycin [topical] + Tretinoin (RETIN A, All-trans retinoic acid) [topical]	1473	12 to <24 weeks	1473
Benzoyl peroxide [topical] + Lincosamide [topical] + Retinoid [topical]	600	Benzoyl peroxide [topical] + Clindamycin [topical] + Adapalene [topical]	118	12 to <24 weeks	118
		Benzoyl peroxide [topical] + Clindamycin [topical] + Tazarotene [topical]	100	12 to <24 weeks	100

		Benzoyl peroxide [topical] + Clindamycin [topical] + Tretinoin (RETIN A, All-trans retinoic acid) [topical]	382	12 to <24 weeks	382
Azelaic acid [topical] + Tetracycline [oral]	50	Azelaic Acid [topical] + Minocycline [oral]	50	24+ weeks	50
Retinoid [topical] + Tetracycline [oral]	379	Adapalene [topical] + Doxycycline [oral]	261	6 to <12 weeks	23
				12 to <24 weeks	238
		Adapalene [topical] + Lymecycline [oral]	118	12 to <24 weeks	118
Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral]	556	Benzoyl peroxide [topical] + Adapalene [topical] + Doxycycline [oral]	365	12 to <24 weeks	365
		Benzoyl peroxide [topical] + Adapalene [topical] + Lymecycline [oral]	191	12 to <24 weeks	191
Tetracycline [oral] + Photodynamic therapy	48	Minocycline [oral] + 5-Aminolevulinic Acid (ALA) using red light	48	0 to <6 weeks	48

Table 34: Model fit statistics for efficacy. Only UK-licensed interventions included.

Model	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[a]	DIC[b]
FE, fixed class	---	184.0	854.9
RE, fixed class	**5.74 (3.26, 8.97)**	**138.0**	**828.1**
FE, random class (placebos coded the same)	---	152.5	835.4
FE, random class (placebos coded separately)	---	150.0	835.2
RE, random class (placebos coded the same)	4.22 (0.48, 7.90)	138.1	830.3
RE, random class (placebos coded separately)	3.75 (0.34, 7.49)	137.5	831.0
UME - RE, intervention level	3.55 (0.31, 7.88)	137.5	837.5
UME - RE, class level	4.99 (2.60, 8.15)	139.7	831.2

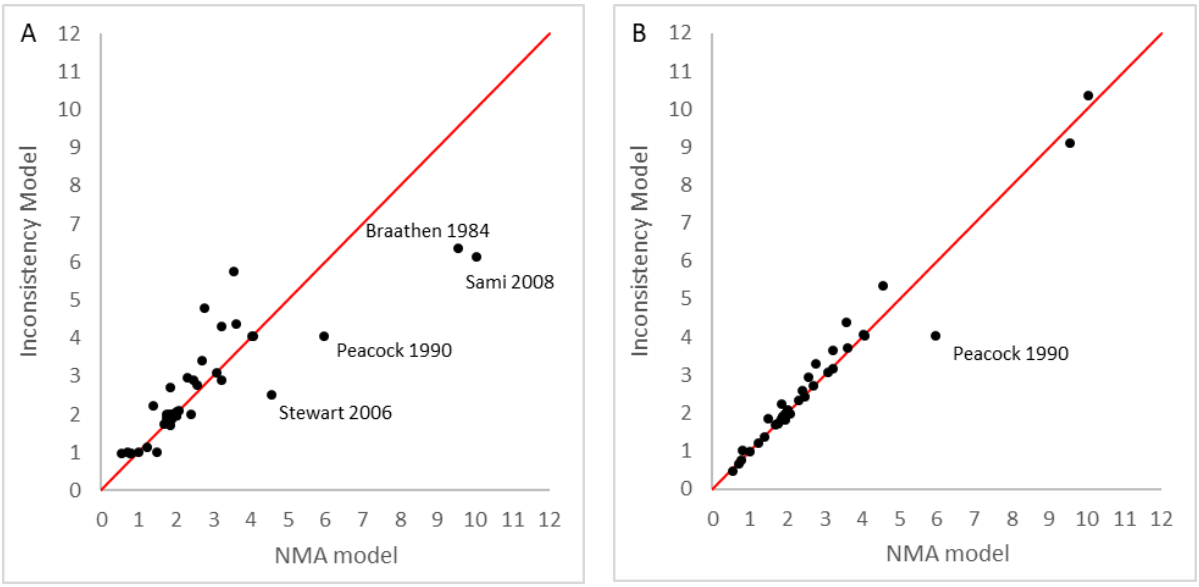
Abbreviations: CrI, credible interval; DIC, deviance information criteria; FE, fixed study effects; RE, random study effects; SD, standard deviation; UME, unrelated mean effects

[a] *Posterior mean residual deviance compared to 133 total data points*

[b] *Lower values of DIC preferred*

Although there were no meaningful differences between the fit of the random effects consistency and inconsistency models, the between-study SD slightly decreased in the inconsistency models, suggesting some evidence of inconsistency (Table 34). The area below the line of equality in Figure 18 highlights where the inconsistency model better predicted data points, and there were notable improvements in the prediction of data in Braathen 1984, which compared Clindamycin [topical], Tetracycline [oral], and Placebo [oral] + Vehicle, all with a duration of 6 to <12 weeks, Peacock 1990, which compared Clindamycin [topical] and Minocycline [oral], all with a duration of 12 to <24 weeks, Sami 2008, which compared Pulsed Dye Laser, Intense Pulsed Light (IPL), and Blue + Red light, and Stewart 2006, which compared two variations of Minocycline [oral] and Placebo [oral], all with a duration of 12 to <24 weeks.

Figure 18: Deviance contributions for the random study, fixed class effects consistency and inconsistency models at (A) the intervention level and (B) the class level for efficacy.



For most comparisons, there were no meaningful differences between the fit and DIC of the node split models and the consistency model, apart from Lincosamide [topical] vs. Placebo (4 vs. 1) (Table 35); there were differences between the direct and indirect estimates of this class comparisons (Figure 19).

A table of the direct, indirect, and NMA estimates for all pairwise relative effects between classes is available in supplement 10.

Table 35: Node split model fit statistics for efficacy

Node split model	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[a]	DIC[b]	p-value[c]
Benzoyl peroxide [topical] vs. Placebo (3 vs. 1)	5.78 (3.28, 9.05)	137.9	886.9	0.40
Lincosamide [topical] vs. Placebo (4 vs. 1)	5.31 (2.96, 8.36)	136.1	884.0	0.02
Retinoid - total cumul dose < 120mg/kg (single course) [oral] vs. Placebo (8 vs. 1)	5.75 (3.28, 9.00)	138.4	887.3	0.57
Tetracycline [oral] vs. Placebo (10 vs. 1)	5.81 (3.30, 9.10)	137.5	886.6	0.45
Photodynamic therapy vs. Placebo (15 vs. 1)	5.79 (3.24, 9.08)	138.0	887.0	0.47
Benzoyl peroxide [topical] + Lincosamide [topical] vs. Placebo (19 vs. 1)	5.75 (3.23, 9.07)	138.0	887.0	0.35

Node split model	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[a]	DIC[b]	p-value[c]
Benzoyl peroxide [topical] + Lincosamide [topical] vs. Benzoyl peroxide [topical] (19 vs. 3)	5.77 (3.28, 8.97)	138.1	887.1	0.36
Benzoyl peroxide [topical] + Macrolide [topical] vs. Benzoyl peroxide [topical] (20 vs. 3)	5.74 (3.19, 9.02)	138.2	887.2	0.41
Tetracycline [oral] vs. Lincosamide [topical] (10 vs. 4)	5.78 (3.24, 9.06)	138.6	887.7	0.73
Retinoid - total cumul dose ≥ 120mg/kg (single course) [oral] vs. Retinoid - total cumul dose < 120mg/kg (single course) [oral] (9 vs. 8)	5.76 (3.25, 9.02)	138.6	887.8	0.89
Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral] vs. Retinoid - total cumul dose ≥ 120mg/kg (single course) [oral] (26 vs. 9)	5.78 (3.28, 9.04)	138.5	887.8	0.90
Retinoid [topical] + Tetracycline [oral] vs. Tetracycline [oral] (25 vs. 10)	5.82 (3.37, 9.08)	137.7	886.7	0.28
Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral] vs. Tetracycline [oral] (26 vs. 10)	5.74 (3.24, 8.99)	138.6	887.7	0.74
Retinoid [topical] + Tetracycline [oral] vs. Photodynamic therapy (25 vs. 15)	5.80 (3.29, 9.02)	137.8	886.7	0.29
NMA (no nodes split)[d]	**5.78 (3.27, 9.04)**	**137.9**	**886.3**	

Abbreviations: CrI, credible interval; DIC, deviance information criteria; NMA, network meta-analysis; SD, standard deviation

Values in red suggest evidence of inconsistency (either reduced between study heterogeneity following node-split testing, or p-value <0.05)

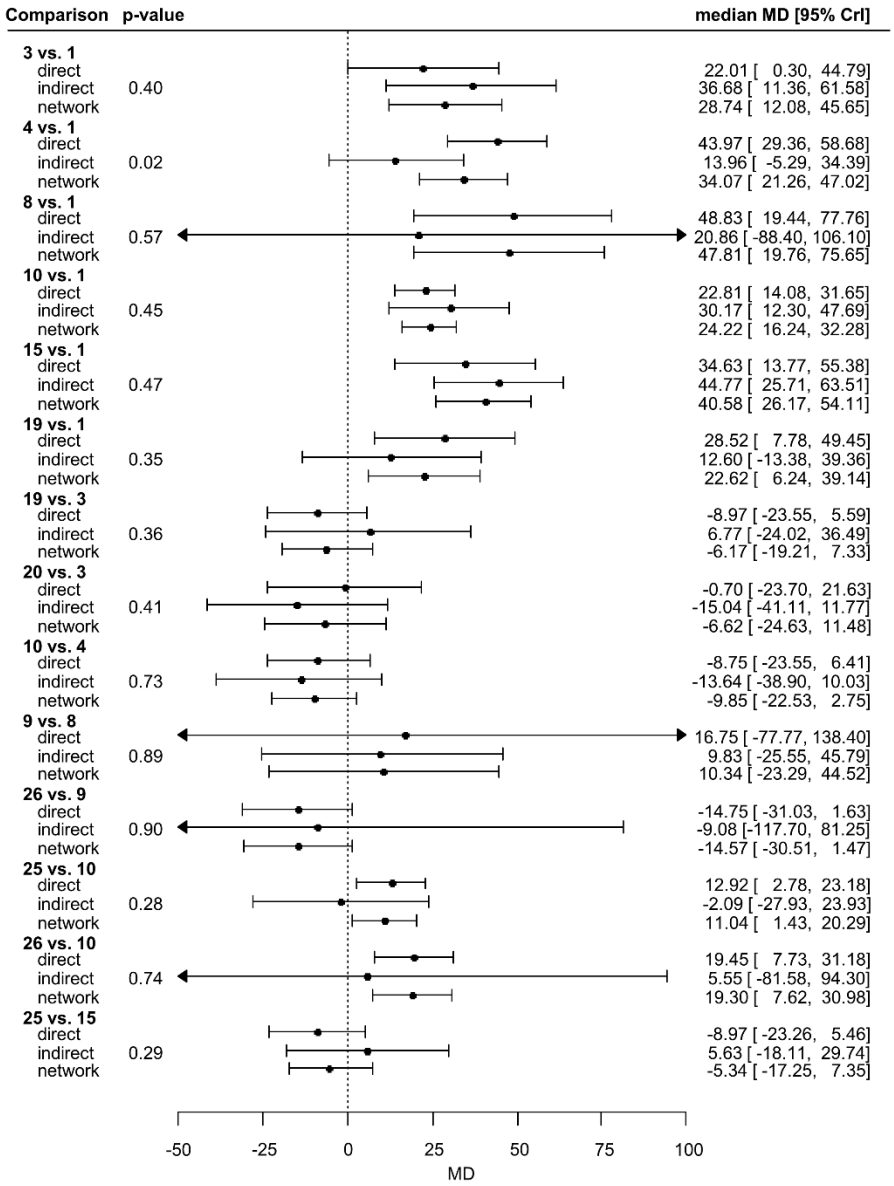
[a] *Posterior mean residual deviance compared to 133 total data points*

[b] *Lower values of DIC preferred*

[c] *p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates*

[d] *Model fit statistics produced in R2OpenBUGS*

Figure 19: Forest plot of direct, indirect and network meta-analysis estimates of class comparisons for efficacy.



Class codes: 1 - Placebo, 2 - No treatment, 3 - Benzoyl peroxide [topical], 4 - Lincosamide [topical], 5 - Retinoid [topical], 6 - Macrolide [topical], 7 - Nicotinamide [topical], 8 - Retinoid - total cumul dose < 120mg/kg (single course) [oral], 9 - Retinoid - total cumul dose ≥ 120mg/kg (single course) [oral], 10 - Tetracycline [oral], 11 - Co-cyprindiol [oral], 12 - Photochemical therapy [red], 13 - Photochemical therapy [blue and red], 14 - Photochemical + photothermal therapy, 15 - Photodynamic therapy, 16 - Photothermal + photodynamic therapy, 17 - Photothermal therapy, 18 - Benzoyl peroxide [topical] + Anti-fungal [topical], 19 - Benzoyl peroxide [topical] + Lincosamide [topical], 20 - Benzoyl peroxide [topical] + Macrolide [topical], 21 - Benzoyl peroxide [topical] + Retinoid [topical], 22 - Lincosamide [topical] + Retinoid [topical], 23 - Benzoyl peroxide [topical] + Lincosamide [topical] + Retinoid [topical], 24 - Azelaic acid [topical] + Tetracycline [oral], 25 - Retinoid [topical] + Tetracycline [oral], 26 - Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral], 27 - Tetracycline [oral] + Photodynamic therapy.

There was sufficient variation in the ratings of studies to fit bias models on two risk of bias domains:

- Domain 2: Deviation from interventions
- Domain 4: Outcome measurement (efficacy)

No evidence of bias arising from these domains was found, nor was small study effect bias, as the 95% credible intervals of the posterior mean bias include zero (

1 Table 36).

Table 36: Bias model fit statistics for efficacy

Model	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[a]	DIC[b]	Bias	
				Posterior median (95% CrI)	Between Study SD (95% CrI)
NMA model: RE, fixed class	**5.74 (3.26, 8.97)**	**138.0**	**828.1**	**---**	**---**
Bias model: Domain 2	5.25 (2.80, 8.40)	137.0	828.3	11.56 (-8.25, 34.42)	12.88 (0.62, 42.30)
Bias model: Domain 4	4.95 (2.20, 8.27)	135.3	826.6	12.63 (-4.03, 36.44)	17.29 (2.07, 41.60)
Bias model: Small study	5.27 (2.37, 8.64)	137.8	829.9	47.20 (-98.03, 190.40)	64.55 (3.38, 173.80)

Abbreviations: CrI, credible interval; DIC, deviance information criteria; RE, random study effects; NMA, network meta-analysis; SD, standard deviation
[a] Posterior mean residual deviance compared to 133 total data points
[b] Lower values of DIC preferred

Evidence suggested that the following interventions are more effective than Placebo, in decreasing order of effectiveness (supplement 10):

- Retinoid - total cumul dose ≥ 120mg/kg (single course) [oral]
- Photothermal therapy
- Nicotinamide [topical]
- Photothermal + photodynamic therapy
- Retinoid - total cumulative dose < 120mg/kg (single course) [oral]
- Tetracycline [oral] + Photodynamic therapy
- Lincosamide [topical] + Retinoid [topical]
- Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral]
- Photodynamic therapy
- No treatment
- Azelaic acid [topical] + Tetracycline [oral]
- Retinoid [topical] + Tetracycline [oral]
- Lincosamide [topical]
- Benzoyl peroxide [topical] + Retinoid [topical]
- Photochemical therapy [red]
- Benzoyl peroxide [topical]
- Tetracycline [oral]
- Benzoyl peroxide [topical] + Lincosamide [topical] + Retinoid [topical]
- Benzoyl peroxide [topical] + Lincosamide [topical]
- Benzoyl peroxide [topical] + Macrolide [topical]
- Retinoid [topical]

No classes were less effective than Placebo (supplement 10).

Retinoid - total cumul dose ≥ 120mg/kg (single course) [oral] is the highest ranked class for both females and males, with posterior mean ranks of 3.4 (95% CrI 1st to 11th) and 3.3 (95% CrI 1st to 10th), respectively (Table 37). The lowest ranked class is Placebo at 26.4 (95% CrI 25th to 27th) for females and 25.5 (95% CrI 24th to 26th) for males (Table 37).

Table 37: Posterior mean rank and 95% credible intervals of classes for efficacy

Class	Posterior Mean Rank (95% CrI)	
	Females	Males
Retinoid - total cumulative dose ≥ 120mg/kg (single course) [oral]	3.4 (1, 11)	3.3 (1, 10)
Photothermal therapy	4.3 (1, 17)	4.2 (1, 16)
Nicotinamide [topical]	6.4 (1, 19)	6.3 (1, 19)
Retinoid - total cumulative dose < 120mg/kg (single course) [oral]	7.1 (1, 20)	7.0 (1, 20)
Photothermal + photodynamic therapy	7.3 (1, 22)	7.2 (1, 21)
Lincosamide [topical] + Retinoid [topical]	7.7 (2, 15)	7.5 (2, 15)
Tetracycline [oral] + Photodynamic therapy	7.8 (2, 17)	7.6 (2, 17)
Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral]	8.1 (3, 16)	8.0 (3, 15)
Photodynamic therapy	9.5 (4, 16)	9.3 (4, 16)

Class	Posterior Mean Rank (95% CrI)	
	Females	Males
No treatment	11.0 (2, 25)	10.7 (2, 24)
Azelaic acid [topical] + Tetracycline [oral]	11.5 (2, 25)	11.2 (2, 24)
Retinoid [topical] + Tetracycline [oral]	12.5 (7, 19)	12.2 (6, 18)
Benzoyl peroxide [topical] + Retinoid [topical]	13.1 (3, 24)	12.8 (3, 23)
Lincosamide [topical]	13.2 (6, 21)	12.9 (6, 20)
Photochemical therapy [red]	15.5 (5, 25)	15.1 (5, 24)
Benzoyl peroxide [topical]	15.6 (6, 23)	15.2 (6, 22)
Photochemical + photothermal therapy	16.1 (4, 26)	15.7 (4, 25)
Co-cyprindiol [oral]	17.1 (3, 27)	not applicable
Tetracycline [oral]	18.6 (14, 23)	18.1 (13, 22)
Benzoyl peroxide [topical] + Lincosamide [topical] + Retinoid [topical]	18.8 (10, 25)	18.3 (10, 24)
Benzoyl peroxide [topical] + Anti-fungal [topical]	19.0 (6, 26)	18.4 (6, 25)
Benzoyl peroxide [topical] + Lincosamide [topical]	19.1 (10, 25)	18.6 (10, 24)
Benzoyl peroxide [topical] + Macrolide [topical]	19.5 (13, 24)	19.0 (13, 23)
Photochemical therapy [blue and red]	21.9 (5, 27)	21.2 (5, 26)
Retinoid [topical]	23.6 (20, 26)	22.8 (19, 25)
Macrolide [topical]	23.8 (17, 27)	23.0 (17, 26)
Placebo	26.4 (25, 27)	25.5 (24, 26)

1 *Abbreviations: CrI, credible interval*

2 ***Discontinuation for any Reason***

3 After excluding trials with zero events in all arms, 85 trials of 40 classes of 76 interventions
4 licensed in the UK were included for this outcome (

Figure 20, Figure 21, **Error! Reference source not found.**). A continuity correction was applied to data in 10 studies containing at least one zero cell to stabilize the results. The final results presented in this guideline are based on the random study effects, fixed class effects model, as the posterior residual deviance indicated good model fit, the DICs suggested this model was preferred, and there were no meaningful differences between the DICs of this model and the random study, fixed class effects model (Table 39).

Figure 20: Network diagram of direct evidence between classes included in discontinuation for any reason analysis. The width of the lines is proportional to the number of studies making the comparisons, while the size of the nodes is proportional to the number of observations on a particular class.

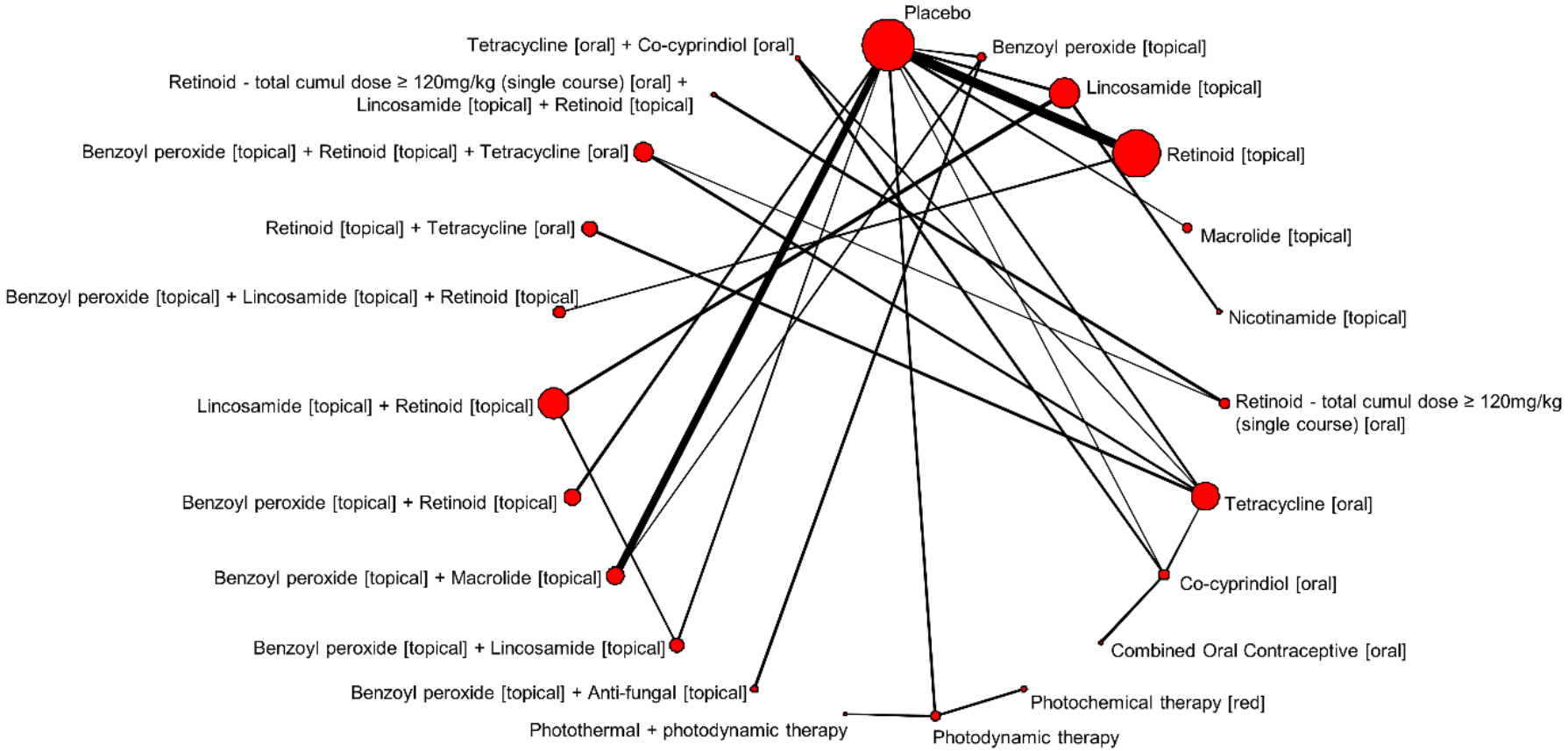


Figure 21: Network diagram of direct evidence between interventions included in discontinuation for any reason analysis. The width of the lines is proportional to the number of studies making the comparisons, while the size of the nodes is proportional to the number of observations on a particular intervention.

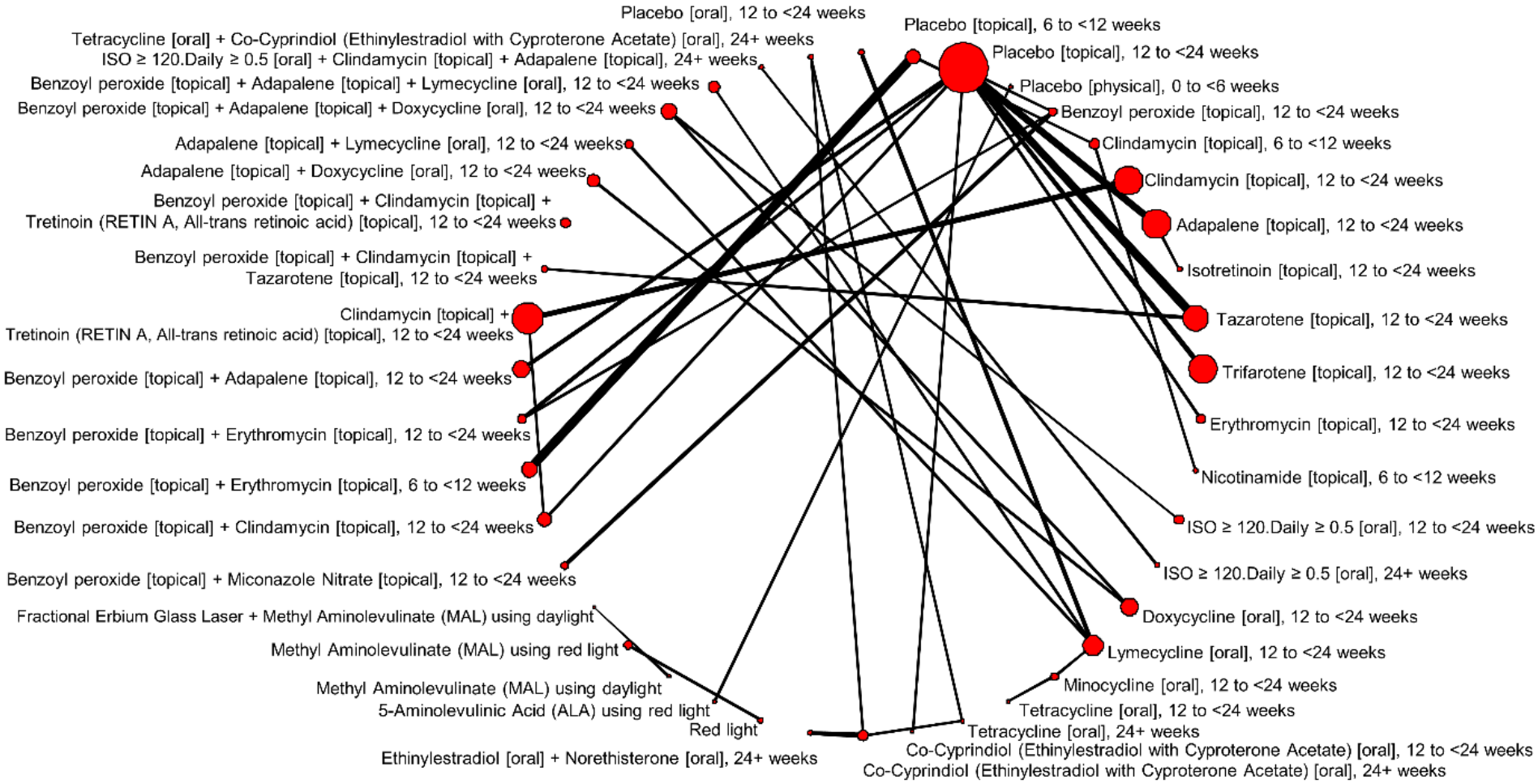


Table 38: Number of observations for each class, intervention and duration in discontinuation for any reason analysis

Class	n	Treatment	n	Duration	n
Placebo	4133	Placebo [oral]	53	12 to <24 weeks	53
		Placebo [topical]	4055	6 to <12 weeks	317
				12 to <24 weeks	3738
		Placebo [physical]	25	0 to <6 weeks	25
Benzoyl peroxide [topical]	114	Benzoyl peroxide [topical]	114	12 to <24 weeks	114
Lincosamide [topical]	1416	Clindamycin [topical]	1416	6 to <12 weeks	159
				12 to <24 weeks	1257
Retinoid [topical]	3449	Adapalene [topical]	1248	12 to <24 weeks	1248
		Isotretinoin [topical]	40	12 to <24 weeks	40
		Tazarotene [topical]	947	12 to <24 weeks	947
		Trifarotene [topical]	1214	12 to <24 weeks	1214
Macrolide [topical]	127	Erythromycin [topical]	127	12 to <24 weeks	127
Nicotinamide [topical]	38	Nicotinamide (Niacinamid) [topical]	38	6 to <12 weeks	38
Retinoid - total cumulative dose ≥ 120mg/kg (single course) [oral]	163	Isotretinoin≥120.Daily≥0.5 [oral]	163	12 to <24 weeks	133
				24+ weeks	30
Tetracycline [oral]	1188	Doxycycline [oral]	456	12 to <24 weeks	456
		Lymecycline [oral]	595	12 to <24 weeks	595
		Minocycline [oral]	91	12 to <24 weeks	91
		Tetracycline [oral]	46	12 to <24 weeks	21
				24+ weeks	25
Co-cyprindiol [oral]	175	Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	175	12 to <24 weeks	14
				24+ weeks	161
Combined Oral Contraceptive [oral]	32	Ethinylestradiol [oral] + Norethisterone [oral]	32	24+ weeks	32
Photochemical therapy [red]	53	Red light	53		53
Photodynamic therapy	141	5-Aminolevulinic Acid (ALA) using red light	25		25
		Methyl Aminolevulinate (MAL) using daylight	16		16

		Methyl Aminolevulinate (MAL) using red light	100		100
Photothermal + photodynamic therapy	16	Fractional Erbium Glass Laser + Methyl Aminolevulinate (MAL) using daylight	16		16
Benzoyl peroxide [topical] + Anti-fungal [topical]	81	Benzoyl peroxide [topical] + Miconazole Nitrate [topical]	81	12 to <24 weeks	81
Benzoyl peroxide [topical] + Lincosamide [topical]	280	Benzoyl peroxide [topical] + Clindamycin [topical]	280	12 to <24 weeks	280
Benzoyl peroxide [topical] + Macrolide [topical]	477	Benzoyl peroxide [topical] + Erythromycin [topical]	477	6 to <12 weeks	357
				12 to <24 weeks	120
Benzoyl peroxide [topical] + Retinoid [topical]	434	Benzoyl peroxide [topical] + Adapalene [topical]	434	12 to <24 weeks	434
Lincosamide [topical] + Retinoid [topical]	1439	Clindamycin [topical] + Tretinoin (RETIN A, All-trans retinoic acid) [topical]	1439	12 to <24 weeks	1439
Benzoyl peroxide [topical] + Lincosamide [topical] + Retinoid [topical]	207	Benzoyl peroxide [topical] + Clindamycin [topical] + Tazarotene [topical]	60	12 to <24 weeks	60
		Benzoyl peroxide [topical] + Clindamycin [topical] + Tretinoin (RETIN A, All-trans retinoic acid) [topical]	147	12 to <24 weeks	147
Retinoid [topical] + Tetracycline [oral]	356	Adapalene [topical] + Doxycycline [oral]	238	12 to <24 weeks	238
		Adapalene [topical] + Lymecycline [oral]	118	12 to <24 weeks	118
Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral]	556	Benzoyl peroxide [topical] + Adapalene [topical] + Doxycycline [oral]	365	12 to <24 weeks	365
		Benzoyl peroxide [topical] + Adapalene [topical] + Lymecycline [oral]	191	12 to <24 weeks	191
Retinoid - total cumul dose ≥ 120mg/kg (single course) [oral] + Lincosamide [topical] + Retinoid [topical]	30	Isotretinoin≥120.Daily≥0.5 [oral] + Clindamycin [topical] + Adapalene [topical]	30	24+ weeks	30
Tetracycline [oral] + Co-cyprindiol [oral]	37	Tetracycline [oral] + Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	37	24+ weeks	37

1

Table 39: Model fit statistics for discontinuation for any reason

Model	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[a]	DIC[b]
FE, fixed class	---	124.5	564.586
RE, fixed class	**0.40 (0.19, 0.68)**	**94.74**	**548.326**
FE, random class (placebos coded the same)	---	107.7	553.063
FE, random class (placebos coded separately)	---	108.1	554.268
RE, random class (placebos coded the same)	0.28 (0.02, 0.64)	98.92	552.298
RE, random class (placebos coded separately)	0.28 (0.02, 0.66)	99.07	553.015
UME - FE, intervention level	0.35 (0.04, 0.74)	97.69	556.802
UME - FE, class level	0.39 (0.20, 0.66)	94.51	550.058

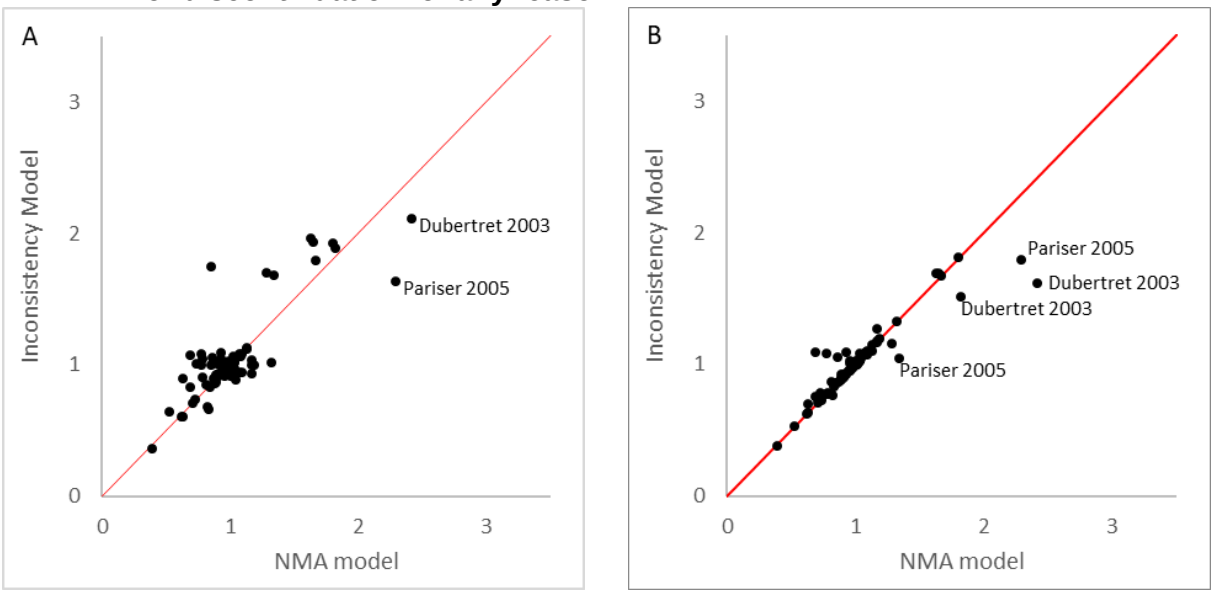
Abbreviations: CrI, credible interval; DIC, deviance information criteria; FE, fixed study effects; RE, random study effects; SD, standard deviation; UME, unrelated mean effects

[a] *Posterior mean residual deviance compared to 93 total data points*

[b] *Lower values of DIC preferred*

The random effects consistency model provided a better fit than the inconsistency model at the intervention level, and there were no meaningful differences between the fit of the random effects consistency and inconsistency model at the class level (Table 39). The area below the line of equality in Figure 22 highlights where the inconsistency model better predicted data points, and there were notable improvements in the prediction of data in Dubertret 2003, a three-arm trial which compared two variations of Lymecycline [oral] and Placebo [oral], all with a duration of 12 to <24 weeks, and Pariser 2005, a three-arm trial which compared two variations of Adapalene [topical] and Placebo [topical], all with a duration of 12 to <24 weeks.

Figure 22: Deviance contributions for the fixed study, fixed class effects consistency and inconsistency models at (A) the intervention level and (B) the class level for discontinuation for any reason.



No evidence of inconsistency was found through the node splitting analysis at the class level, as there were no meaningful differences between the fit and DIC of the node split models and the consistency model, nor were there any notable differences between the direct and indirect estimates (**Error! Reference source not found.**, Figure 23).

A table of the direct, indirect, and NMA estimates for all pairwise relative effects between classes is available in supplement 10.

Table 40: Node split model fit statistics for discontinuation for any reason

Node split model[a]	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[b]	DIC[c]	p-value[d]
Lincosamide [topical] vs. Placebo (3 vs. 1)	0.41 (0.20, 0.70)	95.28	549.9	0.73
Tetracycline [oral] vs. Placebo (8 vs. 1)	0.41 (0.20, 0.70)	95.05	549.7	0.58
Co-cyprindiol [oral] vs. Placebo (9 vs. 1)	0.41 (0.20, 0.69)	95.07	549.6	0.57
Benzoyl peroxide [topical] + Lincosamide [topical] vs. Placebo (15 vs. 1)	0.41 (0.20, 0.71)	95.09	549.7	0.73
Lincosamide [topical] + Retinoid [topical] vs. Lincosamide [topical] (18 vs. 3)	0.41 (0.20, 0.70)	95.23	549.8	0.73
Co-cyprindiol [oral] vs. Tetracycline [oral] (9 vs. 8)	0.41 (0.19, 0.69)	95.16	549.7	0.58
Lincosamide [topical] + Retinoid [topical] vs. Benzoyl peroxide [topical] + Lincosamide [topical] (18 vs. 15)	0.41 (0.20, 0.70)	95.23	549.8	0.73

Node split model[a]	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[b]	DIC[c]	p-value[d]
NMA (no nodes split)	**0.40 (0.19, 0.68)**	**94.74**	**548.326**	

Abbreviations: CrI, credible interval; DIC, deviance information criteria; NMA, network meta-analysis; SD, standard deviation

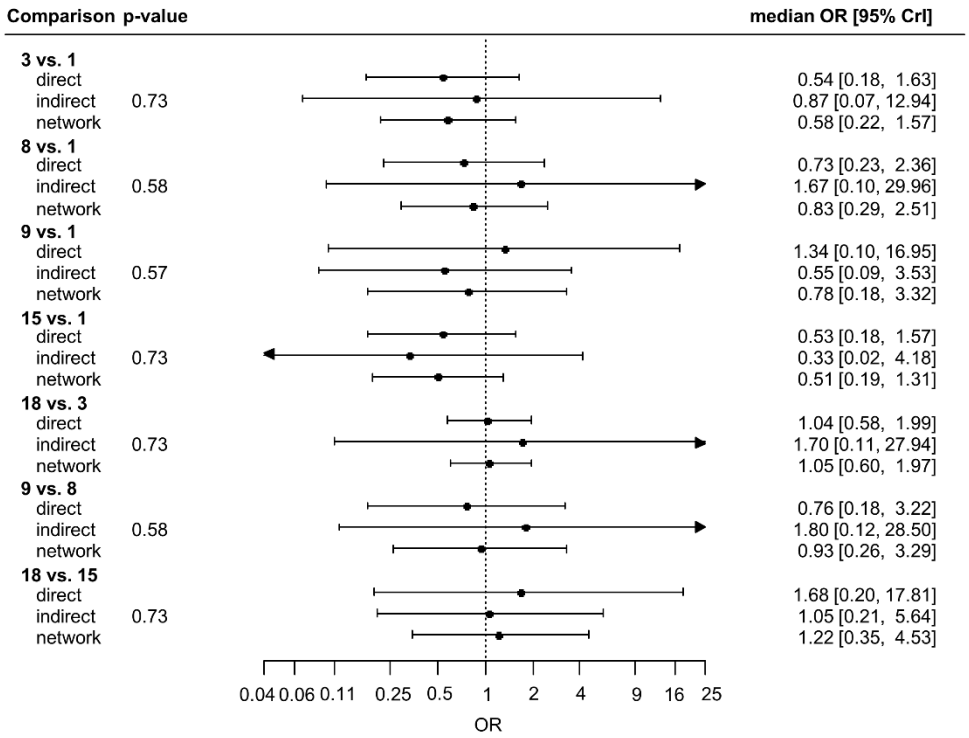
[a] *Continuity correction applied to studies containing zero cells*

[b] *Posterior mean residual deviance compared to 93 total data points*

[c] *Lower values of DIC preferred*

[d] *p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates*

Figure 23: Forest plot of direct, indirect and network meta-analysis estimates of class comparisons for discontinuation for any reason.



Class codes: 1 - Placebo, 2 - Benzoyl peroxide [topical], 3 - Lincosamide [topical], 4 - Retinoid [topical], 5 - Macrolide [topical], 6 - Nicotinamide [topical], 7 - Retinoid - total cumul dose ≥ 120mg/kg (single course) [oral], 8 - Tetracycline [oral], 9 - Co-cyprindiol [oral], 10 - Combined Oral Contraceptive [oral], 11 - Photochemical therapy [red], 12 - Photodynamic therapy, 13 - Photothermal + photodynamic therapy, 14 - Benzoyl peroxide [topical] + Anti-fungal [topical], 15 - Benzoyl peroxide [topical] + Lincosamide [topical], 16 - Benzoyl peroxide [topical] + Macrolide [topical], 17 - Benzoyl peroxide [topical] + Retinoid [topical], 18 - Lincosamide [topical] + Retinoid [topical], 19 - Benzoyl peroxide [topical] + Lincosamide [topical] + Retinoid [topical], 20 - Retinoid [topical] + Tetracycline [oral], 21 - Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral], 22 - Retinoid - total cumul dose ≥ 120mg/kg (single course) [oral] + Lincosamide [topical] + Retinoid [topical], 23 - Tetracycline [oral] + Co-cyprindiol [oral].

There was sufficient variation in the ratings of studies to fit bias models on two risk of bias domains:

- Domain 2: Deviation from interventions
- Domain 4: Outcome measurement (efficacy)

No evidence of bias arising from these domains was found, nor was small study effect bias, as the 95% credible intervals of the posterior mean bias include zero (

Table 41).

There was no evidence suggesting that any of the classes decreased or increased the odds of discontinuation compared to Placebo, for both females and males (supplement 10).

Macrolide [topical] was the highest ranked class for females, with a posterior mean ranks of 7.7 (95% CrI 1st to 19th) (Table 42). Retinoid - total cumul dose ≥ 120mg/kg (single course) [oral] was the highest ranked class for males, with a posterior mean rank of 6.5 (95% CrI 1st to 18th) (Table 42). The lowest ranked class was Retinoid [topical] at 17.7 (95% CrI 11th to 23rd) for females and 16.1 (95% CrI 10th to 20th) for males (Table 42).

Table 41: Bias model fit statistics for discontinuation for any reason

Model	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[a]	DIC[b]	Bias	
				Posterior median (95% CrI)	Between Study SD (95% CrI)
NMA model: RE, fixed class	0.40 (0.19, 0.68)	94.74	548.326	---	---
Bias model: Domain 2	0.39 (0.17, 0.68)	94.54	549.961	0.07 (-1.39, 1.54)	0.78 (0.06, 3.23)
Bias model: Domain 4	0.30 (0.04, 0.64)	97.01	550.06	-0.29 (-1.17, 0.76)	0.48 (0.03, 1.64)
Bias model: Small study	0.28 (0.01, 0.62)	94.86	549.33	-0.67 (-19.25, 15.78)	6.55 (0.46, 13.8)

Abbreviations: CrI, credible interval; DIC, deviance information criteria; RE, random study effects; NMA, network meta-analysis; SD, standard deviation
[a] Posterior mean residual deviance compared to 133 total data points
[b] Lower values of DIC preferred

Table 42: Posterior mean rank and 95% credible intervals of classes for discontinuation for any reason

Class	Posterior Mean Rank (95% CrI)	
	Females	Males
Macrolide [topical]	7.7 (1, 19)	7.3 (1, 17)
Retinoid - total cumul dose ≥ 120mg/kg (single course) [oral]	7.7 (1, 21)	6.5 (1, 18)
Photochemical therapy [red]	7.9 (1, 23)	7.3 (1, 20)
Retinoid - total cumul dose ≥ 120mg/kg (single course) [oral] + Lincosamide [topical] + Retinoid [topical]	8.7 (1, 23)	7.4 (1, 20)
Benzoyl peroxide [topical]	9.0 (1, 22)	8.3 (1, 19)
Benzoyl peroxide [topical] + Lincosamide [topical]	9.3 (2, 20)	8.8 (2, 18)
Benzoyl peroxide [topical] + Macrolide [topical]	9.5 (2, 18)	9.0 (3, 16)
Photodynamic therapy	9.6 (1, 23)	8.9 (1, 20)
Photothermal + photodynamic therapy	9.9 (1, 23)	9.2 (1, 20)
Lincosamide [topical]	10.6 (3, 20)	9.9 (3, 18)
Lincosamide [topical] + Retinoid [topical]	11.3 (2, 22)	10.5 (2, 19)
Nicotinamide [topical]	12.4 (1, 23)	11.4 (1, 20)
Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral]	12.6 (3, 22)	10.6 (3, 19)
Benzoyl peroxide [topical] + Anti-fungal [topical]	13.3 (1, 23)	11.9 (1, 20)
Co-cyprindiol [oral]	13.3 (3, 22)	not applicable
Benzoyl peroxide [topical] + Lincosamide [topical] + Retinoid [topical]	13.4 (2, 23)	12.2 (2, 20)
Tetracycline [oral] + Co-cyprindiol [oral]	13.5 (2, 23)	not applicable
Tetracycline [oral]	14.2 (6, 21)	11.9 (4, 19)
Benzoyl peroxide [topical] + Retinoid [topical]	15.0 (4, 23)	13.6 (4, 20)
Combined Oral Contraceptive [oral]	15.9 (2, 23)	not applicable
Placebo	16.4 (10, 21)	15.0 (10, 19)
Retinoid [topical] + Tetracycline [oral]	17.0 (6, 23)	14.4 (5, 20)
Retinoid [topical]	17.7 (11, 23)	16.1 (10, 20)

Abbreviations: CrI, credible interval

Discontinuation due to Side Effects

After excluding trials with zero events in all arms, 32 trials of 33 interventions and 18 classes were included for this outcome (

Figure 24, Figure 25,

Table 43). A continuity correction was applied to data in 17 studies containing at least one zero cell to stabilize the results. The final results presented in this guideline are based on the fixed study effects, fixed class effects model, as the posterior residual deviance indicated adequate model fit, and there were no meaningful differences between the DICs (**Error! Reference source not found.**).

Figure 24: Network diagram of direct evidence between classes included in discontinuation due to side effects analysis. The width of the lines is proportional to the number of studies making the comparisons, while the size of the nodes is proportional to the number of observations on a particular class.

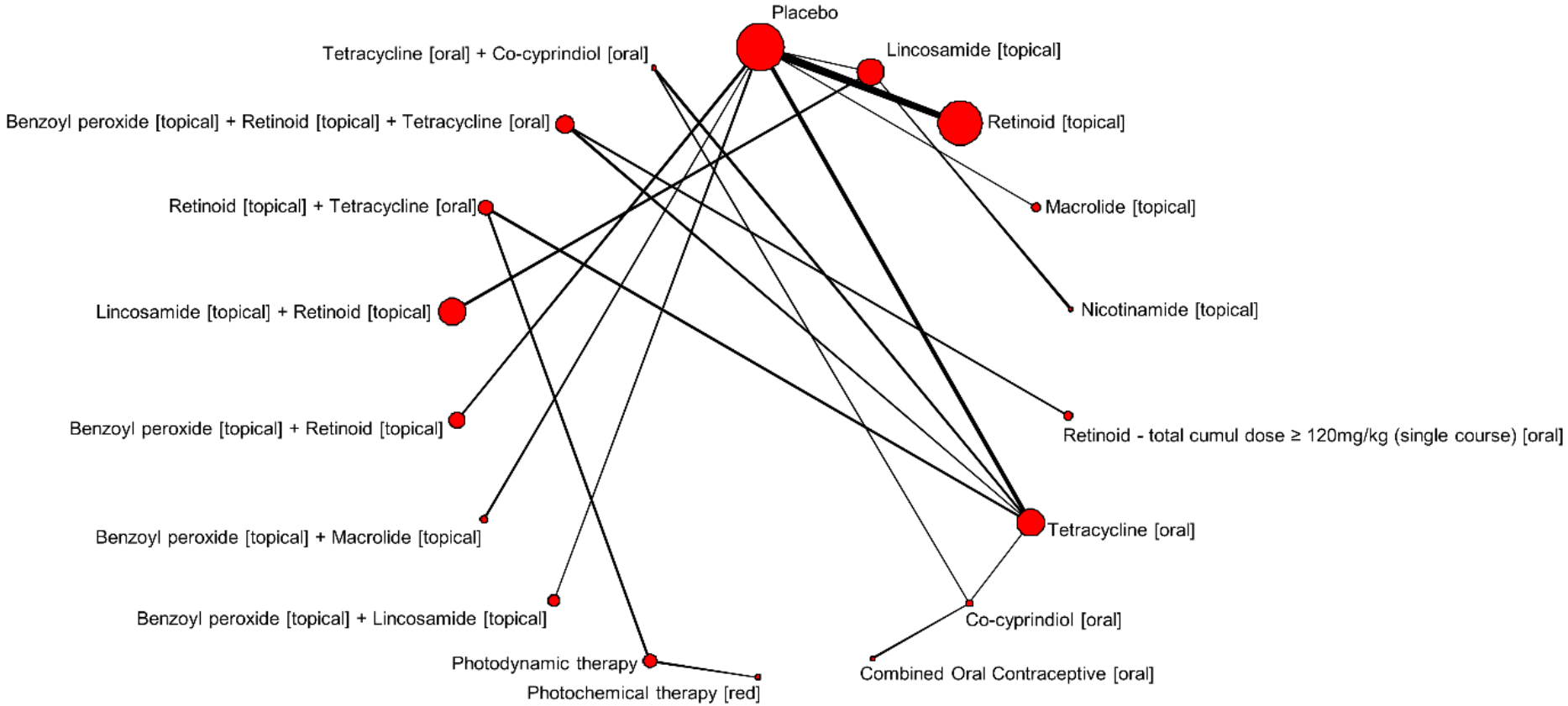


Figure 25: Network diagram of direct evidence between interventions included in discontinuation due to side effects analysis. The width of the lines is proportional to the number of studies making the comparisons, while the size of the nodes is proportional to the number of observations on a particular intervention.

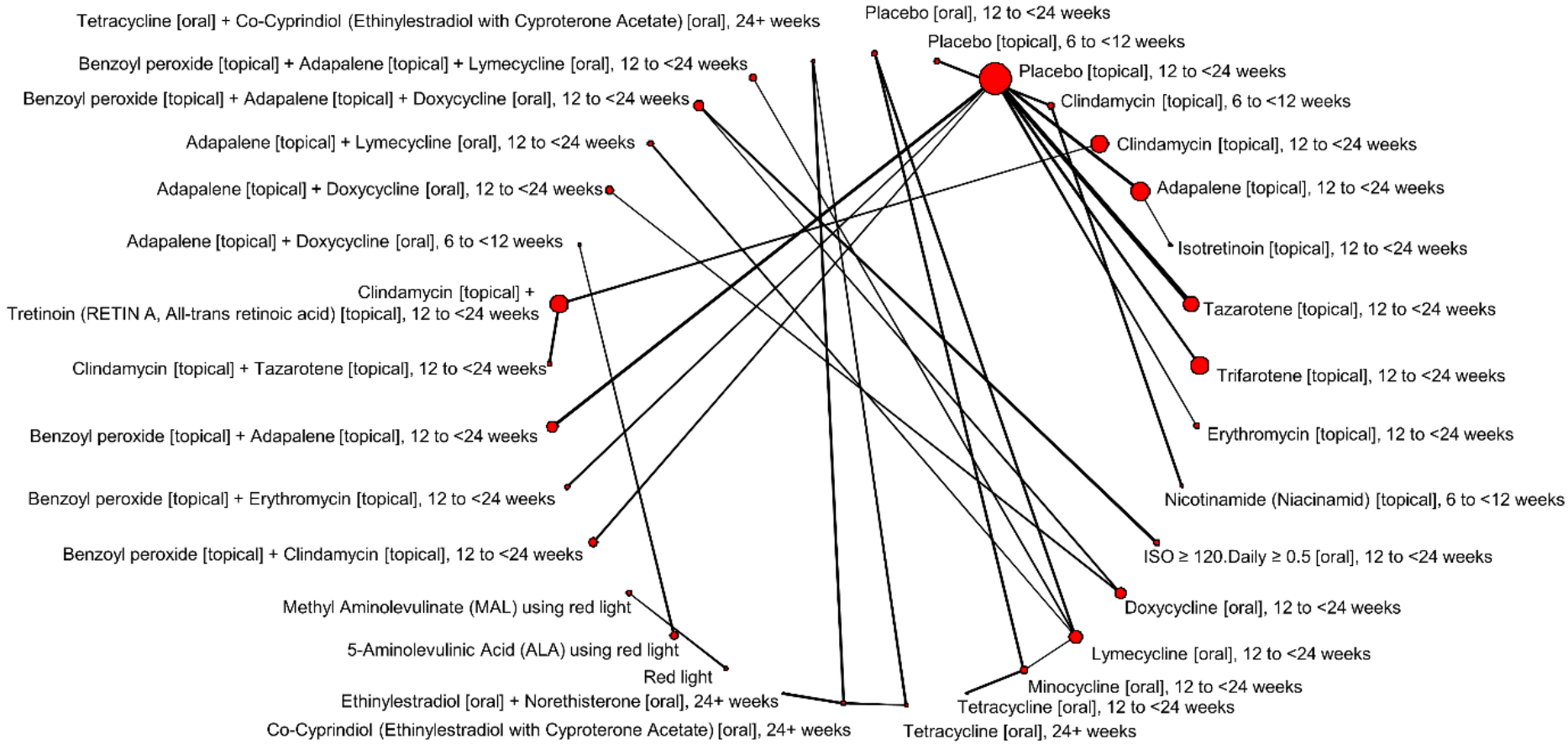


Table 43: Number of observations for each class, intervention and duration in discontinuation due to side effects analysis

Class	n	Treatment	n	Duration	n
Placebo	3920	Placebo [oral]	108	12 to <24 weeks	108
		Placebo [topical]	3812	6 to <12 weeks	124
				12 to <24 weeks	3688
Lincosamide [topical]	1266	Clindamycin [topical]	1266	6 to <12 weeks	159
				12 to <24 weeks	1107
Retinoid [topical]	3388	Adapalene [topical]	1248	12 to <24 weeks	1248
		Isotretinoin [topical]	40	12 to <24 weeks	40
		Tazarotene [topical]	886	12 to <24 weeks	886
		Trifarotene [topical]	1214	12 to <24 weeks	1214
Macrolide [topical]	127	Erythromycin [topical]	127	12 to <24 weeks	127
Nicotinamide [topical]	38	Nicotinamide (Niacinamid) [topical]	38	6 to <12 weeks	38
Retinoid - total cumul dose ≥ 120mg/kg (single course) [oral]	133	ISO≥120.Daily≥0.5 [oral]	133	12 to <24 weeks	133
Tetracycline [oral]	1307	Doxycycline [oral]	456	12 to <24 weeks	456
		Lymecycline [oral]	595	12 to <24 weeks	595
		Minocycline [oral]	210	12 to <24 weeks	210
		Tetracycline [oral]	46	12 to <24 weeks	21
				24+ weeks	25
Co-cyprindiol [oral]	88	Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	88	24+ weeks	88
Combined Oral Contraceptive [oral]	32	Ethinylestradiol [oral] + Norethisterone [oral]	32	24+ weeks	32
Photochemical therapy [red]	53	Red light	53		53
Photodynamic therapy	303	5-Aminolevulinic Acid (ALA) using red light	203		203
		Methyl Aminolevulinate (MAL) using red light	100		100
Benzoyl peroxide [topical] + Lincosamide [topical]	253	Benzoyl peroxide [topical] + Clindamycin [topical]	253	12 to <24 weeks	253
Benzoyl peroxide [topical] + Macrolide [topical]	90	Benzoyl peroxide [topical] + Erythromycin [topical]	90	12 to <24 weeks	90

Benzoyl peroxide [topical] + Retinoid [topical]	434	Benzoyl peroxide [topical] + Adapalene [topical]	434	12 to <24 weeks	434
Lincosamide [topical] + Retinoid [topical]	1262	Clindamycin [topical] + Tazarotene [topical]	75	12 to <24 weeks	75
		Clindamycin [topical] + Tretinoin (RETIN A, All-trans retinoic acid) [topical]	1187	12 to <24 weeks	1187
Retinoid [topical] + Tetracycline [oral]	379	Adapalene [topical] + Doxycycline [oral]	261	6 to <12 weeks	23
				12 to <24 weeks	238
		Adapalene [topical] + Lymecycline [oral]	118	12 to <24 weeks	118
Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral]	556	Benzoyl peroxide [topical] + Adapalene [topical] + Doxycycline [oral]	365	12 to <24 weeks	365
		Benzoyl peroxide [topical] + Adapalene [topical] + Lymecycline [oral]	191	12 to <24 weeks	191
Tetracycline [oral] + Co-cyprindiol [oral]	37	Tetracycline [oral] + Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	37	24+ weeks	37

Table 44: Model fit statistics for discontinuation due to side effects

Model	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[a]	DIC[b]
FE, fixed class	**---**	**70.25**	**298.251**
RE, fixed class	0.28 (0.01, 0.97)	69.28	299.625
FE, random class (placebos coded the same)	---	68.57	300.319
FE, random class (placebos coded separately)	---	68.47	300.057
RE, random class (placebos coded the same)	0.29 (0.01, 0.98)	68.28	301.605
RE, random class (placebos coded separately)	0.29 (0.02, 0.99)	68.2	301.779
UME - FE, intervention level	---	69.42	305.111
UME - FE, class level	---	70.03	298.063

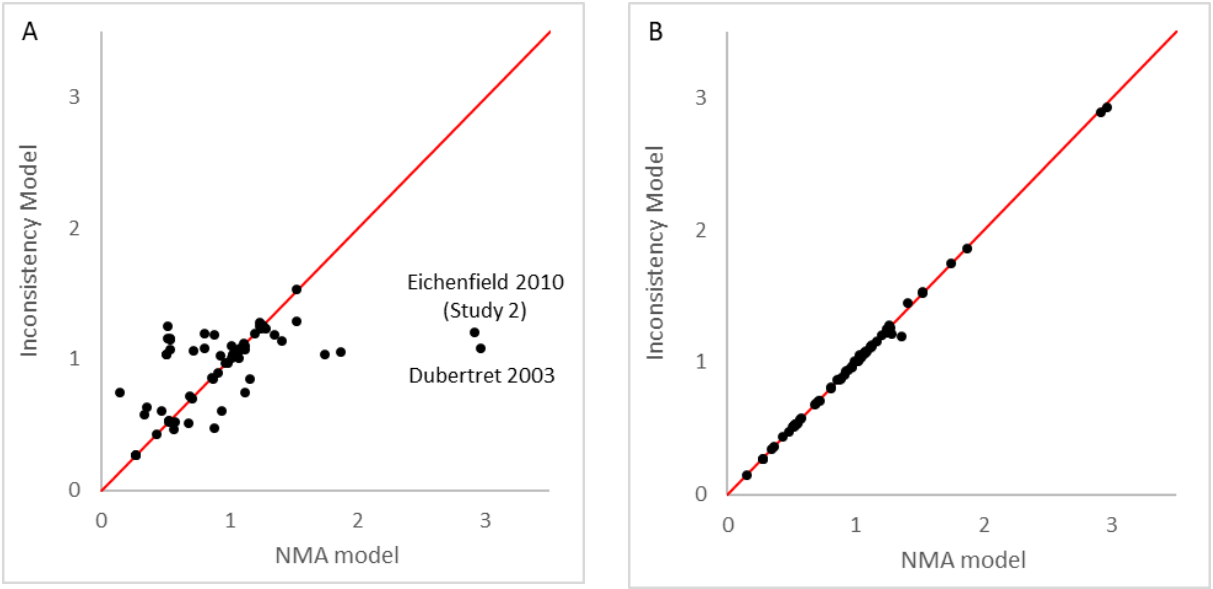
Abbreviations: CrI, credible interval; DIC, deviance information criteria; FE, fixed study effects; RE, random study effects; SD, standard deviation; UME, unrelated mean effects

[a] *Posterior mean residual deviance compared to 73 total data points*

[b] *Lower values of DIC preferred*

Based on the DIC, the fixed effects consistency model was preferred over the inconsistency model at the tintervention level, and there were no meaningful differences between the fit of the random effects consistency and inconsistency model at the class level (**Error! Reference source not found.**). The area below the line of equality in Figure 26 highlights where the inconsistency model better predicted data points, and there were notable improvements in the prediction of data in Dubertret 2003, a three-arm trial which compared two variations of Lymecycline [oral] and Placebo [oral], all with a duration of 12 to <24 weeks, and Eichenfield 2010 (Study 2), a two-arm trial which compared Adapalene [topical] and Placebo [topical], all with a duration of 12 to <24 weeks.

Figure 26: Deviance contributions for the fixed study, fixed class effects consistency and inconsistency models at (A) the intervention level and (B) the class level for discontinuation due to side effects.



There were no loops with three independent sources of direct evidence at the class level, and so node splitting models could not be fitted at this level. Node splitting was conducted at the intervention level and there was evidence of inconsistency for the following treatment comparisons:

- Lymecycline [oral], 12 to <24 weeks vs. Placebo [oral], 12 to <24 weeks (p-value = 0.053)
  - Direct estimate (log-odds ratio (LOR) (95% CrI)): -0.67 (-2.41, 1.42)
  - Indirect estimate (LOR (95% CrI)): 2.09 (0.31, 4.89)
  - NMA estimate (LOR (95% CrI)): 0.87 (-0.30, 2.41)
- Minocycline [oral], 12 to <24 weeks vs. Placebo [oral], 12 to <24 weeks (p-value = 0.478)
  - Direct estimate (LOR (95% CrI)): 2.16 (0.30, 5.18)
  - Indirect estimate (LOR (95% CrI)): -0.62, (-2.31, 1.41)
  - NMA estimate (LOR (95% CrI)): 0.87 (-0.30, 2.41)

A table of the direct, indirect, and NMA estimates for all pairwise relative effects between classes is available in supplement 10.

There was sufficient variation in the ratings of studies to fit bias models on one risk of bias domains:

- Domain 2: Deviation from interventions
- Domain 4: Outcome measurement (efficacy)

No evidence of bias arising from domain 2 was found, nor was there evidence of small study effect bias, as the 95% credible intervals of the posterior mean bias include 0 (Table 45). There is evidence of bias arising from domain 4 (Table 45).

In terms of the bias-adjusted results, there was evidence suggesting that the following classes increased the odds of discontinuation due to side effects compared to Placebo (

Figure 27, Figure 28 for females and males, respectively):

- Tetracycline [oral] (females and males)
- Retinoid [topical] + Tetracycline [oral] (females and males)
- Retinoid [topical] (females and males)
- Co-cyprindiol [oral] (females only)
- Tetracycline [oral] + Co-cyrpindiol [oral] (females only)

There was no evidence suggesting any of the classes decreased the odds of discontinuation due to side effects compared to Placebo (

Figure 27, Figure 28).

Table 45: Bias model fit statistics for discontinuation due to side effects

Model	Posterior total residual deviance[a]	DIC[b]	Bias	
			Posterior median (95% CrI)	Between Study SD (95% CrI)
NMA model: FE, fixed class	**70.25**	**298.251**	---	---
Bias model: Domain 2	71.6	301.1	0.48 (-6.46, 8.34)	1.84 (0.07, 9.16)
Bias model: Domain 4	64.7	294.5	-2.15 (-4.09, -0.30)	0.46 (0.02, 2.99)
Bias model: Small study	70.8	301	14.2 (-46.2, 100.3)	4.94 (0.28, 19.8)

Abbreviations: CrI, credible interval; DIC, deviance information criteria; FE, fixed study effects; NMA, network meta-analysis; SD, standard deviation
Posterior median bias values in red suggest evidence of bias, as the 95% credible intervals do not include zero.
[a] *Posterior mean residual deviance compared to 73 total data points*
[b] *Lower values of DIC preferred*

Figure 27: Forest plot of unadjusted NMA estimates (blue circles) and bias-adjusted estimates in terms of Domain 4: Outcome measurement (efficacy) for females (red squares)

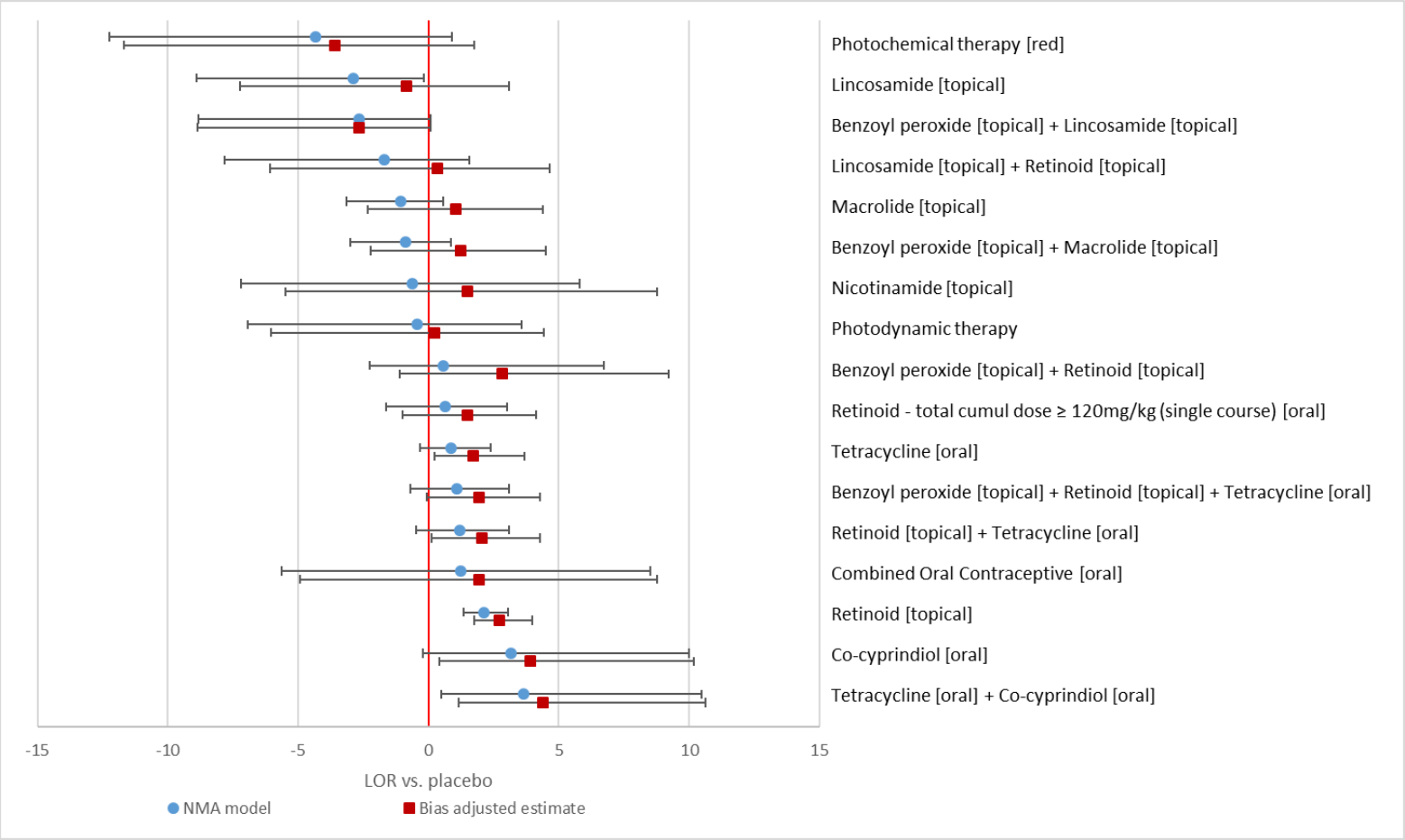
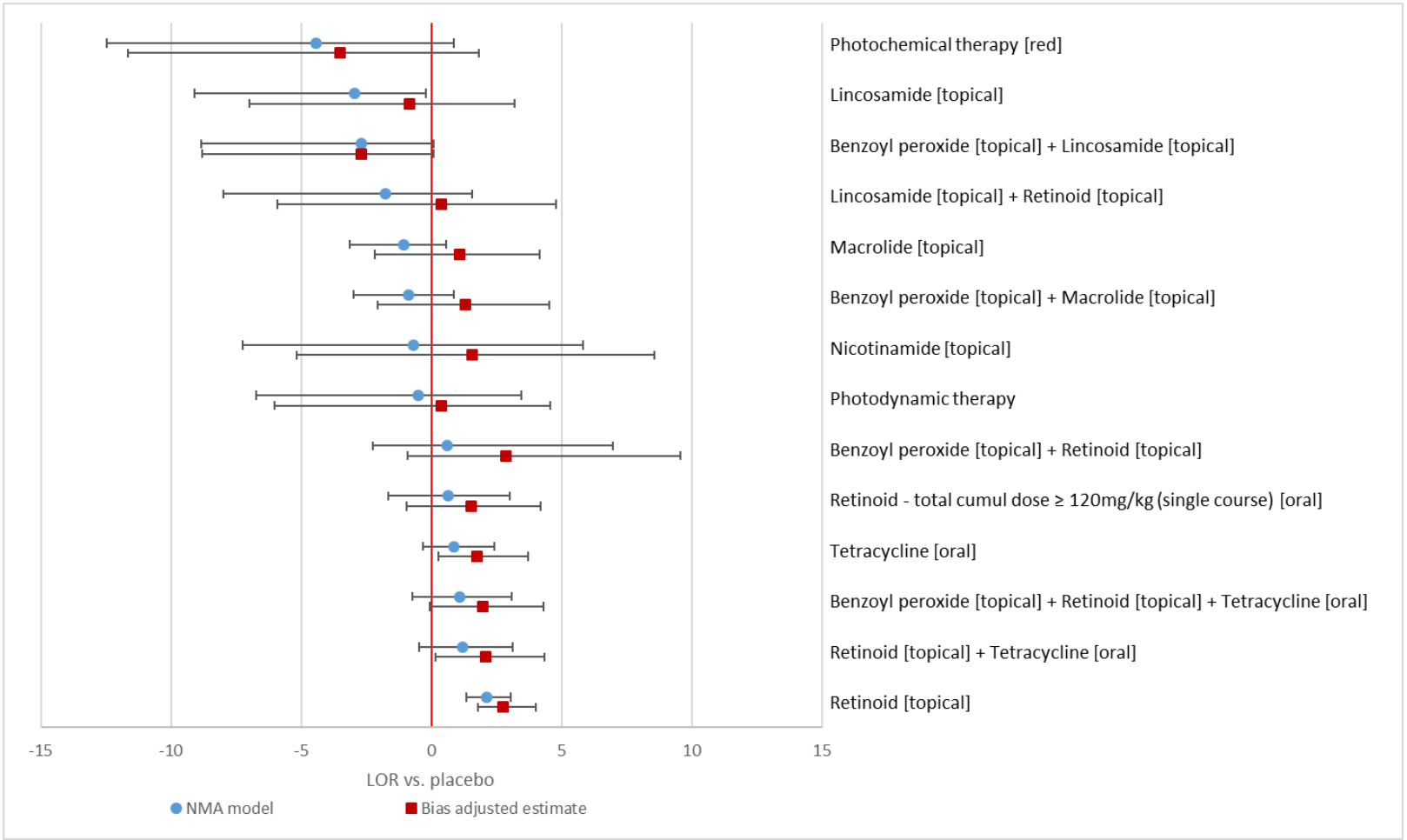


Figure 28: Forest plot of unadjusted NMA estimates (blue circles) and bias-adjusted estimates in terms of Domain 4: Outcome measurement (efficacy) for males (red squares)



Photochemical therapy [red] was the highest ranked class for both females and males, with posterior mean ranks of 2.4 (95% CrI 1st to 9th) and 2.3 (95% CrI 1st to 8th), respectively (**Error! Not a valid bookmark self-reference.**). The lowest ranked class was Tetracycline [oral] + Co-cyprindiol [oral] at 16.4 (95% CrI 10th to 18th) for females and Retinoid [topical] at 12.8 (95% CrI 8th to 15th) for males (**Error! Not a valid bookmark self-reference.**).

Table 46: Posterior mean rank and 95% credible intervals of classes for discontinuation due to side effects[a]

Class	Posterior Mean Rank (95% CrI)	
	Females	Males
Photochemical therapy [red]	2.4 (1, 9)	2.3 (1, 8)
Benzoyl peroxide [topical] + Lincosamide [topical]	2.5 (1, 7)	2.4 (1, 6)
Lincosamide [topical]	4.4 (1, 13)	4.2 (1, 12)
Placebo	5.7 (3, 10)	5.3 (2, 9)
Photodynamic therapy	7.2 (2, 17)	6.9 (2, 15)
Lincosamide [topical] + Retinoid [topical]	7.6 (2, 17)	7.1 (2, 14)
Macrolide [topical]	8.8 (2, 17)	8.1 (2, 14)
Benzoyl peroxide [topical] + Macrolide [topical]	9.3 (3, 17)	8.7 (3, 15)
Retinoid - total cumul dose ≥ 120mg/kg (single course) [oral]	9.7 (4, 16)	9.1 (4, 15)
Nicotinamide [topical]	10.3 (2, 18)	9.4 (2, 15)
Combined Oral Contraceptive [oral]	10.4 (1, 18)	not applicable
Tetracycline [oral]	10.6 (6, 14)	10 (6, 13)
Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral]	11.5 (6, 16)	10.7 (6, 15)
Retinoid [topical] + Tetracycline [oral]	11.8 (6, 17)	11.1 (6, 15)
Benzoyl peroxide [topical] + Retinoid [topical]	13.2 (4, 18)	11.9 (4, 15)
Retinoid [topical]	13.9 (8, 18)	12.8 (8, 15)
Co-cyprindiol [oral]	15.3 (8, 18)	not applicable
Tetracycline [oral] + Co-cyprindiol [oral]	16.4 (10, 18)	not applicable

Abbreviations: CrI, credible interval
[a] Based on bias-adjusted relative effects in terms of Domain 4: Outcome measurement (efficacy)

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Appendix N – Threshold analysis report from the NICE Guidelines Technical Support Unit (TSU)

Threshold analysis report for review question: For people with moderate to severe acne vulgaris what are the most effective treatment options?

Prepared by: NICE TSU, Bristol (Nicky J. Welton, Caitlin Daly, David Phillippo)

Introduction

The TSU was invited to explore the application of the threshold analysis method (Phillippo 2018 & 2019) in the Acne vulgaris guideline for treatments for people with moderate to severe acne, and to apply the method where relevant. Threshold analysis can be used to assess the robustness of recommendations made to potential limitations in the evidence, when the recommendations are based on a Network Meta-Analysis (NMA). Such limitations arise because the observed estimates differ from the true effects of interest, for example due to study biases, sampling variation, or issues of relevance. Threshold analysis quantifies precisely how much the evidence could change before the recommendation changes, and what the revised recommendation would be.

Requirements for use of the method are that there is a clear decision rule that is used to base the recommendations on the NMA results. For example: choose the treatment class with the highest estimated reduction in percentage change from baseline total lesion counts. Currently the methods are only available to be used on one outcome at a time.

The TSU attended the Acne Guideline Committee meetings on 20th July and 7th Aug 2020, where they observed the discussion of the clinical and economic evidence and drafting of preliminary recommendations. In this report, we begin by summarising the draft preliminary recommendations made by the committee, prior to discussion of the threshold analyses at the meeting on the 2nd Sept 2020. We then discuss the links between the draft preliminary recommendations and the NMA results to identify decision rules that could be used in the threshold method. For those draft preliminary recommendations where a decision rule could be identified, we perform the threshold analysis and present the results. We end with a brief summary of our findings.

Draft Preliminary Recommendations Following the Guideline Committee Meeting on 20th July and 7th August 2020

The relevant parts of the draft preliminary recommendations (prior to the threshold analysis) for treatments for people with moderate to severe acne that are informed by the NMA are as follows:

Topical treatments (with or without an oral antibiotic)

1.5.2 For mild, moderate or severe acne offer one of the following treatments, taking account of the person preferences [indication in brackets]:

- fixed combination of topical benzoyl peroxide and topical adapalene; with either oral lymecycline or oral doxycycline [moderate to severe acne]
- topical azelaic acid with either oral lymecycline or oral doxycycline [moderate to severe acne]
- a fixed combination of a topical retinoid with topical clindamycin [moderate to severe and mild to moderate acne]

- a fixed combination of topical benzoyl peroxide and topical adapalene [moderate to severe and mild to moderate acne]
- a fixed combination of topical benzoyl peroxide with topical clindamycin [during pregnancy]

1.5.5 Do not use topical or oral antibiotics as monotherapy, or a combination of topical and oral antibiotics only.

Oral isotretinoin treatment

1.5.11 Consider oral isotretinoin, prescribed in a hospital dermatology setting, for people aged 12 or older who have:

- nodulo-cystic or conglobate acne
- acne vulgaris with a severe inflammatory component (acne fulminans without systemic symptoms)
- acne of at least moderate severity causing psychological distress or adding to a mental health condition
- moderate to severe acne which has not responded to prior treatment with an systemic antibacterial (as in 1.5.2).

1.5.12 Give isotretinoin at a daily dose of 0.5–1 mg/kg until a total cumulative dose of 120–150 mg/kg has been reached, unless a reduced daily dose is indicated.

Physical treatments

Recommendations were not made at the July and August 2020 committee meetings. However, subsequently at the meeting on the 18th Sept the committee added a recommendation to:

- Consider Photothermal + photodynamic therapy as a treatment option for people aged 18 and over with moderate to severe acne where standard treatments are ineffective, not tolerated or contraindicated.

Threshold Analysis

Decision Rule Linking Recommendations to NMA Results: Moderate-Severe Population

The committee considered the topical and oral treatments separately to the physical treatments. Of the physical treatments (light therapies), the committee only made a consider recommendation for photothermal + photodynamic therapy where standard treatments are ineffective, not tolerated, or contraindicated. This was because, although a number physical therapies appeared to rank in a high position in terms of clinical and cost-effectiveness, they had a more limited evidence base and the clinical experience with these treatments is very limited within the NHS context. We therefore focus on the topical and oral treatments in the threshold analysis.

Further restrictions on the treatments for consideration were made by the committee. Treatments with fewer than 50 observations each (in total across study arms) were excluded. Antibiotic monotherapies were excluded due to concerns with antibiotic resistance. Finally, the committee decided not to make a recommendation for the combination of topical benzoyl peroxide and topical macrolide because this treatment is not available as a fixed combination and therefore it would be impractical for people with acne vulgaris to apply as two separate formulations, but also impractical and potentially costly for pharmacists to prepare as a single formulation on an individual basis. The remaining treatment classes are displayed in

Table 47, and the NMA results for the moderate-severe population for these classes relative to placebo are shown in

Figure 29.

For this population the recommendations for first line treatment are from the following classes:

- fixed combination of topical benzoyl peroxide and topical adapalene; with either oral lymecycline or oral doxycycline. Class: benzoyl peroxide (topical)+retinoid (topical) + tetracycline (oral)
- topical azelaic acid with either oral lymecycline or oral doxycycline. Class: azelaic acid (topical)+tetracycline (oral)
- a fixed combination of a topical retinoid with topical clindamycin. Class: retinoid (topical) + lincosamide (topical)
- a fixed combination of topical benzoyl peroxide and topical adapalene. Class: benzoyl peroxide (topical) + retinoid (topical)

These recommendations link to the NMA results in

Figure 29 as follows. The oral retinoid classes had the highest mean difference in efficacy, however the committee considered them unsuitable as a first-line treatment for people with acne according to MHRA and BNF advice due to having a higher risk of serious side effects. These classes were therefore excluded from the first line recommendations.

Amongst the first line options the retinoid (topical) + lincosamide (topical) class and the benzoyl peroxide (topical)+retinoid (topical) + tetracycline (oral) class have the highest efficacy, and are recommended. The classes with the next highest mean difference in efficacy are the azelaic acid (topical)+tetracycline (oral) class, the retinoid (topical) + tetracycline (oral) class, and the benzoyl peroxide (topical) + retinoid (topical) class. Two of these are recommended, but retinoid (topical) + tetracycline (oral) is not, because the committee decided to recommend the fixed combination of topical benzoyl peroxide and adapalene with an oral tetracycline as an option instead, as it was both more clinically and cost-effective than topical adapalene alone combined with an oral tetracycline. Whilst this is a logical rationale for excluding this class from the recommendations, it cannot be justified solely on the NMA results (as it is similarly effective to classes which are recommended). In order to perform a threshold analysis which links the recommendations to the NMA results we had to exclude retinoid (topical) + tetracycline (oral).

To assess the robustness of the first line decision to the NMA evidence, we therefore conducted a threshold analysis based on the classes listed in

Table 47 (excluding the oral retinoids and retinoid (topical) + tetracycline (oral)) with a decision rule to recommend the top 4 classes within this set. If the top 4 treatment classes change, this implies that one of the non-recommended treatment classes would be recommended in place of one of the currently recommended interventions. This allows us to assess how robust this recommendation is to changes in the evidence.

For 2nd line treatment, the recommendation is to give isotretinoin at a daily dose of 0.5–1 mg/kg until a total cumulative dose of 120–150 mg/kg has been reached, unless a reduced daily dose is indicated. The choice of cumulative dose is based on the comparison between the high and low dose oral retinoid classes (

Figure 29), where high dose isotretinoin is more effective than low dose isotretinoin. We therefore performed a second threshold analysis based on just these two classes, with the decision rule is to recommend the top class within this set. We can assess how robust this recommendation is to changes in the evidence by looking to see how much the evidence would have to change for the top treatment class to change.

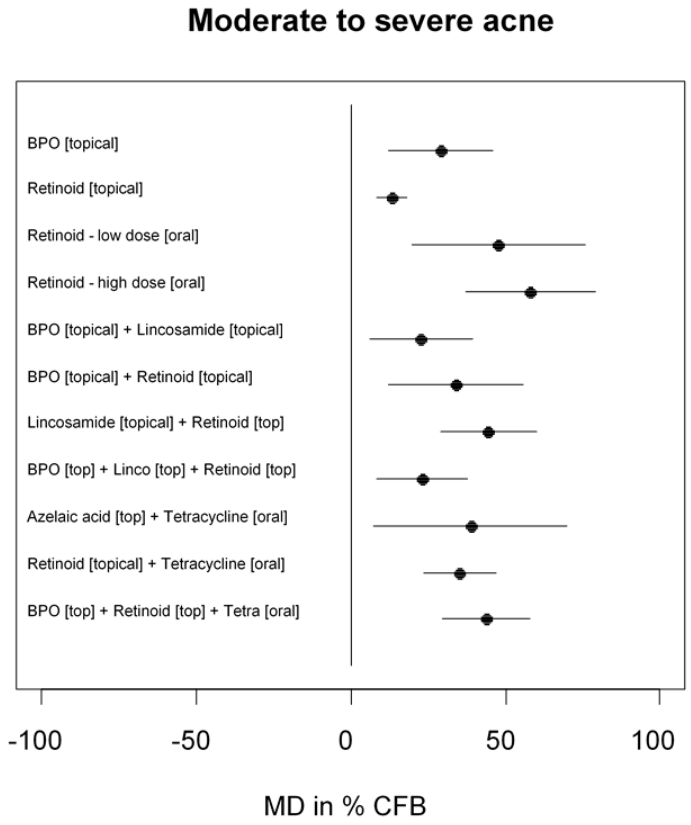
Table 47: NMA of efficacy of treatments for people with moderate to severe acne: treatment classes, number of observations to each class, whether included in the decision for topical and oral treatments, and reason for exclusion if not

Class Code	Treatment Class	Number of observations to treatment class	Included?	Reason for exclusion
8	Retinoid - total cumul dose < 120mg/kg (single course) [oral]	938	Yes (2nd line only)	Excluded from 1st line decision due to side-effects
9	Retinoid - total cumul dose ≥ 120mg/kg (single course) [oral]	182	Yes (2nd line only)	Excluded from 1st line decision due to side-effects
1	Placebo	4122	Yes	
3	Benzoyl peroxide [topical]	80	Yes	
5	Retinoid [topical]	3570	Yes	
19	Benzoyl peroxide [topical] + Lincosamide [topical]	276	Yes	
21	Benzoyl peroxide [topical] + Retinoid [topical]	217	Yes	
22	Lincosamide [topical] + Retinoid [topical]	1548	Yes	
23	Benzoyl peroxide [topical] + Lincosamide [topical] + Retinoid [topical]	600	Yes	
24	Azelaic acid [topical] + Tetracycline [oral]	50	Yes	
25	Retinoid [topical] + Tetracycline [oral]	379	Yes, but excluded from threshold analysis	Excluded from threshold analysis since not recommended due to being inferior to the same combination with Benzoyl peroxide [topical] added, and not directly linked to the NMA results.
26	Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral]	556	Yes	
20	Benzoyl peroxide [topical] + Macrolide [topical]	365	No	No fixed combination available
2	No treatment	25	No	small sample
4	Lincosamide [topical]	1479	No	antibiotic monotherapy

Class Code	Treatment Class	Number of observations to treatment class	Included?	Reason for exclusion
6	Macrolide [topical]	109	No	antibiotic monotherapy
7	Nicotinamide [topical]	29	No	small sample
10	Tetracycline [oral]	1386	No	antibiotic monotherapy
11	Co-cyprindiol [oral]	12	No	small sample
12	Photochemical therapy [red]	53	No	physical therapy
13	Photochemical therapy [blue and red]	15	No	physical therapy and small sample
14	Photochemical + photothermal therapy	71	No	physical therapy
15	Photodynamic therapy	298	No	physical therapy
16	Photothermal + photodynamic therapy	14	No	physical therapy and small sample
17	Photothermal therapy	46	No	physical therapy and small sample
18	Benzoyl peroxide [topical] + Anti-fungal [topical]	25	No	physical therapy and small sample
27	Tetracycline [oral] + Photodynamic therapy	48	No	physical therapy and small sample

1

Figure 29: People with moderate to severe acne: Forest plot of NMA estimates for the treatment classes under consideration for topical/oral recommendations



Threshold Analysis Results

The results from the threshold analysis for topical and oral treatment classes for the moderate-to-sever population are displayed in

Figure 30, which shows, for each pair of interventions ("contrast") where we have evidence, the range of values for which the evidence from that contrast could change without changing the recommendations.

Figure 30 also shows the treatment class the recommendation would switch to and highlights in pink where the recommendations change for contrast estimates that are within their credibility limits (ie within sampling error). The recommendations are to recommend 4 classes (codes 21, 22, 24, and 26), and so the decision will only change if the treatment class that the decision switches to is not already recommended. It can be seen that if the evidence on the contrast 21v1 (Benzoyl peroxide [topical] + Retinoid [topical] vs Placebo) had an effect less than 28.78 (which is easily within the credible interval due to the wide uncertainty), then class 3 (Benzoyl peroxide [topical]) would enter the top 4 treatment classes. Benzoyl peroxide [topical] would also enter the top 4 treatment classes if the effect of several other contrasts (Benzoyl peroxide [topical] + Lincosamide [topical] vs placebo; Benzoyl peroxide [topical] + Lincosamide [topical] vs Benzoyl peroxide [topical]; Benzoyl peroxide [topical] vs placebo) were near to their credible limits. The only other contrast highlighted is 23vs 5 (Benzoyl peroxide [topical] + Lincosamide [topical] + Retinoid [topical] vs Retinoid [topical]). If the 23vs5 effect were more than 20.65 (near the top of the credible interval), then class Benzoyl peroxide [topical] + Lincosamide [topical] + Retinoid [topical] would enter the top 4 treatment classes.

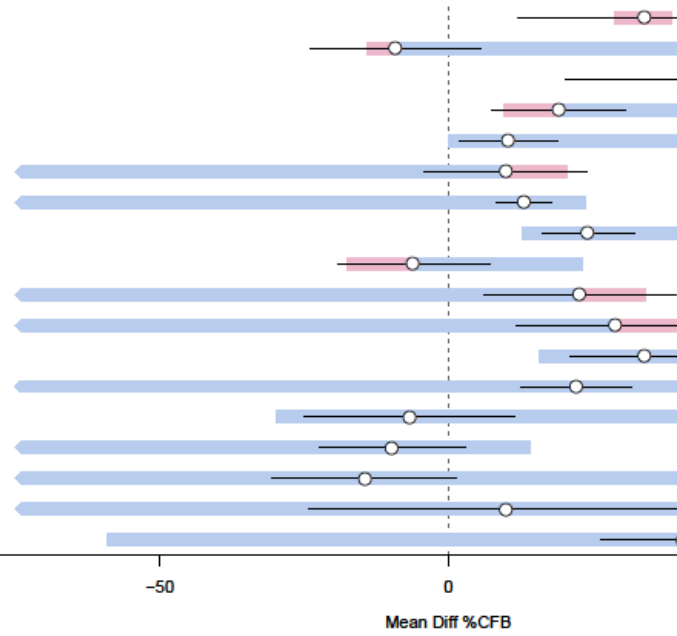
We also conducted a threshold analysis for the recommendations on the oral retinoid class, the results of which are displayed in Figure 31. It can be seen that the decision might switch from high dose (class 9) to low dose (class 8) oral retinoid if the contrast 8vs1 (low dose oral retinoid vs Placebo) were higher than 59.50 (which is within the credible interval). Also if the contrast 26 vs 9 (Benzoyl peroxide [topical] + Retinoid [topical] + Tetracycline [oral] vs High dose oral retinoid) were greater than -3.00 (close to the top of the credible interval) then the decision would switch to low dose oral retinoid.

Conclusions

For the moderate-to-severe population the draft preliminary recommendations are very sensitive to the evidence comparing Benzoyl peroxide [topical] + Retinoid [topical] vs Placebo, with plausible changes in the evidence meaning that Benzoyl peroxide [topical] would enter the top 4 treatment classes. For the draft preliminary recommendation on oral retinoids, the recommendation for high dose oral retinoids is sensitive to the evidence comparing low dose oral retinoid vs Placebo, with plausible changes in the evidence meaning that low dose oral retinoid would be the most effective class. Note that to conduct the analyses for the moderate-to-severe population we had to exclude retinoid (topical) + tetracycline (oral) as a decision option, because it had similar efficacy to other interventions that were recommended. The rationale for this was that the committee decided to recommend the fixed combination of topical benzoyl peroxide and adapalene with an oral tetracycline as an option instead, as it was both more clinically and cost-effective than topical adapalene alone combined with an oral tetracycline.

Figure 30: Threshold analysis results by contrast for topical and oral treatment classes for people with moderate to severe acne, by intervention contrast, sorted by increasing threshold magnitude.

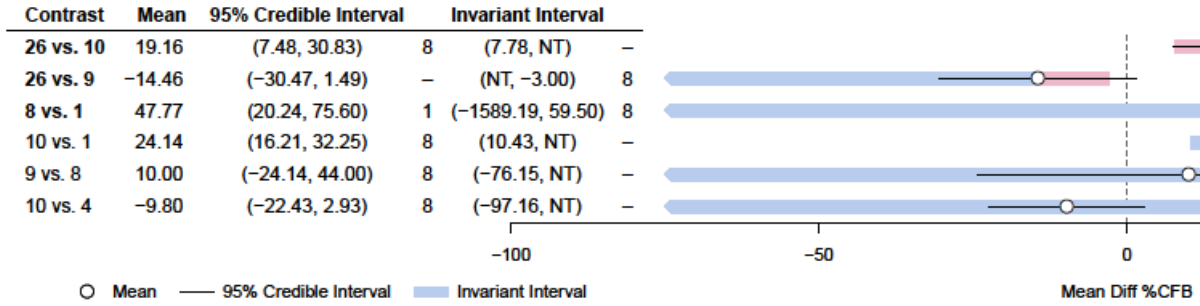
Contrast	Mean	95% Credible Interval		Invariant Interval	
21 vs. 1	33.95	(12.06, 55.69)	3	(28.78, 38.64)	24
24 vs. 8	−9.19	(−23.97, 5.58)	24	(−13.95, 2497.73)	26
8 vs. 1	47.77	(20.24, 75.60)	24	(42.53, 19739.32)	23
26 vs. 10	19.16	(7.48, 30.83)	26	(9.61, 210.91)	3
22 vs. 4	10.36	(2.02, 19.06)	22	(0.11, 609.66)	3
23 vs. 5	9.96	(−4.13, 23.98)	24	(−979.57, 20.65)	23
5 vs. 1	13.13	(8.32, 18.04)	1	(−3276.43, 23.86)	23
10 vs. 1	24.14	(16.21, 32.25)	26	(12.75, 144.81)	3
19 vs. 3	−6.16	(−19.18, 7.21)	3	(−17.65, 23.31)	19
19 vs. 1	22.72	(6.29, 39.39)	26	(−1703.42, 34.30)	3
3 vs. 1	28.87	(11.81, 45.92)	23	(−3970.82, 44.66)	3
4 vs. 1	33.95	(21.03, 46.87)	22	(15.80, 13099.15)	5
20 vs. 1	22.15	(12.72, 31.80)	26	(−586.20, 43.64)	3
20 vs. 3	−6.73	(−24.99, 11.59)	3	(−29.69, 4819.97)	23
10 vs. 4	−9.80	(−22.43, 2.93)	26	(−102.13, 14.26)	22
26 vs. 9	−14.46	(−30.47, 1.49)	3	(−277.47, 40.39)	24
9 vs. 8	10.00	(−24.14, 44.00)	26	(−487.45, 72.67)	24
15 vs. 1	40.63	(26.51, 54.45)	26	(−59.06, 848.43)	3



The optimal decision rule is to recommend treatment classes 22, 26, 24, and 21. The study / contrast estimate (labelled "Mean") and credible intervals are shown by the black lines. The blue shaded areas show the invariant interval where the optimal set of recommended interventions does not change, and the intervention that would enter the recommended intervention set is indicated by the figures either side of the invariant interval, and the decision only changes if this is not in the set {22, 26, 24, 21}. The pink area indicates where the recommendations changes within the credible limits of the current estimates. Intervention codes are as defined in

Table 47.

Figure 31: Threshold analysis results by contrast for retinoid oral treatment classes for people with moderate to severe acne, by intervention contrast, sorted by increasing threshold magnitude. The optimal decision rule is to recommend treatment class 9 (oral retinoid high dose).



The study / contrast estimate (labelled "Mean") and credible intervals are shown by the black lines. The blue shaded areas show the invariant interval where the optimal set of recommended interventions does not change, and the intervention that would enter the recommended intervention set is indicated by the figures either side of the invariant interval. The pink area indicates where the recommendations changes within the credible limits of the current estimates. Intervention codes are as defined in

Table 47. NT = No Threshold, no change to the evidence in this direction could lead to a new decision.

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