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Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne

M Ozolins, EA Eady, A Avery, WJ Cunliffe, C O'Neill, NB Simpson and HC Williams

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Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne

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Abstract

Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne

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Objectives: To determine the relative efficacy and cost-effectiveness of five of the most commonly used antimicrobial preparations for treating mild to moderate facial acne in the community; the propensity of each regimen to give rise to local and systemic adverse events; whether pre-existing bacterial resistance to the prescribed antibiotic resulted in reduced efficacy; and whether some antimicrobial regimens were less likely to give rise to resistant propionibacterial strains.
Design: This was a parallel group randomised assessor-blind controlled clinical trial. It was a pragmatic design with intention-to-treat analysis. All treatments were given for 18 weeks, after a 4-week treatment free period. Outcomes were measured at 0, 6, 12 and 18 weeks.
Setting: Primary care practices and colleges in and around Nottingham and Leeds, and one practice in Stockton-on-Tees, England.
Participants: Participants were 649 people aged 12–39 years, all with mild to moderate inflammatory acne of the face.
Interventions: Study participants were randomised into one of five groups: 500 mg oral oxytetracycline (non-proprietary) twice daily (b.d.) + topical vehicle control b.d.; 100 mg oral Minocin MR® (minocycline) once daily (o.d.) + topical vehicle control b.d.; topical Benzamycin® (3% erythromycin + 5% benzoyl peroxide) b.d. + oral placebo o.d.; topical Stiemycin® (2% erythromycin) o.d. + topical Panoxyl® Aquagel (5% benzoyl peroxide) o.d. + oral placebo o.d., and topical Panoxyl® Aquagel (5% benzoyl peroxide) b.d. + oral placebo o.d. (the active comparator group).
Main outcome measures: The two primary outcome measures were: (1) the proportion of patients with at least moderate self-assessed improvement as recorded on a six-point Likert scale, and (2) change in inflamed lesion count (red spots).
Results: The best response rates were seen with two of the topical regimens (erythromycin plus benzoyl peroxide administered separately o.d. or in a combined proprietary formulation b.d.), compared with benzoyl peroxide alone, oxytetracycline (500 mg b.d.) and minocycline (100 mg o.d.), although differences were small. The percentage of participants with at least moderate improvement was 53.8% for minocycline (the least effective) and 66.1% for the combined erythromycin/benzoyl peroxide formulation (the most effective); the adjusted odds ratio for these two treatments was 1.74 [95% confidence interval (CI) 1.04 to 2.90]. Similar efficacy rankings were obtained using lesion counts, acne severity scores and global rating by assessor. Benzoyl peroxide was the most cost-effective and minocycline the least cost-effective regimen (ratio of means 12.3; difference in means –0.051 units/£, 95% CI –0.063 to –0.039). The efficacy of oxytetracycline was similar to that of minocycline, but at approximately one-seventh of the cost. For all regimens, the largest reductions in acne severity were recorded in the first 6 weeks. Reductions in disability scores using the Dermatology Quality of Life Scales were largest for both topical erythromycin-containing regimens and minocycline. The two topical erythromycin-containing regimens produced the largest reductions in the prevalence and population density of cutaneous propionibacteria, including

antibiotic-resistant variants, and these were equally effective in participants with and without erythromycin-resistant propionibacteria. The clinical efficacy of both tetracyclines was compromised in participants colonised by tetracycline-resistant propionibacteria. None of the regimens promoted an overall increase in the prevalence of antibiotic-resistant strains. Systemic adverse events were more common with the two oral antibiotics. Local irritation was more common with the topical treatments, particularly benzoyl peroxide. Residual acne was present in most participants (95%) at the end of the study.

Conclusions: The response of mild to moderate inflammatory acne to antimicrobial treatment in the community is not optimal. Only around half to two-thirds of trial participants reported at least a moderate improvement over an 18-week study period; extending treatment beyond 12 weeks increased overall benefit slightly. Around one-quarter dropped out when using such treatments, and 55% sought further treatment after 18 weeks. Topical antimicrobial therapies performed at least as well as oral antibiotics in terms of clinical efficacy. Benzoyl peroxide was the most cost-effective and minocycline the least cost-effective therapy for facial acne. The efficacy of all three topical regimens was not compromised by pre-existing propionibacterial resistance. Benzoyl peroxide was associated with a greater frequency and severity of local irritant reactions. It is suggested that the use of a combination of topical benzoyl peroxide and erythromycin gives less irritation and better quality of life. There was little difference between erythromycin plus benzoyl peroxide administered separately and the combined proprietary formulation in terms of efficacy or local irritation, except that the former was nearly three times more cost-effective. The data on cost-effectiveness, and outcomes in patients with resistant propionibacterial floras, did not support the first line use of minocycline for mild to moderate inflammatory acne of the face. Three priority areas for clinical research in acne are: defining end-points in acne trials (i.e. what is a satisfactory outcome?); developing and validating better patient-based measures for assessing treatment effects on facial and truncal acne; and exploring patient characteristics that may modify treatment effects (efficacy and tolerability).

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List of abbreviations

AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
B&C	Burke and Cunliffe
BMI	body mass index
BNF	British National Formulary
BP	benzoyl peroxide
CASS	Combined Acne Severity Score
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
CL	confidence limit
CNS	central nervous system
DLQI	Dermatology Life Quality Index
DNA	did not attend
DQOLS	Dermatology Quality of Life Scales
ery. + BP bd	topical erythromycin plus benzoyl peroxide twice daily
ery. od + BP od	topical erythromycin once daily plus benzoyl peroxide once daily
ery. + zinc acetate	topical erythromycin and zinc acetate
GI	gastrointestinal
IBS	irritable bowel syndrome
IL-1α	interleukin-1α
Inf	infections
ITT	intention to treat
LGI	Leeds General Infirmary
LSmean	least squared mean
MIC	minimum inhibitory concentration
M/S	musculoskeletal
NF-κB	nuclear factor-κB
N/K	not known
NNT	number needed to treat
NR	not recorded
OR	odds ratio
OTC	over the counter
oxytet.	oxytetracycline
PPAR	peroxisome proliferator-activated receptor
Psych	psychiatric
Pt W/D	patient withdrawn
RCT	randomised controlled trial
Repro	reproductive system
Resp	respiratory system
SD	standard deviation
SF-36	Short Form 36
TLR	Toll-like receptor
top. erythromycin	topical erythromycin
Trt Rec	treatment received
WTA	willingness to accept
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Acne is one of the most common skin disorders in young people. Having acne can give rise to feelings of embarrassment, loss of self-esteem and depression, as well as physical symptoms (such as soreness and pain) associated with individual lesions. Most people with acne are treated in primary care. GPs have at least 30 different acne preparations to choose from, which can be prescribed singly or in combination, yet there are virtually no good comparative data to guide them or their patients to make the best choice in terms of efficacy, cost-effectiveness, compliance, tolerability and overall patient satisfaction. Antibiotic resistance in the bacteria implicated in acne pathogenesis (*Propionibacterium acnes* and *Propionibacterium granulosum*) may be associated with a reduction in clinical efficacy, and some antibiotic preparations may be more likely to promote resistance than others.

Objectives

This study therefore sought to determine:

- the relative efficacy and cost-effectiveness of five of the most commonly used antimicrobial preparations for treating mild to moderate facial acne in the community
- the propensity of each regimen to give rise to local and systemic adverse events
- whether pre-existing bacterial resistance to the prescribed antibiotic resulted in reduced efficacy
- whether some antimicrobial regimens were less likely to give rise to resistant propionibacterial strains.

Methods

Design

The study was a randomised controlled clinical trial using parallel comparative groups and a pragmatic design with intention-to-treat analysis. Initially, 11 groups were to be compared, but major recruitment difficulties and high dropout rates prompted an early decision in consultation with the HTA Executive to restrict the study to just five treatment groups. Because matched placebos would have been prohibitively expensive to produce, blinding of study participants was only partially achieved. Assessors were blinded to the intervention status of participants.

Setting

Primary care practices and colleges in and around the cities of Nottingham and Leeds, and one practice in Stockton-on-Tees, England.

Participants

Participants were 649 people aged 12–39 years, all of whom had mild to moderate inflammatory acne of the face. Those with exclusively truncal or comedonal acne were excluded from the study. All acne treatments (oral and topical) were stopped for 4 weeks before the study.

Interventions

Study participants were randomised into one of the following five treatment groups:

- 500 mg oral oxytetracycline (non-proprietary) twice daily (b.d.) + topical vehicle control b.d.
- 100 mg oral Minocin MR® (minocycline) once daily (o.d.) + topical vehicle control b.d.
- Topical Benzamycin® (3% erythromycin + 5% benzoyl peroxide) b.d. + oral placebo o.d.
- Topical Stiemycin® (2% erythromycin) o.d. + topical Panoxyl® Aquagel (5% benzoyl peroxide) o.d. + oral placebo o.d.
- Topical Panoxyl® Aquagel (5% benzoyl peroxide) b.d. + oral placebo o.d. (the active comparator group).

In addition to comparing the treatments, these five interventions were specifically chosen to answer the following additional questions for the NHS:

- Is oral minocycline clinically superior to oral oxytetracycline? (Rationale: minocycline is several times more expensive per day's use.)
- Is a leading current topical treatment (Benzamycin) as effective as oral treatment?

- Are topical erythromycin and benzoyl peroxide when prescribed separately as effective as a commercially available combined formulation, Benzamycin? (Rationale: Benzamycin is three times as expensive as the constituents sold separately.)
- How does a cheap over-the-counter topical (benzoyl peroxide) compare with proprietary topical and oral antibiotics?

Main outcome measures

The two primary outcome measures were:

- the proportion of patients with at least moderate self-assessed improvement as recorded on a six-point Likert scale at 18 weeks using baseline photographs as a reference
- the reduction in mean number of inflamed lesions (red spots) at 18 weeks.

Secondary outcome measures included three other measures of acne severity: the Burke and Cunliffe grade (a pictorial assessment method), assessor global assessment of the participant, and a new acne severity score that combined an assessment of inflamed lesions, non-inflamed lesions and redness in each of four areas of the face. Disability and effects on quality of life were assessed using the Short Form 36 questionnaire, the Dermatology Life Quality Index and the Dermatology Quality of Life Scales. Local irritation was assessed by both participant and assessor and indirectly by the use of moisturisers. The proportion of participants for whom the worst aspect of their acne had improved was also recorded, as were re-referral rates after treatment completion. Other adverse events and dropout rates were recorded at each visit.

Bacterial skin colonisation with propionibacteria resistant to erythromycin, clindamycin or the tetracyclines was estimated at baseline and on all subsequent visits using a semi-quantitative scoring method to derive data on both prevalence and population density.

Results

The best response rates were seen with two of the topical regimens (erythromycin plus benzoyl peroxide administered separately o.d. or in a combined proprietary formulation b.d.), compared with benzoyl peroxide alone, oxytetracycline (500 mg b.d.) and minocycline (100 mg o.d.), although treatment differences were small. The percentage of participants with at least moderate improvement was 53.8% for minocycline (the least effective) and 66.1% for the combined erythromycin/benzoyl peroxide formulation (the most effective); the adjusted odds ratio for these two treatments was 1.74 [95% confidence interval (CI) 1.04 to 2.90]. Similar efficacy rankings were obtained using lesion counts, acne severity scores and global rating by assessor. Benzoyl peroxide was the most cost-effective and minocycline the least cost-effective regimen for treating mild to moderate inflammatory acne of the face (ratio of means 12.3; difference in means –0.051 units/£, 95% CI –0.063 to –0.039). The efficacy of oxytetracycline was similar to that of minocycline, but at approximately one-seventh of the cost. For all regimens, the largest reductions in acne severity were recorded in the first 6 weeks (around 45–50% of participants with at least moderate improvement). Reductions in disability scores using the Dermatology Quality of Life Scales were largest for both topical erythromycin-containing regimens and minocycline. All treatments showed antibacterial activity *in vivo*. The two topical erythromycin-containing regimens produced the largest reductions in the prevalence and population density of cutaneous propionibacteria, including antibiotic-resistant variants, and these were equally effective in participants with and without erythromycin-resistant propionibacteria. The clinical efficacy of both tetracyclines was compromised in participants colonised by tetracycline-resistant propionibacteria. None of the regimens promoted an overall increase in the prevalence of antibiotic-resistant strains. Systemic adverse events were more common with the two oral antibiotics. Local irritation was more common with the topical treatments, particularly benzoyl peroxide. Residual acne was present in most participants (95%) at the end of the study.

Conclusions

The response of mild to moderate inflammatory acne to antimicrobial treatment in the community is not optimal. Only around half to two-thirds of trial participants reported at least a moderate improvement over an 18-week study period; extending treatment beyond 12 weeks increased overall benefit slightly. Around one-quarter of participants dropped out when using such treatments, and 55% sought further treatment after 18 weeks. Most improvement was seen within the first 6 weeks.

Perhaps the single most important finding of this study is that the topical antimicrobial therapies performed at least as well as oral antibiotics in terms of clinical efficacy. Benzoyl peroxide was the

most cost-effective and minocycline the least cost-effective therapy for facial acne. The efficacy of all three topical regimens was not compromised by pre-existing propionibacterial resistance. In addition to causing fewer systemic adverse events, topical preparations are less likely to induce resistance in other common bacteria, a finding that may be important for reducing the more widespread problem of bacterial resistance in the community. These findings need to be tempered by the fact that topical therapy can be more difficult to use for truncal acne, and the cost of treatment is directly related to the size of the area treated.

Even though benzoyl peroxide was the most cost-effective treatment, it was associated with a greater frequency and severity of local irritant reactions. The results suggest that the use of a combination of topical benzoyl peroxide and erythromycin gives rise to less irritation and better quality of life. There was little difference between erythromycin plus benzoyl peroxide administered separately and the combined proprietary formulation in terms of efficacy or local irritation, except that the former was nearly three times more cost-effective. The data on cost-effectiveness, and outcomes in patients with resistant propionibacterial floras, did not support the first line use of minocycline for mild to moderate inflammatory acne of the face.

Implications for healthcare

- Most people in the community with mild to moderate inflammatory acne of the face respond only partially to topical or systemic antimicrobial treatments.
- Benzoyl peroxide is a cost-effective way of managing mild to moderate facial acne in the community. Efficacy is not compromised by pre-existing bacterial resistance, and the risk of systemic side-effects is negligible.
- Most of the treatment effect is seen within the first 6 weeks of treatment. The clinical corollary of this is that if an antimicrobial treatment does not appear to be working adequately for facial acne after 6 weeks, then a change may be considered, rather than waiting for several months as many texts have previously recommended.
- The efficacy of systemic tetracycline-based treatments is compromised by pre-existing propionibacterial resistance to the tetracyclines. Local prevalence rates of skin colonisation with antibiotic-resistant propionibacteria may affect the relative efficacy of these treatments.
- This study has for the first time provided some comparative data for the most popular antimicrobial treatments for facial acne on a level playing field; however, the role of antibiotics in longer term management strategies remains to be elucidated.
- The results of this study, taken together with the Department of Health Action Plan (June 2000) to reduce selective pressure from antibiotic use, suggest that a reappraisal of antibiotics as first-line agents for the treatment of localised acne should be undertaken and that industry-independent evidence of the relative efficacy of non-antibiotic-based regimens in mild to moderate disease should be sought urgently.

Recommendations for research

Although this trial has helped to inform the selection of antimicrobial treatment for mild to moderate inflammatory acne of the face, prescribers are still faced with a lack of good quality evidence to help them to make informed decisions about many other aspects of acne management, such as choosing between antimicrobials and other types of treatment, how to manage truncal acne, when and how to combine treatments, whether and when to refer for oral isotretinoin, and the extent to which patient characteristics such as ethnicity or social class modulate outcomes. A small number of high-quality acne trials is needed to address the key issues for prescribers and patients as opposed to manufacturers and regulators. There is a need for more research on trial methodology and agreement between those who fund trials upon some degree of standardisation with respect to the selection and use of outcome measures. This study has shown how difficult it is capture all aspects of acne with a single measure, but also that the use of multiple measures is not an ideal solution. Three priority areas for clinical research in acne are:

- defining end-points in acne trials: what is a satisfactory outcome?
- developing and validating better patient-based measures for assessing treatment effects on facial and truncal acne
- exploring patient characteristics that may modify treatment effects (efficacy and tolerability).

Chapter 1
Introduction

Prevalence, morbidity and pathogenesis of acne

Prevalence and morbidity

Acne vulgaris is one of the most common skin diseases, with prevalence reaching 100% among adolescents.[1] The overall severity of acne appears to have been decreasing over the past 30 years as a result of effective therapy and the use of oral contraceptives in women (oestrogens suppress sebum secretion).[2,3] In adults, especially women, the prevalence of both late onset and persistent acne seems to be increasing.[4] In the UK, most people with acne are treated in primary care.

Even mild acne can cause great distress to the sufferer, striking at a time of their life when physical attractiveness matters most, and in an age that has become increasingly conscious of external appearance. Soreness, pain and itching may occur, but it is the appearance of the lesions that causes most concern to those with the disease. Dark marks following inflammatory acne (postinflammatory pigmentation) can take months or years to disappear in people with a dark skin. A degree of permanent scarring is a common feature of acne and severe scarring can result in facial disfigurement. Two previous studies found that acne has a negative affect on the quality of young people's life, although this can be improved with effective treatment.[5,6] The extent of distress is not necessarily related to the severity and extent of acne, and it is important not to trivialise acne based on a superficial evaluation. Acne sufferers are at increased risk of depression and suicide.[7] Another study has shown that many acne sufferers encounter difficulties in getting a job.[8]

Treatments available from a GP or pharmacy only suppress acne, as opposed to curing it. This means that most people seeking treatment for their acne will require several courses before the disease spontaneously resolves, usually but not always by the early twenties.

Mechanisms and causes of acne

Acne affects the pilosebaceous follicles of the face and upper trunk. The activity of the sebaceous glands is partly under the control of circulating androgens such as testosterone. However, circulating levels of testosterone in ordinary acne vulgaris are normal, and it appears that it is the sebaceous glands themselves that are over-responsive to normal levels of circulating androgens of adrenal and gonadal origin.[9] This hypersensitivity to normal levels of androgens leads to excessive production of sebum (grease), with the cells lining the sebaceous glands (sebocytes) being capable of synthesising testosterone locally from adrenal precursors.[10] Overproduction, increased adhesiveness and abnormal differentiation of skin cells (keratinocytes) lining the ducts of these overproducing follicles lead to excess build-up of horny skin cells (hypercornification). This process is probably mediated by chemical messengers such as interleukin-1α (IL-1α), transforming growth factor-β[11] and/or local deficiency of linoleic acid.[12] The build-up of horny skin cells in the follicular duct results in a functional but often incomplete blockage of the duct and the formation of visible non-inflamed lesions such as blackheads (*Figure 1*). Evidence suggests that the microbial residents of follicles probably play no part in this process.[13] Chronic inflammation, associated with inflammatory cells of a predominantly $CD4^+$ T-cell infiltrate, often results when the resident skin commensals, *Propionibacterium acnes* and/or *Propionibacterium granulosum*, become trapped within such follicles.[13] These organisms are potent adjuvants of the inflammatory response and can up-regulate the immune response to autoantigens within the follicle. If the follicle wall remains functionally intact, and the cellular infiltrate is confined to the dermis, the resulting lesion is a papule (dark spots in *Figure 1*). Pustules (light lesions in *Figure 2*) result when neutrophils infiltrate the follicular duct. If the follicle wall ruptures liberating ductal contents into the dermis, inflammation is intensified. More severe or nodular acne occurs in patients who show a significantly heightened cellular immune response to cutaneous propionibacteria.[14,15] Acne is consistent with a delayed-type hypersensitivity reaction to one or more persistent lesional antigens (not necessarily microbial) or an infection with a slow-growing bacterium such as *P. acnes* or *P. granulosum*. Failure to treat acne effectively in this inflammatory stage can lead to irreversible scarring (*Figure 3*).

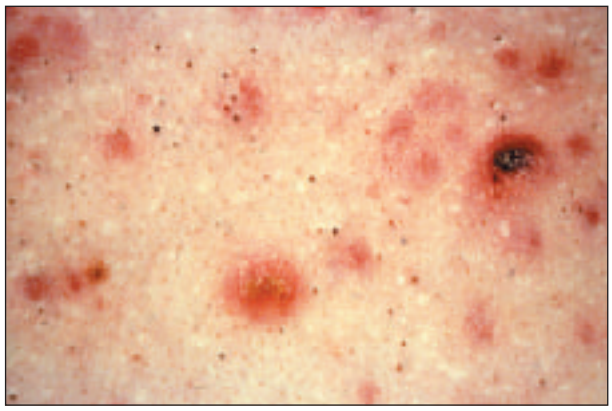

FIGURE 1 *Close-up of skin of an acne patient, illustrating a mixture of non-inflammatory lesions (blackheads) and inflammatory lesions (papules). [This figure is shown in colour on the CD and on the website.]*

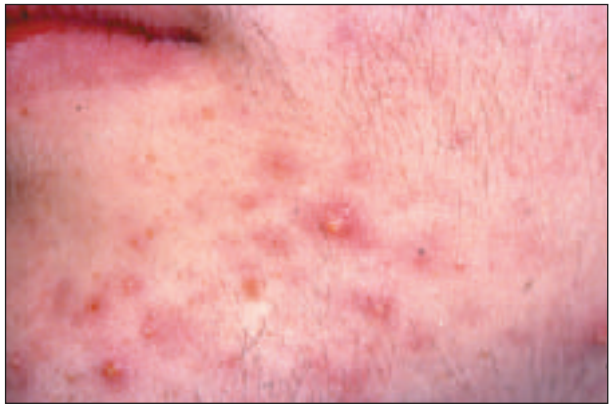

FIGURE 2 *Pustules in the chin area of a patient with long-standing acne. [This figure is shown in colour on the CD and on the website.]*

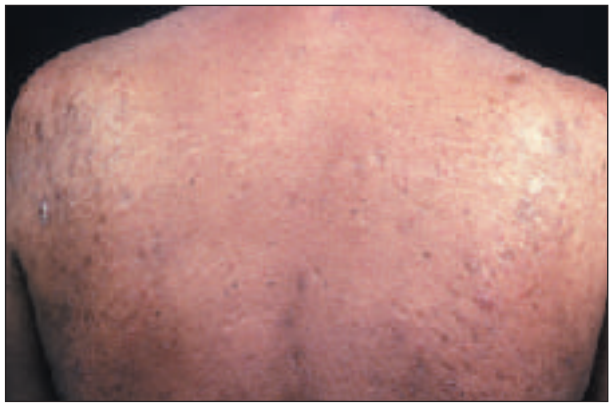

FIGURE 3 *Widespread acne and scarring of the upper back. [This figure is shown in colour on the CD and on the website.]*

Recent evidence of disease pathogenesis

The fundamental view of acne pathogenesis has changed little in the past 20 years or so, but accumulating evidence on candidate mediators is beginning to reshape ideas about predisposing factors and fill in the detail about key control processes. Leukotriene B_4, a potent chemical attractant for inflammatory cells such as macrophages and neutrophils that binds to the peroxisome proliferator-activated receptor (PPAR-α), may be involved in mediating inflammation in acne. A specific lipoxygenase inhibitor has been shown to be clinically effective and to reduce the concentration of inflammatory lipids in sebum.[16] PPARs [members of the superfamily of nuclear binding transcription factors that include the androgen receptor and nuclear factor-κB (NF-κB)], are now widely recognised to be important in the control of sebaceous gland sebum production (especially PPAR-γ) and their activation is required *in vitro* to induce the expected sebocyte differentiation with dihydrotestosterone.[17] *In vivo* PPARs may also mediate responses to cutaneous inflammation.[18] To date, evidence of any specific role of PPARs in acne pathogenesis is lacking. Corticotrophin-releasing hormone, the most proximal element of the hypothalamic–pituitary–adrenal axis, has also been implicated in sebaceous gland lipogenesis and mediates behavioural responses to stress.[19] Interestingly, stress has long been associated with acne – acne causes stress and stress is believed by sufferers to exacerbate acne in a vicious circle that may be hard to break. The discovery of numerous substance P-reactive nerve fibres in close proximity to sebaceous glands, that substance P increases the size and activity of sebaceous glands, and the observation that acne patients show an increased expression of neutral endopeptidase (the enzyme that degrades substance P) within sebaceous germinative cells collectively suggest some involvement of the neuroimmune–endocrine axis in acne pathogenesis.[20,21] Substance P is a proinflammatory neuropeptide produced by endothelial cells, macrophages and keratinocytes in response to psychological stress, which mediates its effects on cytokine production via NF-κB-dependent and -independent pathways. Another neuropeptide, α-melanocyte-stimulating hormone, has been found in and around pilosebaceous follicles and is produced by keratinocytes and macrophages.[22] These cell types, as well as sebocytes, have been shown to express the melanocortin receptor.[23] Binding of α-melanocyte-stimulating hormone to this receptor inhibits activation of NF-κB and thereby down-regulates the production of proinflammatory cytokines, such as IL-1, and up-regulates the production of immunosuppressive cytokines, such as IL-8 and IL-10. The peptide also possesses antimicrobial activity[24] although inhibitory effects on *P. acnes* have not yet been demonstrated.

NF-κB may also be implicated in acne via the binding of *P. acnes* to pathogen pattern recognition receptors [otherwise known as Toll-like receptors (TLRs)] on the surface of macrophages and/or keratinocytes. *Propionibacterium acnes* has been shown to induce the production of the cytokines IL-8 and IL-12 (presumably via activation of NF-κB) by binding to TLR2. TLR2 has been demonstrated on the surface of macrophages surrounding pilosebaceous follicles.[25] Related to this may be the marked up-regulation of β-defensin-2 shown by immunohistochemistry to be present in and around inflamed acne lesions.[26] β-Defensins (antimicrobial peptides) are produced by keratinocytes in response to the binding of microbial pathogens such as *P. acnes I* to TLRs and contain binding motifs for NF-κB. Taken together, these new observations all suggest a significant level of cross-talk between the immunological and endocrine aspects of acne, mediated at least in part via nuclear binding transcription factors, and that both can be modulated by neurological stimuli. It thus appears that acne is a truly multifactorial disease and that the number of genetic loci involved in determining susceptibility, severity and morphotype will be considerable. Moreover, little is known about the relative contribution of genetic and environmental risk factors that make some people more susceptible to acne than others. Twin studies suggest that both are important.[27] Indirect evidence of the role of some genetic loci in acne is now emerging via the identification of polymorphisms in candidate genes.[28,29]

Which treatment is best?

Antibiotic therapy to reduce the propionibacterial load is currently the main method of acne management, especially for inflammatory lesions. Direct anti-inflammatory activity via effects on leucocytes has been proposed as an alternative or complementary mode of action of antibiotics in acne,[30] and the immunomodulatory effects of tetracyclines (as opposed to their antimicrobial effects) are already harnessed in the treatment of periodontitis and rheumatoid arthritis. Oral isotretinoin (Roaccutane®) cures acne in 60–70% of people after a single course, but is only available from specialists in many countries and it is associated with a number of adverse drug reactions including teratogenicity and a disputed propensity to trigger depression and suicidal ideation.[31] The drug indirectly reduces propionibacterial numbers by over 99% via its effects on sebum production and follicular morphology, resulting in perturbation of the organism's habitat or niche. Previous studies have shown that tetracyclines, macrolides and the related lincosamide, clindamycin, are effective for acne, but information on how well they work relative to each other is conflicting. In 1995 more than half of over three million prescriptions for acne medications dispensed in the UK were for topical or oral antibiotics.[32]

A systematic review of topical antibiotic trials for acne carried out in 1990 found them to be of poor methodological quality.[33] A similar finding was obtained in a 2000 review of minocycline trials.[34] Lack of standardisation and heterogeneity in methods of data manipulation and presentation meant that data could not be pooled to increase statistical power. Treatments had usually been compared in terms of clinical efficacy as assessed by clinicians. Patient-based outcome measures, such as global improvement, quality of life and willingness to pay, were rarely used. Furthermore, the relative value for money of different antibiotic-based treatment regimens has not been estimated and there is a paucity of reliable criteria to help prescribers to make informed choices between available products. In the absence of such comparative data, it is difficult for a GP to make a rational choice between the 30 or so acne products currently listed in the British National Formulary (BNF).

The resistance problem

One consequence of the heavy reliance on antibiotics to manage acne has been a large increase in propionibacterial resistance to the most commonly used agents, erythromycin and clindamycin.[35] In contrast, propionibacterial resistance to the orally administered tetracyclines remains relatively uncommon.[36]

A previous study demonstrated a strong correlation between skin colonisation by erythromycin-resistant propionibacteria and inadequate response to orally administered erythromycin.[37] As a consequence, oral erythromycin is now less commonly prescribed for acne. There is a conspicuous lack of information on how resistance affects clinical efficacy for other commonly used antibiotic-based treatment regimens for acne, and especially whether resistance is clinically relevant for topical products that deliver high concentrations of antibiotic to pilosebaceous ducts. The results of clinical trials of antiacne antibiotics carried out several years ago when resistant

propionibacterial strains were rare may no longer be valid today. It is also not known whether some agents are more likely than others to promote *P. acnes* resistance.

Which treatments to compare?

Over three million prescriptions were written in 1995 for acne in the UK, at great cost to the NHS.[32] The cost of different antiacne preparations varies widely (sometimes several-fold), so it is important to know whether the cheaper ones are as cost-effective as the more expensive ones. Therefore, an industry-independent randomised controlled trial (RCT) of leading antimicrobial treatments for acne was undertaken to rank clinical efficacy and cost-effectiveness in a general practice setting. The study also aimed to assess the effect of pre-existing propionibacterial resistance on treatment outcomes and to reveal whether the selected treatment regimens promote resistance during a standard course of therapy. Benzoyl peroxide, a commonly used antiacne biocide available on prescription and over the counter (OTC), was used as a comparator.

Clinicians are increasingly using alternatives to antibiotics and, there is an equally compelling case for assessing the efficacy and cost-effectiveness of the available comedolytic agents in comparison with each other and with antimicrobials. This trial was originally envisaged as part of the first stage to identify the best single agents to use as stand-alone therapies. When this has been done, the next logical step would be to test whether there is any additional benefit from the use of combined regimens that include the best of the comedolytics and the best of the antibacterial agents. Having completed the study, the authors still recommend this approach, with particular emphasis on topical retinoids (see Appendix 5, list A, point 1).

The original study design included 11 treatments, chosen on the basis of high prescribing, variation in cost, pharmaceutical company claims of efficacy, and propensity to cause resistance:

- 500 mg oral **oxytetracycline** (non-proprietary) b.d.
- 100 mg oral **Minocin MR®** (minocycline) o.d.
- 500 mg oral **erythromycin** (non-proprietary) b.d. + topical vehicle control b.d.
- topical **Panoxyl® Aquagel** (5% benzoyl peroxide) b.d.
- topical **Stiemycin®** (2% erythromycin) b.d. + oral placebo o.d.
- topical **Dalacin T®** solution (1% clindamycin) b.d. + oral placebo o.d.
- topical **Benzamycin®** (3% erythromycin + 5% benzoyl peroxide) b.d.
- topical **Zineryt®** (4% erythromycin + 1.2% zinc acetate) b.d. + oral placebo o.d.
- topical **Stiemycin** (2% erythromycin) o.d. + topical **Panoxyl Aquagel** (5% benzoyl peroxide) o.d.
- topical **Topicycline®** (0.22% tetracycline) b.d. + 500 mg oral **oxytetracycline** (non-proprietary) b.d.
- topical **Panoxyl Aquagel** (5% benzoyl peroxide) b.d. + 500 mg oral **oxytetracycline** (non-proprietary) b.d.

Recruiting teenagers with acne from the community, who were willing to be tested on already established treatments proved to be far more difficult than anticipated. A decision was made with the HTA Board 5 months into the study to reduce the number of treatment groups from 11 to five, namely:

- 500 mg oral **oxytetracycline** (non-proprietary) b.d.
- 100 mg oral **Minocin MR** (minocycline) o.d.
- topical **Panoxyl Aquagel** (5% benzoyl peroxide) b.d.
- topical **Benzamycin** (3% erythromycin + 5% benzoyl peroxide) b.d.
- topical **Stiemycin** (2% erythromycin) o.d. + **Panoxyl Aquagel** (5% benzoyl peroxide) o.d.

The main factors informing the choice of the five continued treatments were:

- the need to produce useful and clear answers to the NHS that would inform future GP prescribing for acne based on commonly used treatment modalities in the community
- to keep things as simple as possible so that the results would be clinically meaningful and readily understood by a wide range of people
- to avoid an undue emphasis on assessing oral antibiotics, particularly for mild acne, in view of concerns of increasing antibiotic resistance in the community.

In addition,

- there is reasonably strong evidence that patients colonised with erythromycin-resistant propionibacteria respond poorly to oral erythromycin.[37] It was felt that there was an argument for its limited use without continuing with it in this trial

- plain oral tetracycline was favoured over oral tetracycline and topical benzoyl peroxide in combination to keep the comparisons clean and simple.

The selected treatments are typical of commonly used regimens, and help to answer the following questions.

1. Is oral minocycline clinically superior to oral tetracycline (oxytetracycline)? (Rationale: minocycline is several times more expensive per day's use, but data do not show it to be more effective.[34])
2. Is a leading current topical treatment (Benzamycin) as effective as oral treatment?
3. Are topical erythromycin and benzoyl peroxide, when prescribed separately, as effective as Benzamycin? (Rationale: Benzamycin is a formulation of topical erythromycin and benzoyl peroxide together, at three times the cost of the constituents sold separately.)
4. How does a cheap OTC topical (benzoyl peroxide) compare with proprietary topical and oral antibiotics?

Chapter 2
Methods

Participants

The study participants were mainly recruited from 97 GP surgeries in the Leeds and Nottingham areas, although sometimes from as far away as Stockton-on-Tees and Grimsby. Eighty-three participants (13%) were recruited from seven colleges in an effort to reach the final recruitment target. Entry criteria for the study were as follows:

- mild to moderate acne (grades 0.25–3.0 on the Burke and Cunliffe scale[38])
- aged 12–39 years
- at least 15 inflamed and 15 non-inflamed lesions
- no acne therapy in the 4 weeks before starting trial therapy.

Participants were excluded by the following exclusion criteria:

- primarily comedonal or nodular acne
- exclusively truncal acne
- rosacea
- late-onset acne (after the age of 26 years)
- acne secondary to endocrine disorders or drugs
- pregnancy or breast-feeding
- significant systemic disease
- current therapy with interacting medication
- known hypersensitivity to one of the test medications
- dysmorphophobia (abnormal perception of body image)
- dermatological disease other than acne vulgaris affecting the face
- previous treatment with oral isotretinoin (Roaccutane)
- therapy with the oral contraceptive Dianette® (cyproterone acetate + ethinyloestrodial) within 3 months
- current acne care and treatment from a hospital dermatologist
- participation in another clinical trial within 3 months of starting on study treatment.

Interventions

This was a parallel group RCT. The steering group received advice on the relevance to consumers of the trial aims and questions from the Acne Support Group.

All treatments were to be given for 18 weeks, after a 4-week treatment washout period. The reported mean time on treatment was 16.3 weeks (median 18.0 weeks), and the mean time in the study was 16.4 weeks (median 18.0 weeks). (Originally the study aimed to follow up patients for 24 weeks, but this was altered to 18 weeks at the same time as the number of treatment groups was reduced. No patients had reached 18 weeks in the study, but they were given the option to continue to 24 weeks as was originally proposed to them. Only 30 patients chose to continue past 18 weeks, and no data were recorded at 24 weeks.)

Treatments were supplied by the Queen's Medical Centre pharmacy, Nottingham, and given to participants by the clinical assessors, trained for this study. The treatments and instructions were contained in identical cubic cardboard boxes, so that it was not possible to identify the contents from the outside of the box, only the patient ID number. All participants were also supplied with unperfumed soap and E45® moisturising cream, although they could use their own non-medicated products if they preferred. The five main treatments were:

- 500 mg oral **oxytetracycline** (non-proprietary) b.d. + topical vehicle control b.d.
- 100 mg oral **Minocin MR** (minocycline) o.d. + topical vehicle control b.d.
- topical **Panoxyl Aquagel** (5% benzoyl peroxide) b.d. + oral placebo o.d. This was designated as the active comparator group, as benzoyl peroxide was the leading and most established topical treatment for acne when the protocol was written.
- topical **Benzamycin** (3% erythromycin + 5% benzoyl peroxide) b.d. + oral placebo o.d. (referred to as ery. + BP bd)
- topical **Stiemycin** (2% erythromycin) o.d. + topical **Panoxyl Aquagel** (5% benzoyl peroxide) o.d. + oral placebo o.d. (referred to as ery. od + BP od).

A total of 112 participants were randomised to the six discontinued treatment groups:

- 500 mg oral **erythromycin** (non-proprietary) b.d. + topical vehicle control b.d.
- topical **Stiemycin** (2% erythromycin) b.d. + oral placebo o.d.
- topical **Dalacin T** solution (1% clindamycin) b.d. + oral placebo o.d.
- topical **Zineryt** (4% erythromycin + 1.2% zinc acetate) b.d. + oral placebo o.d.
- topical **Topicycline** (0.22% tetracycline) b.d. + 500 mg oral **oxytetracycline** (non-proprietary) b.d.
- topical **Panoxyl Aquagel** (5% benzoyl peroxide) b.d. + 500 mg oral **oxytetracycline** (non-proprietary) b.d.

Participants were asked to take or apply their medications according to the instructions provided by the study investigators (package inserts provided by the manufacturer were not removed, apart from those for oxytetracycline and erythromycin tablets, which were repacked). The study-specific instruction leaflets advised the following.

- Treatments can take a while to take effect, and can sometimes cause minor stomach upsets.
- With minocycline capsules: if a participant experienced headaches accompanied by dizziness, unsteadiness, light-headedness or drowsiness they should consult their GP immediately to rule out benign intracranial hypertension (an uncommon side-effect of minocycline).
- Oxytetracycline, erythromycin and placebo tablets were ideally to be taken morning and night 12 hours apart; minocycline capsules were to be taken in the morning.
- Oxytetracycline was to be taken on an empty stomach, avoiding food and milky drinks within an hour of taking the tablets. Erythromycin was to be taken either just before or during a meal, and not at the same time as indigestion remedies. It was recommended that minocycline was not taken with a meal.
- Topical treatments were to be applied morning and night, in a thin layer to the whole face (not just spots), after washing and drying it; the topical preparations were for use on the face only, and not other areas of the body.
- If irritation occurred application could be reduced to once a day, and use of the moisturiser was advised.
- Participants were advised to contact their assessor or GP if they experienced any problems with the treatments.
- Participants on topical erythromycin and benzoyl peroxide administered separately were asked to apply the erythromycin in the morning and benzoyl peroxide at night.
- Once reconstituted, Benzamycin needs to be kept refrigerated.

Benzamycin, Zineryt and Topicycline were reconstituted on receipt by the participant as these products only remain active for 12, 5 and 8 weeks, respectively, after making up. It was not practical for them to be made up by the pharmacist before delivery, as medications were bulk-packed in advance.

Initially, treatments were dispensed every 12 weeks, but this was soon revised to every 6 weeks (each visit), in an effort to encourage participants to attend. The amounts of medication dispensed at each visit are given in Appendix 1.

The topical vehicle control was the base of Isotrex®, which was donated by the manufacturer (Stiefel Laboratories). It was a non-alcoholic cream, compositionally different to the vehicles of the three active topical products. Tubes were labelled as 'The cream'. It has been referred to as a vehicle control, rather than placebo, as the vehicle itself may have some antiacne effect. Manufacturing a placebo cream for this study was not feasible in terms of time and cost. The placebo tablets were low-dose vitamin C tablets (initially 30 mg, but later 50 mg when the former dose was discontinued), and labelled with 'The tablets'. It was thought unethical to include any participants on placebo/vehicle alone for such a length of time, hence all groups included at least one active treatment. The oral placebo and vehicle control were used to standardise treatment regimens, and to some extent to increase blinding.

Objectives of trial

Primary

To rank antimicrobial therapies for acne

- in order of their **clinical effectiveness**
- in order of their **cost-effectiveness**

with the primary end-point at **18 weeks**.

Secondary

Speed of action

- To determine which therapies demonstrated beneficial effects after 6 and 12 weeks and hence to compare the rate of clinical response.
- To identify those products that attained maximal efficacy before the primary end-point (18 weeks).

Combination versus single product
A limited number of oral and topical combinations were to be evaluated to determine whether cheaper combinations were equally or more effective than single, more expensive drugs.

Propensity to promote resistance
All participants were screened for carriage of antibiotic-resistant propionibacteria before and during treatment to identify those agents that are less likely to promote resistance and those that are effective in people who are colonised by subpopulations of resistant strains.

Outcomes

Measurements were made at 0, 6, 12 and 18 weeks by four trained clinical assessors. Each participant was seen by the same assessor throughout the study. To assist the patient and assessor global assessments, three photographs (full face, and left and right side views) of each participant were taken at week 0. Further photographs were taken at week 18 (end of the study) to use as a quality-control measure (external validation of gradings).

Primary outcome measures
Two primary outcome measures were used.

Patient self-assessment
Participants were asked to rate the overall improvement in their facial acne at weeks 6, 12 and 18, on a six-point Likert scale with the following categories: worse, no improvement, slight improvement, moderate improvement, excellent improvement and completely cleared. A category of at least moderate improvement at week 18 was classified as a success. Photographs taken at baseline were used to aid participants' judgements for this assessment.

Inflamed lesion counts
The face was divided into four areas for ease of counting: left cheek, right cheek, forehead, and nose/chin. Inflamed lesions and nodules were counted at each visit. Non-inflamed lesions were not counted because of poor repeatability during piloting. The four counts were added together for the analysis. If an area was not counted at baseline (e.g. a participant had a beard or lesions that were difficult to count) that area was also not counted at subsequent visits.

Secondary outcome measures
Burke and Cunliffe grade
This was assessed at each visit. This pictorial grade has been used extensively in hospital-based studies.

Assessor global assessment of improvement
This was rated in the same way as for patient's self-assessment.

Combined Acne Severity Score
Inflamed lesions, non-inflamed lesions and redness were each graded for each of four areas of the face (as for inflamed lesion count), at each visit. The possible scores for each category were: 0=absent, 1=minimal, 2=modest, 3=moderate and 4=severe. A global score was obtained by summing the individual scores, to give the Combined Acne Severity Score (CASS). If one area was not scored then the whole score was taken as missing.

Disability and effects on quality of life
The Short Form 36 (SF-36)[39] (week 0 and 18), the Dermatology Life Quality Index (DLQI[40] or CDLQI[41] for children under 16 at week 0; each visit) and the Dermatology Quality of Life Scales (DQOLS;[42] each visit) were administered to the participants. At week 0 questionnaires were completed at the visit. At subsequent visits, they were posted with the appointment reminder for the participant to complete and bring with them to the visit.

Local irritation
This was assessed by:

- participant: scores for stinging, burning, itching, dryness, erythema and scaling were each assessed on a scale of 0=none, 1=mild, 2=moderate and 3=severe, at all visits, with 0–6 weeks split into 2-week blocks
- assessor: scores for dryness, erythema and scaling were each assessed on a scale of 0=none, 1=mild, 2=moderate and 3=severe, at all four visits
- use of moisturiser: recorded at all visits as: not at all, less often than once a day, once a day, twice a day, or more often than twice a day.

Worst aspect of having acne
Participants were also asked at week 0 what the worst aspect of having acne was for them. At week 18 they were then asked how that aspect had improved during the study (on the same scale used for global assessments).

Re-referral rates
These were assessed 3 months after participants had completed the 18-week course of treatment.

Adverse events

Disclosure of adverse events was prompted by the following questions.

- Have you felt unwell since beginning your treatment?
- Have you experienced any symptoms which you previously didn't have?
- Have you experienced any worsening of any existing symptoms?

A short description of the event was recorded, along with the severity, outcome and dates of the event.

Detection and quantification of antibiotic-resistant propionibacteria

Swab samples were taken at each visit and analysed. Sterile swabs moistened in wash fluid (0.075 M sodium phosphate buffer, pH 7.9, containing 0.1% Triton-X 100) were rubbed with firm pressure over the skin surface of entire face but avoiding the eyes. Swabs were used on site to inoculate immediately plates of culture medium (2% tryptone, 1% yeast extract, 0.5% glucose agar containing 2 mg l^{-1} of furazolidone to inhibit the growth of staphylococci, TYEGF) with and without selective antibiotics. The following antibiotics were used: tetracycline 5 mg l^{-1}, minocycline 5 mg l^{-1}, erythromycin 0.5 mg l^{-1} and clindamycin 0.5 mg l^{-1}. After 7 days of anaerobic incubation at 37°C, propionibacterial growth on the non-selective medium and in the presence of each antibiotic was scored on a scale of 0–5: 0 (no growth), 1+ (1–10 colonies), 2+ (11–50), 3+ (51–200), 4+ (semi-confluent growth) and 5+ (confluent growth).[36]

Utilities for guiding the assessment of cost-effectiveness

The utility questionnaire was based on the one devised by Motley and Finlay.[43] The questions asked at **week 0** were:

1. Imagine that a new product is available for the treatment of spots. Imagine that this product is much more effective than previous treatments, and is almost certain to cure your spots altogether, but is not available on the NHS. How much would you be prepared to pay for this treatment?
2. Suppose now that the treatment is available on prescription. How much would we have to offer you to take the money instead of the treatment?

The questions asked at **week 18** were:

1. Looking at the pretreatment photograph of yourself, and comparing it with your appearance today: how much would you be prepared to pay for the treatment you have received during the study, if it was not available on the NHS?
2. Suppose now that you could have either the treatment or cash. How much would we have to offer you to take the money instead of the treatment?
3. Compared to the treatment you have received: how much would you be prepared to pay for a complete cure for your spots, which was not available on the NHS?
4. Suppose now that the cure is available on prescription. How much would we have to offer you to take the money instead of the cure?

Available responses were £5, £25, £50, £100, £500, £1000, £5000, £10,000 and >£10,000; as well as £0 at week 18 only.

Quality of measurements

Lighting conditions for counts and gradings were standardised where possible by use of a daylight examination lamp. Practicalities, however, meant that on some occasions this was not used. Photographs were used as an objective reminder of the severity of acne at baseline when making assessments of global improvement. (Photographs were taken using Canon EOS 5 camera bodies fitted with Canon 100-mm f2.8 macro lenses and Canon ML 3 ring flashes onto Kodak Elite Chrome 100 slide film.)

A further reason for taking the photographs was for independent checks to be made of the assessors' grades. Owing to delays with processing the scanned images, these checks were not made in time for this report.

All four assessors were trained in grading and counting of spots, by staff in the Dermatology Department at Leeds General Infirmary (a recognised centre for training in acne assessment), who are experienced in spot counting. Monitoring sessions were held throughout the study where all four assessors assessed the same people, and also reassessed the same person (to gain both interassessor and intra-assessor measurements). Each assessor had a manual of instructions for carrying out assessments. Each participant was seen by the same assessor throughout the study in recognition that acne grading and lesion counting are very subjective and there is more interassessor than intra-assessor variation.

Allocation of Burke and Cunliffe acne grades was determined by comparison with a series of

standard photographs with descriptions as anchors.

Sample size

The sample size calculations were based on the patient global self-assessment ($\alpha = 0.05$, $\beta = 0.2$, hence 80% power). Original calculations indicated that to demonstrate a 20% relative difference between any two treatments (without adjustment for multiple testing), allowing for a dropout (early withdrawal) rate of 23%, and a comparator (benzoyl peroxide) response rate of 75%, a minimum of 132 participants was required per group (total of 1452 over the original 11 treatment groups). (The anticipated dropout rate of 23% corresponds to the average withdrawal rate estimated by the clinical research ethics committee of the Royal College of General Practitioners for 74 trials carried out in general practice.[44])

Because of the major recruitment difficulties it was decided, in consultation with representatives of the NHS HTA in February 1999, to revise the total sample size primarily by decreasing the number of treatment groups from 11 to five. Since there were few directly comparable data on which to base the original sample size, it was considered prudent at this stage to reassess the calculations by checking the response rate in the benzoyl peroxide (comparator) group. This interim look revealed that 67% of participants rated themselves as at least moderately improved on benzoyl peroxide (10/15 participants, with dropouts counted as no improvement). The overall 38% dropout rate at this point ($n = 150$ with similar rates for each treatment group) was higher than the anticipated 23% rate based on previous hospital-based studies. Using their experience over the first few months, the authors considered how many participants they could feasibly start on treatment over the remaining study time, allowing for 21% of recruited people not to be randomised (as per cohort 1). This came to 600 in total on the five treatments, that is, 120 per treatment group over all three recruitment cohorts. Using data from 5/11 (the five chosen treatment groups) of the 210 participants from the first cohort meant that each assessor needed to randomise 85 participants to treatment during each of cohorts 2 and 3. With an estimated dropout rate of 38% on treatment, a minimum relative difference of 30% could be detected in relation to the benzoyl peroxide comparator with 80% power at the 5% significance level. The second primary outcome measure was total inflamed lesion count. The benzoyl peroxide group (15 participants) produced a 36.2% reduction in inflamed lesions. A further 22% drop could be detected with this sample size, with 80% power at the 5% significance level.

Since the comparator group data were reviewed at the interim assessment only to guide final sample size, no adjustment to the final significance level was considered necessary. The assessors and investigators remained blinded to the participant treatment allocation.

The authors were successful in randomising 649 participants to the five treatments, and the overall dropout rate was 27%. The final benzoyl peroxide [intention-to-treat (ITT)] patient global improvement rate was 60%, and reduction in inflamed lesions was 35.9%. A relative change of 30% in patient global assessment (60 to 78%) could be detected with 94 per group, or 129 per group allowing for 27% to dropout; a relative difference of 20% (60 to 72%) would have required 214 (294 allowing for dropouts) per group. An ITT analysis was used so all participants were included, giving between 127 and 131 per treatment group.

Randomisation

Sequence generation

The randomisation was generated using SAS PROC PLAN with a block size of 11. There was no stratification. When the six treatments were dropped the same randomisation scheme was kept, missing out the patient numbers for discontinued treatments. This approach was chosen as the easiest and cheapest to implement in the pharmacy, since a lot of the treatment packing was already completed.

Allocation concealment

Treatments were provided in opaque cardboard boxes labelled with the patient number, and were passed to the participant by the assessor, still concealed in the box. Boxes were allocated sequentially, each assessor starting at different points in the sequence. Assessors were required to record any occasions and reasons where this was not the case; there were 30 cases amongst all 761, all accidental incorrect allocation, usually where the assessor had taken the wrong boxes with them to the surgery, or passed the participant a number that was not the next in sequence. It was not thought that these incidences led to bias, hence no correction has been made. Other changes in the planned allocation occurred when one Leeds assessor had run out of boxes and took three of

the other Leeds assessor's, when a batch of boxes went missing in transit between Nottingham and Leeds, and at the end of the study when the two fastest recruiting assessors had to allocate numbers from the third assessor's list after finishing their own.

Sealed code-break envelopes were issued to the surgeries, and a code-break list was also stored at the Leeds General Infirmary for 24-hour access. Both these routes were available for GPs to break the code, only if breaking the code was necessary for the participant's additional treatment. Code-break envelopes were collected from the surgeries at the end of the trial, and checked to see which were opened and why. Although GPs did not perform any assessments in the trial, it was still considered important to keep them blind to treatment, as they could withdraw participants from the trial.

Implementation

The random scheme was generated by the trial coordinator. Participants were enrolled and allocated treatment numbers by the clinical assessors, who had no knowledge of which treatment they were allocating to the participant.

Blinding/masking

The assessors were blinded to treatment. Participants were instructed not to reveal their treatments to their assessor. The assessor delivered the treatment to the participant in a cardboard box, which was identical for all treatments. Medication returns were made via the assessor in the same boxes.

It was not practical to reformulate all of the oral and topical preparations for this study to have identical appearance, taste, odour, and so on. Costs for manufacturing suitable placebos would be prohibitively expensive, and time for all the associated testing and production was unavailable. So that participants were following similar procedures they each received both oral and topical preparations, and were told that one of them may have been a placebo. Some treatments consisted of two active treatments and some one. If any assessor became aware of the identity of a participant's treatment (usually unwittingly revealed by the participant), they were required to report details to the trial coordinator. During the whole study, it was reported that 12 out of 761 participants revealed part or all of the treatment to their assessor (see Appendix 2 for details).

Participants were asked at the end of the trial how many active treatments they thought they were on, to test the level of information bias. Only around half of the participants correctly guessed the number of active treatments, a higher proportion being in the minocycline group, and a lower one in the benzoyl peroxide group. To look at this in more detail, a subset of participants (approximately 60, towards the end of the trial) was also asked at the 3-month post study follow-up which of their treatments they thought were active and why, and also whether they had any likes or dislikes about their treatment. Most participants thought that the active treatment was active, while around half thought that the placebo treatment (either vehicle control or tablets) was also active. See Appendix 2 for details of results.

Code-break envelopes were collected from the surgeries at the end of the study, and details are shown in Appendix 2. In summary, 61% of envelopes were returned. Six codes were known to be broken by the GP to help manage patient care (details in Appendix 2) during the study. All but one participant withdrew at this time; the other participant continued as planned. These participants remained in the ITT analysis.

Treatment codes were not added to the database until after data entry and analysis had been performed. The codes generated in SAS® were scrambled using further application of the PROC PLAN procedure in SAS with the CYCLIC option for TREATMENTS. The procedure was thoroughly checked before changing the SEED and rerunning the procedure to produce a SAS dataset of scrambled codes for analysis. The codes were only unscrambled after the analysis code had been written and run, the data analyst remaining blind as to the decoding until the writing-up stage.

Statistical methods

Software

The data were double data entered into a Microsoft® Access 97 database. Some of the data validation, and most of the efficacy and safety analysis, used SAS for Windows™ release 6.12 (SAS Institute). The analysis mainly used the procedures PROC LOGIST and PROC GLM. The cost-effectiveness analysis was conducted in SPSS version 10 (SPSS, Chicago, IL, USA).

Data validation

All data (both numeric and textual) were double data entered. Access tables were transferred (via

Microsoft Excel) to SAS. All numeric data from the two entered databases were compared using SAS PROC COMPARE, discrepancies checked back to the paper forms and corrections made to the master database where necessary. Printouts of all textual fields were checked against each other, and corrections made where necessary.

General principles

For all variables measured repeatedly:

- The **main time-point** for formal analyses was week 18.
- Data at **interim time-points** were summarised only, except for analysis of resistance data at week 12.
- Seven **treatment comparisons** were made:
  - minocycline versus oxytetracycline (see Chapter 1, which treatments to compare? question 1)
  - erythromycin + benzoyl peroxide combined b.d. versus oxytetracycline (question 2)
  - erythromycin + benzoyl peroxide combined b.d. versus minocycline (question 2)
  - erythromycin + benzoyl peroxide combined b.d. versus topical erythromycin + benzoyl peroxide separately o.d. (question 3)
  - benzoyl peroxide versus minocycline (question 4)
  - benzoyl peroxide versus oxytetracycline (question 4)
  - benzoyl peroxide versus erythromycin + benzoyl peroxide combined b.d. (question 4).

  The remaining three comparisons were also included for completeness.
- Treatments were ranked. Ranks were based only on the means/odds ratios, and did not necessarily imply a statistically significant difference.
- **Covariates** investigated were: baseline severity (Burke and Cunliffe grade), weight, baseline value of analysis variable, age, gender, height, body mass index (BMI), complexion, ethnic group, duration of acne, age of onset, family history, previous treatments and assessor. Social class was not available for inclusion in the analysis at the time of this report. Significant covariates were determined using a stepwise procedure (p-value 0.05 to include in the model, 0.10 to drop). It was decided to include baseline, BMI, age, gender and assessor for all analyses, whether significant or not. A baseline by treatment interaction term was included where significant ($p < 0.05$) and the interaction investigated further. Missing covariates were substituted by the mean or most frequent value of all other participants.
- **Least squared means**: where data were analysed by analysis of covariance (ANCOVA), least squared means (LSmeans) were presented. These are means adjusted for covariates and data imbalance.
- A **significance level** of 5% was used with two-tailed tests. Where appropriate, 95% confidence intervals (CIs) were estimated. No statistical adjustment was made for multiple comparisons.

For all analyses:

- An **ITT** population was the main analysis population. Analysis of the per-protocol population may be carried out at a later date if requested. Participants were included in the treatment group to which they were randomised. There was no reason to believe that any participants received a different treatment to the one allocated to their treatment number. Where values were missing, the last available value was carried forward (and carried back for missing baselines), so that all participants could be included in the analysis. For global assessments (patient global, assessor global and worst aspect of acne) the participant was assigned a category of 'no improvement' if they did not complete the study, whatever the reason.
- The following **subgroups** were investigated: surgery versus student recruited participants, and outcome by assessor.
- **Analysis assumptions**, such as normality of data distribution and heterogeneity of variance, were checked.

Brief descriptions of the analyses are given below. For further details see Appendix 3.

Patient global assessment

Differences in proportion of participants responding with at least a moderate improvement (patient global self-assessment) were estimated, along with the number needed to treat. The response rate was also analysed by logistic regression, to take account of covariates.

Proportions of participants improving at each time-point were used to assess when the first sign of and maximum improvement occurred. Modelling of the data with a smoothing function was not carried out at this stage (see Future research list C in Appendix 5).

Lesion counts

Inflamed lesion count changes from baseline were analysed by ANCOVA. Nodule counts were only summarised.

Assessor global assessment
This parameter was analysed by logistic regression, as for patient global assessment.

Burke and Cunliffe grade
ANCOVA was used to estimate changes in grades.

CASS
The change from baseline in total score was analysed by ANCOVA.

Quality of life
Scores for the SF-36, DLQI/CDLQI and DQOLS were calculated, as per standard scoring systems, and changes from baseline analysed using ANCOVA.

The eight SF-36 scales are: physical functioning, role – physical, bodily pain, general health, vitality, social functioning, role – emotional and mental health.

DLQI/CDLQI scores were calculated for each of ten questions, summarised by six sections and a total score for each. Only the total scores were analysed. DLQI and CDLQI scores were analysed separately.

The 41 items on the DQOLS were divided between three scales: psychosocial (17 questions), activities (12) and symptoms (12). The three scales were analysed separately.

Local irritation
The three scales recorded by both the assessor and participant (dryness, erythema and scaling) were tabulated with assessor score against participant (patient) score. Use of moisturiser was considered, informally, together with the dryness scores. For each irritation parameter nested barcharts were plotted of the proportions for each level of severity, by treatment and week.

Side-effects during the first 6 weeks were compared descriptively between participants who completed the study and those who did not.

For each of the nine parameters the number of participants with a worst category of moderate or severe per treatment was analysed by the Cochran–Mantel–Haenszel test. Overall irritation indices were analysed at each visit by analysis of variance (ANOVA).

Utility questions
The responses to each question were summarised by treatment group.

Worst aspect
The worst aspect was analysed by logistic regression.

Dropout rates
The dropout (early withdrawal) rates included all reasons for not completing the study. Data were summarised.

Re-referral rates
Recorded are the numbers of participants who needed, requested and received treatment at the end of the trial, and also the number offered specialist referral. Re-referrals are defined as those who stopped treatment at the end of the trial, but started more (either prescribed or OTC) within 3 months of the end of the trial. Data were only summarised. Participants were allowed to keep their remaining medications at the end of the trial, which meant that many participants did not stop treatment at 18 weeks.

Adverse events
The total number of participants with adverse events, and adverse events by week were recorded, along with summaries by body system.

Antibiotic resistance
Antimicrobial efficacy *in vivo* was determined by summarising the change from baseline in mean growth score of total and antibiotic-resistant propionibacteria and in the prevalence (as a percentage of patients colonised) of viable and antibiotic-resistant propionibacteria at each time-point.

To investigate the association between colonisation by resistant propionibacteria and treatment failure, patient global assessment, lesion counts, and Burke and Cunliffe grade were analysed for the subgroups (relevant resistance in *Table 1*):

- participants colonised or not colonised by tetracycline-resistant organisms at baseline
- participants colonised or not colonised by erythromycin-resistant organisms at baseline
- (for the discontinued treatment groups only) participants colonised or not colonised by clindamycin-resistant organisms at baseline.

Analyses were also performed at week 12, since topicals are often prescribed by GPs for only 12-week courses.

It should be noted that:

- The degree of resistance [minimum inhibitory concentration (MIC)] as well as or instead of the

TABLE 1 *Relevant resistance by treatment group*

Treatment group	Resistance
Oxytetracycline	Tetracycline
Minocycline	Tetracycline, minocycline
Benzoyl peroxide	None
Erythromycin + benzoyl peroxide b.d.	Erythromycin
Erythromycin o.d. + benzoyl peroxide o.d.	Erythromycin

population density of resistant propionibacteria may correlate with response. MIC data, however, are not available for this study.
- Any relationship between resistance status and response could be masked or exacerbated by other factors, for instance adherence to treatment.

Prevalence and time-related resistance patterns were estimated for tetracycline, erythromycin and clindamycin resistant subpopulations.

Cost-effectiveness

Cost-effectiveness was estimated in a number of ways. Summary statistics were calculated for the following ratios for each treatment; the first four in the list were considered to be the main analyses.

- The ratio of patient global assessment at week 18 to the cost of 18 weeks of treatment (allowing for pack size and expiry time of opened packs).
- The ratio of change in lesion counts (week 18 minus baseline) to the cost of 18 weeks of treatment (allowing for pack size and expiry time of opened packs).
- The ratio of patient global assessment at week 12 to the cost of 12 weeks of treatment (allowing for pack size and expiry time of opened packs).
- The ratio of change in lesion counts (week 12 minus baseline) to the cost of 12 weeks of treatment (allowing for pack size and expiry time of opened packs).
- The ratio of patient global assessment at week 18 to the cost of treatment for the number of weeks the participant was on the study (weekly cost multiplied by number of weeks on study treatment; this does not allow for pack sizes).
- The ratio of change in lesion counts (week 18 minus baseline) to the cost of treatment for the number of weeks the participant was on the study (weekly cost multiplied by number of weeks on study treatment).
- The ratio of willingness to pay (WTP = week 18, question 1) to the cost of treatment (using weekly cost).
- The ratio of willingness to accept (WTA = week 18, question 2) to the cost of treatment (using weekly cost).

Unit costs of treatment were obtained from the BNF, September 2001 (see Appendix 3). The total costs of 12 and 18 weeks of treatment using the topical formulations were calculated from estimates of usage based on application to the whole face, and adjusted to nearest pack sizes. Referral costs were added to the medication costs, with dropouts costed as referral to GP. WTP was also tabulated against baseline Burke and Cunliffe grade and patient global assessment.

Discontinued treatment groups

Data were summarised, but only the primary end-points (patient global and lesion counts) analysed. Numbers per group were very small (16–20), but may indicate possible trends and may be useful for sample size estimation in future studies.

Concomitant medications

Data were listed only, and used to check entry criteria and protocol adherence.

Adherence to treatment

Participants were issued with diary cards to indicate whether or not they took each medication as required, and to note any adverse events. Participants were also asked to return their medication packs at each visit. About 40% of medication packs were returned (some of which were incomplete); 75–80% of participants returned at least one diary card. Participants were also asked at each visit whether there was anything that prevented them from taking their medications according to the instructions, and responses were recorded. The data were not analysed for this report, which is intended to capture the pragmatic aspects of acne treatment adherence to typical treatments in the community.

Ethics

The study received ethical approval from the Northern and Yorkshire Multicentre Research Ethics Committee [reference for approval MREC/97/3/43, and Queen's Medical Centre DE059817 (DB)] and all relevant local research ethics committees. The study was explained to each potential participant (and guardian if present) by the clinical assessor and a participant information sheet (a children's version was available) was given to each of them, with the opportunity to ask any questions they might have. Written informed consent was obtained from each person who wished to participate, and additionally from a parent or guardian if the participant was under 16 years of age.

The trial was included on the Cochrane skin group trials register.

Chapter 3
Results

Participant flow

Known protocol violations (unmet entry criteria)

The ages of two participants were outside the specified range. Four participants had fewer than the required number of inflamed lesions. Further details are given in Appendix 4.

Protocol deviations

Twenty-five (4%) of the participants took or probably took (in three cases the participant was unsure of what the antibiotic was) a β-lactam antibiotic during the study; of these, seven were on the antibiotic at the start of treatment. Although as a potentially interacting medication this was a deviation from the protocol, it was not considered to be important for interpretation of the overall results, since evidence suggests that short courses of β-lactam antibiotics do not inhibit propionibacterial growth *in vivo*.

Three participants reported significant systemic disease: rheumatoid arthritis (present at the outset; participant chose to withdraw before week 6), fever and convulsions (thought to be due to recent meningitis vaccination; withdrawn week 6), and pneumonia (withdrawn week 12). Three participants were withdrawn because of pregnancy.

One-hundred and sixty participants (21% of participants; 203 visits) had at least one visit outside the visit window (–7 to +14 days). The utility questionnaire was improved part way into the study (14 October 1998), and ongoing participants were asked to answer the new question 2: 45 participants completed question 2 after week 0, and 141 did not receive the revised questionnaire, and hence only provided data for question 1. The main reasons for mistimed visits were lack of available appointment slots, rescheduling missed visits, avoiding holidays and difficulties in contacting participants. In particular, extra effort was made to chase week 18 visits (main outcome time-point), even when the visit window had passed. Fifty-five participants were given the incorrect version of the DLQI questionnaire to complete for their age, at one or more visits (DLQI instead of CDLQI or vice versa). Further details of protocol deviations are given in Appendix 4.

Withdrawal from the study

The overall early withdrawal rate in the five main groups was 27% (*Table 2*). The withdrawal rate was lower in the ery. + BP bd group at 20%, the biggest difference being at week 6, when the number withdrawn was around half that in other groups. There was little difference between the other groups.

The most frequent category of withdrawals from the study was through the participant's choice (105/178=59%). Reasons were frequently not given, but included unavailability for appointments. Thirty participants did not complete the study owing to an adverse event (either self-withdrawn or by the assessor or GP). Eight were withdrawn by the assessor owing to exacerbation of their acne. Participants who chose to withdraw included a few whose acne worsened, but for whom the assessor did not consider withdrawal necessary. Contact with 30 participants was lost.

Withdrawals per treatment group are shown in *Figure 4*. Reasons for withdrawal by participant are given in Appendix 7.

In the discontinued treatment groups, the overall withdrawal rate was 38%. Improvements to the conduct of the study reduced the overall rate. The highest withdrawal rates were in the topical erythromycin (53%) and erythromycin + zinc acetate (44%) groups; however, it should be

TABLE 2 *Cumulative withdrawal rate (%) by week*

	Week			
Treatment group	**0**	**6**	**12**	**18**
Oxytetracycline	0.8	11.5	21.4	28.2
Minocycline	0.8	13.8	23.8	30.8
Benzoyl peroxide	1.5	15.4	25.4	29.2
Ery. + BP bd	0.0	6.3	14.2	19.7
Ery. od + BP od	0.0	9.9	21.4	29.0
All	0.6	11.4	21.3	27.4

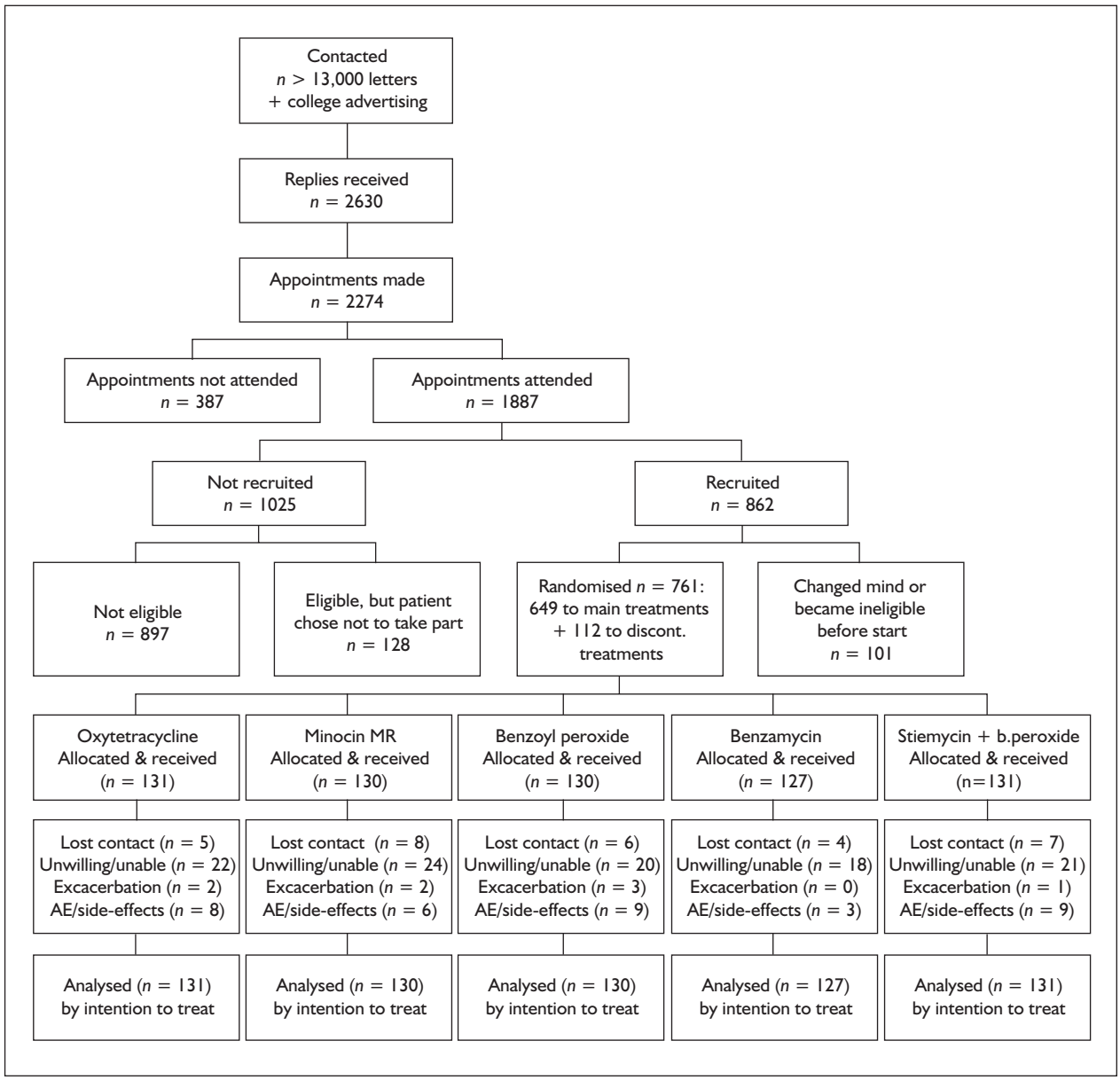

FIGURE 4 *Participant flow. AE, adverse events.*

remembered that the total numbers in each group were small.

Re-referral

There were inconsistencies in the recording of whether the participant needed, requested or received active treatment at the end of the trial, so these data are not considered useful and hence not reported. Thirty participants in total were offered specialist referral at the end of the study, usually owing to lack of improvement or participant request. There were similar numbers in each treatment group.

Within 3 months of the end of the study, 55% of participants sought further treatment (49–61% per treatment group); 89% were prescribed, as opposed to OTC, medications. Participants were frequently prescribed the same treatment (typically minocycline or Benzamycin) they had received in the study (thus prolonging antibiotic treatment beyond 18 weeks, a practice that should not be encouraged). Details are given in Appendix 8.

Recruitment

Participant recruitment took place between July 1998 and April 2000. The first participant was started on study treatment on 7 September 1998; the last participant completed on 28 September 2000.

Initial recruitment of participants was mainly from GP surgeries in the Leeds and Nottingham areas, although occasionally further afield. Recruitment was originally planned in three cohorts to allow the clinical assessors to take annual leave. Because of lower than expected recruitment rates and difficulties in keeping to the strict planned timings, cohorts 2 and 3 were merged, and included recruitment from colleges. Visits were arranged around assessor annual leave.

Before starting cohort 2 four focus groups were held, with young people from various backgrounds, to gain ideas to help to improve recruitment and retention to the study. The sessions were tape-recorded. The results were written up separately, and may form the basis of a paper (Allen J, *et al*. Universities of Nottingham and Leeds, unpublished data). In summary, it seemed that financial reward was likely to be a bigger motivator than desire to improve their disease or altruism, particularly for those with milder acne. Other potentially off-putting factors identified were the extent of the commitment required (long study duration, multiple visits at frequently inconvenient times) and a treatment-free interval before starting the trial treatment. The focus group participants thought that an initial approach by their GP, particularly in person, was more likely to encourage them to take part than receiving a cold mailshot. Experiences and ideas on best practice were also shared among the assessors.

Over 13,000 letters of invitation were sent from surgeries to participants during the study, with a reply rate of around 8.5%. Some participants were actively recruited after a GP appointment for their acne, with the GP giving them an invitation letter for return to the research team. In cohorts 2 and 3 recruitment was also via newspaper articles (local and university), a radio broadcast and recruiting by posters and e-mails from colleges.

Participants from 97 surgeries and seven colleges were randomised to treatment. Eighty-three participants (13% of 649) were from colleges. A further 41 surgeries and two colleges agreed to take part, but no participants were randomised at these centres. Requests to recruit participants actively were made to 298 GPs. Twenty-one surgeries were recruited with the help of Trent Focus (an NHS-funded network of research active primary care workers within Trent Region). Advice on recruitment was also received from the Acne Support Group.

To compensate for their time (particularly identifying suitable patients on their register and mailing them), surgeries were paid £35 for each participant recruited (or a single payment of £35 if patients were mailed, but none was recruited). It was also agreed by the ethics committees that students recruited from colleges could be paid a total of £35 (split between visits), in addition to making a donation to those colleges that recruited a lot of participants.

The flow of participants through the study is given in (*Figure 4*), and in detail in Appendix 6. The main reason for 37% of potential participants not meeting entry criteria was insufficient inflamed lesions.

Baseline data

The five treatment groups all had similar baseline characteristics, apart from the proportion of patients with tetracycline-resistant propionibacteria, which was higher in the ery. + BP bd treatment group (27% versus 12–18%). Most baseline data were missing for two participants (except for gender for both and date of birth for one), for whom the forms were lost in transit between Leeds and Nottingham, so most summaries are for a maximum of 647 participants; other participants had one or more measurement missing.

A summary of baseline characteristics is given in *Table 3*. All participants had facial acne. The majority of participants were fit and healthy. Further details and summaries by treatment group are available in Appendix 9.

Numbers analysed

Data were analysed by ITT, hence all participants were included in the analysis. Numbers analysed in each group were: 131, 130, 130, 127 and 131 for oxytetracycline, minocycline, benzoyl peroxide, ery. + BP bd and ery. od + BP od, respectively. Participants were only omitted from formal analysis where none of the data required for analysis were available for them at any visit. Where covariates were missing the mean or most frequent response for non-missing participant covariates was substituted, apart from baseline Burke and Cunliffe grade, where missing values were substituted by postbaseline data.

In the microbiology analyses, numbers of participants were as per the bottom part of *Table 3*,

TABLE 3 *Baseline characteristics*

Characteristic		*n*	Mean	SD	Range
Age (years)		648	19.7	6.07	11–42
BMI (kg/m^2)		641	22.5	2.52	13–47
Age of onset (years)		646	13.5	2.52	5–25
Duration of acne (years)		646	6.2	5.46	0–29
Time since sought help (years)		608	3.9	4.42	0–26
Baseline severity (B&C grade)		648	1.09	0.685	0.05–3
Gender	293 (45.1%) Male	356 (54.9%) Female			
Ethnic group	599 (92.6%) Caucasian	25 (3.9%) Asian	12 (1.9%) Afro-Caribbean	11 (1.9%) Other	
Skin complexion	424 (65.6%) Fair	210 (32.5%) Medium	12 (1.9%) Dark		
Other acne affected site(s)	216 (33.3%) Neck	373 (57.5%) Back	236 (36.4%) Chest	41 (6.3%) Elsewhere	
Family history	460 (71%) Yes	188 (29%) No			
Previous treatment	566 (87.2%) OTC	582 (89.7%) Prescription	384 (59.2%) Oral	535 (82.4%) Topical	

	Numbers of participants with and without baseline propionibacteria resistant to:					
	Erythromycin		Tetracycline		Clindamycin	
Treatment group	**Without**	**With**	**Without**	**With**	**Without**	**With**
Oxytetracycline	70	61	112	19	77	54
Minocycline	70	59	107	22	77	52
Benzoyl peroxide	73	57	114	16	81	49
Ery. + BP bd	76	61	93	34	76	51
Ery. od + BP od	68	63	108	23	72	59
All	347	301	534	114	383	265

n = 649; data are missing for some participants.
B&C, Burke and Cunliffe.

with two exceptions: in the Ery. od + BP od group numbers for analysis of Burke and Cunliffe score were reduced by one in the 'with erythromycin' and 'without tetracycline' groups (i.e. 62 and 107, respectively).

See Appendix 10 for numbers of missing data for the main efficacy analyses.

Outcomes and estimation

Primary outcomes

Patient global assessment of facial acne

By 6 weeks nearly half of the participants had noted at least a moderate improvement from baseline (47% overall, ranging from 44 to 51% per group) (*Table 4*). Only 2% considered themselves to be worse than at the start of the study (three on oxytetracycline, six on minocycline, two using benzoyl peroxide, two using ery. + BP bd, and none using ery. od + BP od). In all treatment groups, the percentage of people with at least a moderate improvement increased further at 12 weeks (particularly in the ery. + BP bd group) to 53% overall, and further still at 18 weeks to 60% overall. Improvement at 18 weeks was greatest with the topical treatments.

Treatment ranking with respect to patient global assessment:

minocycline < oxytetracycline < benzoyl peroxide < ery. od + BP od < ery. + BP bd

Ranks are based only on the odds ratios, and do not necessarily imply a statistically significant difference.

TABLE 4 *Percentage of participants rating their facial acne at least moderately improved*

Treatment group	Week			95% CI
	6	12	18	
Oxytetracycline	43.5	46.6	55.0	(46.5 to 63.5)
Minocycline	47.7	50.8	53.8	(45.2 to 62.4)
Benzoyl peroxide	47.7	50.0	60.0	(51.6 to 68.4)
Ery. + BP bd	45.7	63.8	66.1	(57.9 to 74.3)
Ery. od + BP od	51.1	55.7	62.6	(54.3 to 70.9)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 5*.

TABLE 5 *Patient global assessment: estimates from logistic regression*

Treatment comparison	Estimate of OR	Lower 95% CL	Upper 95% CL	NNT (95% CI)
Minocycline vs oxytetracycline	0.945	0.575	1.554	84 (9 to –8)
Ery. + BP bd vs oxytetracycline	1.642	0.983	2.740	10 (4 to –134)
Ery. + BP bd vs minocycline	1.737	1.040	2.902	9 (4 to 240)
Ery. od + BP od vs ery. + BP bd	0.842	0.501	1.415	29 (12 to –7)
Benzoyl peroxide vs oxytetracycline	1.187	0.720	1.958	20 (6 to –14)
Benzoyl peroxide vs minocycline	1.256	0.761	2.075	17 (5 to –17)
Benzoyl peroxide vs ery. + BP bd	0.723	0.431	1.213	17 (18 to –6)
Ery. od + BP od vs oxytetracycline	1.383	0.835	2.285	14 (5 to –23)
Ery. od + BP od vs minocycline	1.463	0.885	2.419	12 (5 to –32)
Ery. od + BP od vs benzoyl peroxide	1.164	0.701	1.934	39 (7 to –11)

CL, confidence limit; NNT, number needed to treat; OR, odds ratio.

Where differences between treatments were non-significant the confidence intervals for NTT contain infinity (absolute difference of zero results in number NTT of 1/0, i.e. infinity). For instance, an interval of (9 to –8) contains 9 to infinity and –8 to minus infinity. Alternatively, this can be interpreted as NNT (harm) from 8 to infinity and NNT (benefit) from 9 to infinity, or quoted as NNTH 8 to NNTB 9.[45]

The baseline Burke and Cunliffe grade by treatment interaction was not significant (χ^2 of difference between models = 5.189, $p > 0.2$), and the only significant ratio was benzoyl peroxide to ery. + BP bd ($p = 0.046$), so the analysis has not been split by mild and moderate acne.

Facial inflamed lesion counts

The majority of the improvement in inflamed lesion count occurred within 6 weeks, although mean counts for all groups continued to improve throughout the rest of the study (*Table 6*). Since values were carried forward for missing visits (including those who did not complete the study) these postbaseline values are probably higher than if all participants completed the study.

Ranking of treatments with respect to inflamed lesion counts:

oxytetracycline < minocycline < benzoyl peroxide < ery. + BP bd < ery. od + BP od

Ranks are based only on the means, and do not necessarily imply a statistically significant difference.

The baseline by treatment interaction was significant ($p = 0.019$), so data were analysed separately for participants with baseline severity of 1.0 or more on the Burke and Cunliffe scale, and those less than 1.0 (*Table 8*; see Appendix 11). A Burke and Cunliffe grade of 1.0 was chosen as a generally accepted cut-off point between physiological (acne minor) and clinical acne (acne major).

TABLE 6 *Mean inflamed lesion counts (ITT)*

Treatment group	Week					LSmean	95% CI
	0	6	12	18	18–0		
Oxytetracycline	54.2	39.2	38.2	35.0	–19.2	–18.4	(–22.1 to –14.8)
Minocycline	54.1	35.5	30.8	31.8	–22.3	–22.0	(–25.6 to –18.3)
Benzoyl peroxide	52.3	37.1	32.7	30.0	–22.3	–22.5	(–26.1 to –18.8)
Ery. + BP bd	51.1	33.3	28.3	26.6	–24.5	–25.8	(–29.5 to –22.2)
ery. od + BP od	52.7	33.4	28.4	25.9	–26.9	–26.9	(–30.6 to –23.3)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 7*.

TABLE 7 *Changes in lesion count: differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	–3.5	–8.7	1.6
Ery. + BP bd – oxytetracycline	–7.4	–12.6	–2.2
Ery. + BP bd – minocycline	–3.9	–9.1	1.3
Ery. od + BP od – ery. + BP bd	–1.1	–6.3	4.1
Benzoyl peroxide – oxytetracycline	–4.0	–9.2	1.2
Benzoyl peroxide – minocycline	–0.5	–5.7	4.7
Benzoyl peroxide – ery. + BP bd	3.4	–1.8	8.6
Ery. od + BP od – oxytetracycline	–8.5	–13.7	–3.3
Ery. od + BP od – minocycline	–5.0	–10.1	0.2
Ery. od + BP od – benzoyl peroxide	–4.5	–9.6	0.7

TABLE 8 *Change in inflamed lesion count by baseline severity*

Treatment group	Change in inflamed lesion count (LSmeans) with 95% CI and baseline count	
	Baseline B&C grade <1.0	Baseline B&C grade ≥ 1.0
Oxytetracycline	–13.1 (–18.0 to –8.2) from 40.3 (*n* = 49)	–22.4 (–27.5 to –17.4) from 62.6 (*n* = 82)
Minocycline	–12.9 (–17.6 to –8.1) from 35.8 (*n* = 51)	–26.8 (–31.9 to –21.7) from 65.9 (*n* = 79)
Benzoyl peroxide	–16.9 (–21.8 to –12.1) from 35.8 (*n* = 50)	–26.8 (–31.9 to –21.7) from 62.6 (*n* = 80)
Ery. + BP bd	–13.4 (–18.0 to –8.8) from 40.3 (*n* = 55)	–34.3 (–39.7 to –28.9) from 59.3 (*n* = 72)
Ery. od + BP od	–17.0 (–21.7 to –12.3) from 38.8 (*n* = 52)	–34.3 (–39.5 to –29.1) from 61.9 (*n* = 79)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. Refer to *Tables 81* and *82* in Appendix 11 for comparison CIs.

Ranking for Burke and Cunliffe grade <1:

minocycline < oxytetracycline < ery. + BP bd < benzoyl peroxide < ery. od + BP od

Ranking for Burke and Cunliffe grade ≥ 1:

oxytetracycline < benzoyl peroxide = minocycline < ery. + BP bd = ery. od + BP od

Confidence intervals for analyses split by baseline severity, and ordering split into further severity categories are given in Appendix 11.

The ranks changed slightly for physiological (mild) compared with clinical (mild to moderate and moderate) acne. It should be noted that subsetting the data leads to a smaller sample size, and hence less precise results. Severity was also split into five categories with roughly equal sample sizes. Oxytetracycline was always in one of the bottom two positions and ery. od + BP od always in the top. Ery. + BP bd ranked higher for more severe acne. Numbers in these groups were even smaller and with small differences between treatments it was difficult to see any real trends.

TABLE 9 *Summary of primary outcomes at week 18*

Treatment group	Patient global		Inflamed lesion count: change from baseline (LSmeans)					
			All participants		B&C < 1.0		B&C ≥ 1.0	
	%	Rank	Change	Rank	Change	Rank	Change	Rank
Oxytetracycline	55.0	4	–18.4	5	–13.1	4	–22.4	5
Minocycline	53.8	5	–22.0	4	–12.9	5	–26.8	=3
Benzoyl peroxide	60.0	3	–22.5	3	–16.9	2	–26.8	=3
Ery. + BP bd	66.1	1	–25.8	2	–13.4	3	–34.3	=1
Ery. od + BP od	62.6	2	–26.9	1	–17.0	1	–34.3	=1

B&C, Burke and Cunliffe grade at baseline.
Ranks are based only on the means/ORs, and do not necessarily imply a statistically significant difference.

Nodules
At baseline the majority (578 or 89%) of participants were nodule free; 52 participants had one nodule, eight had two nodules, six had three nodules, one participant had four and four had five nodules.

Using ITT data, the numbers without nodules were 601 (93%), 612 (94%) and 605 (93%) at weeks 6, 12 and 18, respectively. The total number of nodules (summed over participants) decreased in all but the benzoyl peroxide group. Of those with nodules (119 participants at some time in the study), most only had one nodule, a few had two or three and only nine participants had more than three nodules at any time in the study. Although there was an overall decrease over time in the number of nodules, patterns of nodules varied between participants. Only four participants with nodules withdrew because of their spots: two on benzoyl peroxide (one, participant 0044, at week 6 and the other, participant 1182, at week 12), one on minocycline (participant 1265 at week 6) and one on ery. + BP bd (participant 1327 at week 12, owing to needing oral treatment for spots on the scalp).

Summary of primary outcomes at week 18
The ranking of treatments by primary outcome measures showed that the best response was in the two erythromycin plus benzoyl peroxide groups, and the worst response in the oral groups, although differences between groups were small (*Table 9*). For the patient global assessment, only the odds ratio of the best to the worst response (ery. + BP bd to minocycline) of 1.74 was statistically significant (95% confidence interval 1.04 to 2.90). With lesion counts, again only differences between the extremes (oxytetracycline and the two similar erythromycin and benzoyl peroxide combinations) were statistically significant: 95% confidence intervals for ery. + BP bd and ery. od + BP od versus oxytetracycline were –12.6 to –2.2 and –13.7 to –3.3, respectively.

In all treatment groups, most of the improvement seen occurred within 6 weeks, but the improvement rate/mean change continued to improve in all groups up to the end of the study period at 18 weeks. The vast majority of patients had residual acne (at least five inflamed lesions) at weeks 12 and 18. There were just two patients with a Burke and Cunliffe grade and lesion count of zero at week 12, both in the benzoyl peroxide group. At week 18 there were two (different participants) with zero grade (benzoyl peroxide and ery. + BP bd group), but only one with zero lesion count (ery. + BP bd group); the participant in the benzoyl peroxide group still had two lesions, and only 1–9% of participants (depending on treatment group) had fewer than five lesions at week 18. At week 12, 12–22% of participants (depending on treatment group) had a Burke and Cunliffe grade of no more than 0.1, and 16–40% at week 18. Data by treatment group are given in Appendix 11, and include the number of participants with a decrease of at least two-thirds in lesion count (15–31% of participants by week 12 and 21–40% by week 18).

Secondary outcomes

Burke and Cunliffe facial acne grade
The majority of the improvement in Burke and Cunliffe grade occurred within 6 weeks, although mean counts for all groups continued to improve throughout (*Table 10*). Since values were carried forward for missing visits (including those who did not complete the study) these postbaseline values are probably higher than if all participants completed the study.

TABLE 10 *Mean Burke and Cunliffe grade*

Treatment group	Week					LSmean	95% CI
	0	6	12	18	18–0		
Oxytetracycline	1.092	0.811	0.781	0.653	–0.440	–0.431	(–0.512 to –0.350)
Minocycline	1.109	0.774	0.642	0.559	–0.550	–0.543	(–0.624 to –0.462)
Benzoyl peroxide	1.117	0.788	0.679	0.614	–0.503	–0.481	(–0.562 to –0.340)
Ery. + BP bd	1.042	0.681	0.531	0.474	–0.568	–0.602	(–0.684 to –0.520)
Ery. od + BP od	1.070	0.688	0.545	0.448	–0.617	–0.638	(–0.719 to –0.557)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 11*.

TABLE 11 *Confidence intervals for Burke and Cunliffe grade differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	–0.112	–0.226	0.003
Ery. + BP bd – oxytetracycline	–0.171	–0.287	–0.056
Ery. + BP bd – minocycline	–0.060	–0.175	0.056
Ery. od + BP od – ery. + BP bd	–0.036	–0.151	0.080
Benzoyl peroxide – oxytetracycline	–0.050	–0.164	0.065
Benzoyl peroxide – minocycline	0.062	–0.053	0.177
Benzoyl peroxide – ery. + BP bd	0.121	0.006	0.237
Ery. od + BP od – oxytetracycline	–0.207	–0.322	–0.092
Ery. od + BP od – minocycline	–0.095	–0.210	0.019
Ery. od + BP od – benzoyl peroxide	–0.157	–0.272	–0.042

TABLE 12 *Change in Burke and Cunliffe grade by baseline severity*

Treatment group	Change in B&C grade (LSmeans) with 95% CI and baseline grade	
	Baseline B&C grade <1.0	Baseline B&C grade ≥ 1.0
Oxytetracycline	–0.075 (–0.141 to –0.009) from 0.400 (n = 49)	–0.665 (–0.790 to –0.539) from 1.506 (n = 82)
Minocycline	–0.143 (–0.208 to –0.078) from 0.400 (n = 51)	–0.796 (–0.924 to –0.668) from 1.566 (n = 79)
Benzoyl peroxide	–0.136 (–0.201 to –0.071) from 0.429 (n = 50)	–0.702 (–0.829 to –0.575) from 1.547 (n = 80)
Ery. + BP bd	–0.132 (–0.194 to –0.070) from 0.428 (n = 55)	–0.899 (–1.034 to –0.765) from 1.510 (n = 72)
Ery. od + BP od	–0.143 (–0.208 to –0.079) from 0.423 (n = 51)	–0.971 (–0.101 to –0.843) from 1.487 (n = 79)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately.
Refer to *Tables 87* and *88* in Appendix 11 for treatment comparison CIs.

Ranking of treatments with respect to Burke and Cunliffe grade:

oxytetracycline < benzoyl peroxide < minocycline < ery. + BP bd < ery. od + BP od

The baseline by treatment interaction is significant (p = 0.003), so results have also been presented separately for physiological (baseline Burke and Cunliffe grade <1) and clinical acne (grade ≥ 1) (*Table 12*).

Ranks for baseline B&C grade <1:

oxytetracycline < ery. + BP bd < benzoyl peroxide < minocycline = ery. od + BP od

Ranks for baseline B&C grade ≥ 1:

oxytetracycline < benzoyl peroxide < minocycline < ery. + BP bd < ery. od + BP od

The ranks changed slightly for physiological compared with clinical acne. This is probably

TABLE 13 *Percentage of participants with at least moderate improvement in facial acne severity according to the assessor*

Treatment group	Week			95% CI
	6	12	18	
Oxytetracycline	38.2	47.3	50.4	(41.8 to 59.0)
Minocycline	44.6	53.1	50.8	(42.2 to 59.4)
Benzoyl peroxide	46.2	52.3	56.9	(48.4 to 65.4)
Ery. + BP bd	50.4	61.4	59.1	(50.5 to 67.7)
Ery. od + BP od	52.7	64.1	59.5	(51.1 to 67.9)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 14*.

TABLE 14 *Assessor global improvement: logistic regression results*

Treatment comparison	Estimate of OR	Lower 95% CL	Upper 95% CL
Minocycline vs oxytetracycline	1.041	0.632	1.714
Ery. + BP bd vs oxytetracycline	1.467	0.886	2.430
Ery. + BP bd vs minocycline	1.410	0.851	2.337
Ery. od + BP od vs ery. + BP bd	1.021	0.614	1.696
Benzoyl peroxide vs oxytetracycline	1.272	0.771	2.097
Benzoyl peroxide vs minocycline	1.223	0.741	2.018
Benzoyl peroxide vs ery. + BP bd	0.867	0.522	1.440
Ery. od + BP od vs oxytetracycline	1.498	0.907	2.475
Ery. od + BP od vs minocycline	1.440	0.872	2.376
Ery. od + BP od vs benzoyl peroxide	1.178	0.711	1.950

partly a result of smaller numbers per group due to subsetting the data, and hence less precise results. See Appendix 11 for further details and confidence intervals.

Assessor global assessment of facial acne

It should be noted that participants who did not complete the study were analysed with the rating of 'no improvement'. Other missing values were substituted by values carried forward.

The assessor global assessment showed similar results to the patient assessment, with slightly lower percentages of participants improved. By 6 weeks nearly half the participants (46% overall) had at least a moderate improvement from baseline according to the assessors (*Table 13*). Only 3% were considered to be worse than at the start of the study (two in the oxytetracycline, eight minocycline, two benzoyl peroxide, three ery. + BP bd and one ery. od + BP od treatment groups). In all treatment groups, however, the percentage of people with at least a moderate improvement increased further at 12 weeks (particularly in the ery. + BP bd group) to 56% overall, but with no further overall increase at 18 weeks (55% improved). Improvement at 18 weeks was greatest with the topical treatments.

Treatment ranking with respect to assessor global:

oxytetracycline < minocycline < benzoyl peroxide < ery. + BP bd < ery. od + BP od

The baseline Burke and Cunliffe grade by treatment interaction was not significant (χ^2 of difference between models = 4.951, $p > 0.2$), and the only significant ratio was benzoyl peroxide to minocycline ($p = 0.035$), so the analysis has not been split by acne severity.

New CASS

The majority of the improvement in the new CASS occurred within 6 weeks, although mean counts for all groups continued to improve throughout the rest of the study (*Table 15*). Since values were carried forward for missing visits (including those who did not complete the study), these postbaseline values are probably higher than if all participants completed the study.

TABLE 15 *Mean CASS*

Treatment group	Week					LSmean	95% CI
	0	6	12	18	18–0		
Oxytetracycline	19.7	16.0	15.7	15.0	–4.7	–4.6	(–5.6 to –3.5)
Minocycline	19.2	15.4	14.2	13.9	–5.3	–5.5	(–6.5 to –4.5)
Benzoyl peroxide	19.8	15.9	15.1	14.3	–5.4	–5.3	(–6.3 to –4.2)
Ery. + BP bd	18.9	14.5	12.9	12.3	–6.6	–6.8	(–7.9 to –5.8)
Ery. od + BP od	19.3	14.6	13.2	12.5	–6.7	–6.8	(–7.8 to –5.7)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 16*.

TABLE 16 *Confidence intervals for CASS treatment differences*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	–1.0	–2.4	0.5
Ery. + BP bd – oxytetracycline	–2.3	–3.7	–0.8
Ery. + BP bd – minocycline	–1.3	–2.8	0.1
Ery. od + BP od – ery. + BP bd	0.1	–1.4	1.5
Benzoyl peroxide – oxytetracycline	–0.7	–2.1	0.7
Benzoyl peroxide – minocycline	0.3	–1.2	1.7
Benzoyl peroxide – ery. + BP bd	1.6	0.1	3.0
Ery. od + BP od – oxytetracycline	–2.2	–3.7	–0.8
Ery. od + BP od – minocycline	–1.3	–2.7	0.2
Ery. od + BP od – benzoyl peroxide	–1.5	–3.0	–0.1

Ranking of treatments with respect to CASS:

oxytetracycline < benzoyl peroxide < minocycline < ery. od + BP od = ery. + BP bd

The baseline by treatment interaction was not significant ($p = 0.078$), so data were not analysed separately for differing severity.

The worst aspect of having acne

For the vast majority of participants the worst aspect of having acne was its appearance. Participants thought that it was ugly (particularly pustules and big red spots), they were embarrassed and self-conscious, some felt that they looked dirty, scruffy or unprofessional, it affected the clothes they wore, some felt that they had to wear make-up, and it often affected them socially. For a significant number (56) discomfort (mainly pain and/or itching) was the main aspect bothering them. Teasing or name-calling was the worst aspect for 35 participants, while nine participants listed scarring. Several participants mentioned more than one aspect. Fourteen participants were not sure what bothered them (e.g. "it's there", "doesn't feel right", "not sure"), whereas 42 participants said they were not bothered about their acne, although by the end of the study a number of them realised that their acne had been bothering them, and were able to define and assess their worst aspect. Appendix 12 contains a list of reasons.

By 18 weeks around half the participants (slightly less than for global improvement) reported at least moderate improvement in their worst aspect of having acne (*Table 17*).

TABLE 17 *Worst aspect of having acne*

Treatment group	Week 18	95% CI
Oxytetracycline	50.4	(41.8 to 59.0)
Minocycline	46.2	(37.6 to 54.8)
Benzoyl peroxide	50.0	(41.4 to 58.6)
Ery. + BP bd	58.3	(49.7 to 66.9)
Ery. od + BP od	55.0	(46.5 to 63.5)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 18*.

TABLE 18 *Estimates from logistic regression of at least moderate improvement in worst aspect of acne*

Treatment comparison	Estimate of OR	Lower 95% CL	Upper 95% CL
Minocycline vs oxytetracycline	0.847	0.518	1.386
Ery. + BP bd vs oxytetracycline	1.381	0.841	2.270
Ery. + BP bd vs minocycline	1.630	0.991	2.683
Ery. od + BP od vs ery. + BP bd	0.878	0.533	1.445
Benzoyl peroxide vs oxytetracycline	0.960	0.587	1.568
Benzoyl peroxide vs minocycline	1.133	0.692	1.854
Benzoyl peroxide vs ery. + BP bd	0.695	0.422	1.143
Ery. od + BP od vs oxytetracycline	1.212	0.741	1.984
Ery. od + BP od vs minocycline	1.431	0.875	2.341
Ery. od + BP od vs benzoyl peroxide	1.263	0.772	2.068

TABLE 19 *Summary of secondary efficacy outcomes at week 18*

Treatment group	Burke and Cunliffe grade					
	All participants		B&C <1.0		B&C >1.0	
	Change	Rank	Change	Rank	Change	Rank
Oxytetracycline	–0.431	5	–0.075	5	–0.665	5
Minocycline	–0.543	3	–0.143	=1	–0.796	3
Benzoyl peroxide	–0.481	4	–0.136	3	–0.702	4
Ery. + BP bd	–0.602	2	–0.132	4	–0.899	2
Ery. od + BP od	–0.638	1	–0.143	=1	–0.971	1
Treatment group	**Assessor global**		**CASS**		**Worst Aspect**	
			All participants			
	%	Rank	Change	Rank	%	Rank
Oxytetracycline	50.4	5	–4.6	5	50.4	3
Minocycline	50.8	4	–5.5	3	46.2	5
Benzoyl peroxide	56.9	3	–5.3	4	50.0	4
Ery. + BP bd	59.1	2	–6.8	=1	58.3	1
Ery. od + BP od	59.5	1	–6.8	=1	55.0	2

B&C, baseline Burke and Cunliffe grade.

Treatment ranking with respect to worst aspect:

minocycline < benzoyl peroxide < oxytetracycline < ery. od + BP od < ery. + BP bd

The baseline Burke and Cunliffe grade by treatment interaction was not significant (χ^2 for difference in models = 6.458, $p > 0.15$), and the only significant ratios were benzoyl peroxide to minocycline ($p = 0.041$) and ery. + BP bd ($p = 0.037$), so the analysis has not been split by acne severity.

Summary of secondary efficacy outcomes at week 18

See *Table 19*: ranks are based only on the means/ORs, and do not necessarily imply a statistically significant difference.

Quality of life scores using the SF-36

In addition to the scale-related questions, the following standard question (number 2) was asked: "Compared to one year ago, how would you rate your health in general now?" At baseline 62% (393/636) of participants thought that their health was similar now compared to a year ago. Twelve

per cent thought that it was much better now, 20% somewhat better and 6% that it was worse. Proportions were similar at the end of the study to the beginning, apart from the minocycline group where there were 9% less in the 'somewhat better' category, and 9% more in the 'same' category. So, for most people in the study, their health in general was perceived as at least as good as a year previously. It was therefore decided not to analyse these data further as they seemed to contribute little to the study objectives.

SF-36 scales

Higher scores indicate better health for all scales. Each scale was transformed to a range of 0–100. The scales are ordered from the most valid measure of physical health (physical functioning) to the most valid measure of the mental component of health status (mental health). The most precise scales (with 20 or more levels) are physical functioning, general health, vitality and mental health.

Summary statistics for all scales are similar to population norms for the US population aged 18–24 years (31% of our sample) and the Oxford Health Life Survey (OHLS). Comparing the mean scores by age and gender with the OHLS, the Health Survey for England 1996 and British-ONS Survey 1992[46] there were higher (more healthy) scores in this study for role – physical, whereas for physical functioning some age and gender groups had higher means and some lower, although they were generally similar. The small group of women over 35 years old (n = 17) had worse scores on bodily pain, general and mental health, and the four men over 35 were worse on all but role – physical and bodily pain. Means for social functioning, role – emotional and mental health were often lower (worse) among females in this study. The under-16s looked to be a lot better healthwise, although no normative data could be found with which to compare these. So it may be that acne is particularly affecting the mental, emotional and/or social health of women over 16. Scores by age and gender are shown in Appendix 13. Although there were 108 women over the age of 25 in the study, there were only 22 men in this particular age group. Perhaps men are less likely to have acne at this age, or maybe they are less motivated to take part.

Sample sizes were too small for some of the scales;[47] only five (of 80) comparisons were significant at the 5% level, and hence probably spuriously significant. These were body pain for ery. + BP bd vs minocycline, benzoyl peroxide and ery. od + BP od, and social functioning for ery. + BP bd vs oxytetracycline and benzoyl peroxide.

Each scale gave a differing treatment ranking, although benzoyl peroxide had a lower rank more often than the other treatments, and ery. + BP bd was often ranked higher than other treatments; there were no trends for certain treatments to be ranked more highly for either the physical or emotional scales overall.

There was a small increase (improvement) in all groups for physical functioning. There were small decreases for role – physical, general health and vitality in all groups. Perhaps any excitement at taking part in the trial had worn off, or perhaps they were fed up with the extra commitment. There was little change for body pain (half the participants had none at all), role – emotional (median=100 weeks 0 and 18, all groups), mental health and social functioning (small increase in ery. + BP bd group).

Means and ranks are given in the quality of life summary at the end of this section, and in Appendix 13.

DLQI

Participants completed either the DLQI or the CDLQI (children's version) depending on their age. Thirty-four participants completed the DLQI instead of the CDLQI at one or more visits; these data were not included in the analysis as the questions are not interchangeable. The numbers analysed in each treatment group were 93, 82, 97, 90 and 97, respectively.

There was a small improvement in the total DLQI score for all groups within 6 weeks, from a mean of around 5/30 to around 3 or 4. The minocycline, ery. + BP bd and ery. od + BP od groups continued to show improvement until the end of the study. The improvement in total score for the benzoyl peroxide group was statistically significantly less than for all the other groups, although the mean differences were only one or two points on the scale, so this is probably not clinically significant. There was some improvement over time in most of the scales, apart from how much of a problem their treatment had been, which worsened. This was to be expected, as participants were required to stop treatment for the 4 weeks before starting in the study. It would seem that some participants did not understand this question on treatment, as they gave a score of greater than 0 at baseline.

Ranking of treatments with respect to DLQI total score:

benzoyl peroxide < ery. od + BP od < oxytetracycline < ery. + BP bd < minocycline

Means and confidence intervals are given in Appendix 13.

CDLQI

The majority of the improvement in the total CDLQI score occurred within 6 weeks (lower score indicates better health), although mean counts for benzoyl peroxide and minocycline groups continued to improve throughout the rest of the study. Participants completed either the CDLQI or the DLQI, depending on age, so the sample size is small (n = 34, 45, 27, 35, 30 for the treatment groups, ordered as in Chapter 2, section 'Interventions', p. 7). Twenty-one participants completed the CDLQI instead of the DLQI at one or more visits, and these data were removed, since not all questions were comparable.

The improvement in score was a result of improvements in symptoms and feelings, leisure and personal relationships. School and holidays were not affected for any of the children at any point in the study. For most children sleep was unaffected.

Ranking of treatments with respect to total CDLQI score:

oxytetracycline < ery. + BP bd = ery. od + BP od < minocycline < benzoyl peroxide

Means and confidence intervals are given in Appendix 13.

Benzoyl peroxide ranked first in this age group, whereas it ranked last in the over-16-year-olds. This difference may be a result of improved compliance under parental supervision. Alternatively, younger children may not mind using it as much.

DQOLS

For all three DQOL scales n = 639 (129, 129, 127, 126, 128 for treatment groups, respectively). The remaining participants did not have DQOLS data at any visit.

Frequency charts of score were plotted for each scale by treatment and week. The distribution of scores was similar for each treatment group.

Psychosocial scale

The majority of improvement in the DQOL psychosocial scale occurred within 6 weeks, although mean counts for all groups improved further at week 12. Week 18 scores were similar to those at week 12.

Ranking of treatments with respect to DQOL psychosocial scale:

benzoyl peroxide < oxytetracycline < ery. od + BP od < minocycline <ery. + BP bd

Scores in the oxytetracycline and benzoyl peroxide groups were similar, as were scores in the other three treatment groups.

Activities scale

Activity scores were low at baseline (means between 9 and 13/100), as would be expected for the participants in this study. There was a small improvement in mean scores post-week 0. The mean improvement for benzoyl peroxide was smaller than for the other groups (around 2 points as opposed to 4 or 5 points).

Ranking of treatments with respect to DQOL activities scale:

benzoyl peroxide < oxytetracycline < minocycline < ery. + BP bd < ery. od + BP od

Symptoms scale

The majority of the improvement in the DQOL symptom scale occurred within 6 weeks, although mean counts for all groups improved further at week 12. Week 18 scores were similar to those at week 12. Improvement in the symptom score may have been reduced initially because of irritation by the treatments. Least improvement was seen in the benzoyl peroxide group.

Ranking of treatments with respect to DQOL symptoms scale:

benzoyl peroxide < oxytetracycline < ery. + BP bd < ery. od + BP od < minocycline

Means and confidence intervals are given in Appendix 13.

Summary of change in quality of life scores at week 18

The quality of life measures used were not particularly sensitive instruments for assessing changes associated with therapy for mild to moderate inflammatory acne of the face (*Table 20*).

TABLE 20 *Summary of quality of life scores: change from baseline at week 18 (least square means)*

Treatment group	SF-36							
	Physical functioning		Role – physical		Bodily pain		General health	
	Change	Rank	Change	Rank	Change	Rank	Change	Rank
Oxytetracycline	3.9	1	–1.9	5	2.7	2	–0.6	2
Minocycline	1.7	=3	–0.6	2	0.8	3	–0.3	1
Benzoyl peroxide	2.1	2	–1.6	4	–0.6	5	–1.7	5
Ery. + BP bd	1.6	5	–0.1	1	4.7	1	–1.6	4
Ery. od + BP od	1.7	=3	–1.0	3	–0.1	4	–0.7	3

Treatment group	SF-36							
	Vitality		Social functioning		Role – emotional		Mental health	
	Change	Rank	Change	Rank	Change	Rank	Change	Rank
Oxytetracycline	–0.4	1	–0.1	4	–1.3	5	–0.6	2
Minocycline	–1.6	=4	1.2	2	–1.1	4	–1.5	4
Benzoyl peroxide	–1.6	=4	–1.4	5	1.7	1	–1.6	5
Ery. + BP bd	–1.4	3	4.6	1	0.8	2	0.6	1
Ery. od + BP od	–1.1	2	1.0	3	–0.0	3	–0.8	3

Treatment group	DLQI		CDLQI	
	Change	Rank	Change	Rank
Oxytetracycline	–1.4	4	–0.4	5
Minocycline	–2.6	1	–1.4	2
Benzoyl peroxide	–0.7	5	–1.6	1
Ery. + BP bd	–2.2	2	–1.1	=3
Ery. od + BP od	–1.9	3	–1.1	=3

Treatment group	DQOLS					
	Psychosocial		Activities		Symptoms	
	Change	Rank	Change	Rank	Change	Rank
Oxytetracycline	–8.0	4	–4.1	4	–7.4	4
Minocycline	–11.3	2	–4.3	3	–11.2	1
Benzoyl peroxide	–7.1	5	–1.8	5	–5.9	5
Ery. + BP bd	–12.0	1	–5.1	2	–8.8	3
Ery. od + BP od	–10.4	3	–5.2	1	–9.6	2

Ranks are based only on the means, and do not necessarily imply a statistically significant difference.

It is possible that they did not capture the things that really bothered the majority of participants. Overall disability was scored as low, making it hard to measure improvement, although there was a minority of more severely affected participants.

Quality of life treatment ranks were not as consistent as efficacy measures. Benzoyl peroxide generally ranked lower for quality of life than for efficacy (possibly owing to irritancy and bleaching effects), and minocycline generally ranked higher. This might be explained by an effect on truncal acne, which 65% of participants had to some extent. Although truncal acne should also respond to oxytetracycline, it may be postulated that quality of life could be adversely affected by its inconvenient dosing regimen, which may explain why its rankings did not match that of minocycline. As with the clinical parameters, the DQOLS showed most improvement during the first 6 weeks of treatment.

*Utility questionnaires (***Table 21***)*

Week 0, question 1 (WTP – cure): represents expectation of benefit of hypothetical treatment or hope of an effective treatment at the start of the

TABLE 21 *Utility questionnaires: median (mean) amount participants were willing to pay (WTP) or to accept (WTA) at baseline and after 18 weeks of treatment*

Treatment group	Week 0 (£)		Week 18 (£)			
	WTP – cure	WTA – cure	WTP – treatment received	WTA – treatment received	WTP – cure	WTA – cure
Oxytetracycline	25 (238)	500 (2568)	25 (92)	500 (1786)	100 (767)	750 (2578)
Minocycline	25 (258)	500 (2146)	25 (90)	100 (1534)	100 (722)	500 (2228)
Benzoyl peroxide	25 (211)	500 (2709)	25 (230)	500 (1852)	100 (634)	1000 (2857)
Ery. + BP bd	25 (181)	1000 (2780)	25 (211)	500 (1958)	100 (910)	500 (2584)
Ery. od + BP od	50 (410)	500 (2184)	25 (211)	500 (1506)	100 (912)	1000 (2666)

The range extends to both extremes for most questions/treatments.

study. The median amount a participant would be prepared to pay for treatment almost certain to clear spots was £50 in the ery. od + BP od group, and £25 in the rest of the treatment groups.

Week 0, question 2 (WTA – cure): at the start of the study the median amount a participant would have to be offered to take the money instead of the treatment was £500 in all but the ery. + BP bd group (£1000).

Week 18, question 1 (WTP – treatment received): this represents expectations that have/have not been realised, that is, hope removed at the end of treatment. The median amount a participant would be prepared to pay for the treatment received in the study was £25 in all treatment groups. In terms of means, participants were prepared to pay most for the topical treatments (£211–230) and least for the oral ones (£90–92).

Week 18, question 2 (WTA – treatment received): the median amount a participant would have to be offered to take the money instead of the treatment was £500 in all but the minocycline treatment group (£100).

Week 18, question 3 (WTP – cure): at the end of the study the median amount a participant would be prepared to pay for a complete cure was £100 in all groups (means greatest for the two erythromycin plus benzoyl peroxide groups), hence on average participants rated a complete cure more highly than the treatment they received.

Week 18, question 4 (WTA – cure): at the end of the study the median amount a participant would have to be offered to take the money instead of a complete cure varied between £500 and £1000, although means were similar.

Week 18 question 1 results are used in the cost-effective analysis later in this chapter (p. 38).

The range of monetary values used in the utility questionnaire was based on those used by Motley and Finlay[43] with outpatient referrals, and which were followed by pilot testing with the outpatient population at Leeds General Infirmary. In view of the age of the Motley and Finlay's original paper, the upper end of the range was extended by two additional categories (£10,000 and >£10,000). However, where a participant indicated >£10,000 these values have been excluded from the summary (mostly from the WTA questions; see Appendix 14), as the answers were often unusable or too extreme (e.g. £1 million).

Detection and quantification of antibiotic-resistant propionibacteria

There was a small number of false positives in the minocycline resistance data (60/2478 = 2%, verified by MIC estimation), obtained by direct plating onto medium containing the drug. There were 32, nine, eight and 11 at weeks 0, 6, 12 and 18, respectively. They tended to be in batches, suggesting that the drug concentration in the plates had declined, probably because the plates had been kept at too high a temperature for too long. Minocycline is a very unstable antibiotic and perhaps the study team was expecting too much to use it 'in the field'. The data obtained during the study also showed that the breakpoint used to define clinical resistance to minocycline was too high at 5 mg l^{-1}. Poor treatment outcomes on minocycline correlated better with growth in the presence of 5 mg l^{-1} of tetracycline.

Colonisation by resistant bacteria versus treatment failure

Outline results are presented below. Estimates and

TABLE 22 *Percentage (with 95% CI) of participants rating themselves at least moderately improved, split by baseline erythromycin resistance status*

	Week 12		Week 18	
Erythromycin resistance: Treatment group	**Without (*n* = 347)**	**With (*n* = 300)**	**Without (*n* = 347)**	**With (*n* = 300)**
Oxytetracycline	45.7 (34.0 to 57.4)	47.5 (35.0 to 60.0)	50.0 (38.3 to 61.7)	60.7 (48.4 to 73.0)
Minocycline	54.3 (42.6 to 66.0)	47.5 (34.8 to 60.2)	64.3 (53.1 to 75.5)	42.4 (29.8 to 55.0)
Benzoyl peroxide	50.7 (39.2 to 62.2)	49.1 (36.1 to 62.1)	61.6 (50.4 to 72.8)	57.9 (45.1 to 70.7)
Ery. + BP bd	65.2 (53.7 to 76.7)	62.3 (50.1 to 74.5)	66.7 (55.3 to 78.1)	65.6 (53.7 to 77.5)
Ery. od + BP od	60.3 (48.7 to 71.9)	50.8 (38.5 to 63.1)	66.2 (55.0 to 77.4)	58.7 (46.5 to 70.9)

The confidence intervals in this table refer to changes from baseline for each treatment separately, not treatment comparisons.

TABLE 23 *Percentage (with 95% CI) of participants rating themselves at least moderately improved, split by baseline tetracycline resistance status*

	Week 12		Week 18	
Tetracycline resistance: Treatment group	**Without (*n* = 534)**	**With (*n* = 114)**	**Without (*n* = 534)**	**With (*n* = 114)**
Oxytetracycline	48.2 (38.9 to 57.5)	36.8 (15.1 to 58.5)	56.3 (47.1 to 65.5)	47.4 (24.9 to 69.9)
Minocycline	54.2 (44.8 to 63.6)	36.4 (16.3 to 56.5)	59.8 (50.5 to 69.1)	27.3 (8.7 to 45.9)
Benzoyl peroxide	47.4 (38.2 to 56.6)	68.8 (46.1 to 91.5)	59.6 (50.6 to 68.6)	62.5 (38.8 to 86.2)
Ery. + BP bd	66.7 (57.1 to 76.3)	55.9 (39.2 to 72.6)	66.7 (57.1 to 76.3)	64.7 (48.6 to 80.8)
Ery. od + BP od	57.4 (48.1 to 66.7)	47.8 (27.4 to 68.2)	63.9 (54.8 to 73.0)	56.5 (36.2 to 76.8)

The confidence intervals in this table refer to changes from baseline for each treatment separately, not treatment comparisons.

confidence intervals from the analyses at weeks 12 and 18 are presented in Appendix 15.

In summary, there was little difference in efficacy between those who were and those who were not colonised with erythromycin-resistant subpopulations of propionibacteria, except possibly in the minocycline group, where participants colonised with isolates resistant to tetracyclines were simultaneously colonised by isolates resistant to erythromycin. However, efficacy of both tetracyclines at 18 weeks was worse in those with tetracycline resistance, although more so with minocycline than with oxytetracycline.

Patient global assessment by baseline erythromycin resistance status

Baseline erythromycin resistance was not a statistically significant factor in the analysis of patient global improvement ($p = 0.103$ week 18, $p = 0.228$ week 12) (*Table 22*). There was little difference in improvement between those with and without resistance in the benzoyl peroxide and ery. + BP bd groups, and the oxytetracycline group at week 12. The success rate, however, was lower in those with resistance in the ery. od + BP od group, and particularly in the minocycline group. In the oxytetracycline group the success rate was higher in those with resistance at week 18.

Treatment ranking with respect to patient global and erythromycin resistance at baseline:

No resistance, weeks 12 and 18:
oxytetracycline < benzoyl peroxide < minocycline < ery. od + BP od < ery. + BP bd

Resistance, week 12:
oxytetracycline = minocycline < benzoyl peroxide < ery. od + BP od < ery. + BP bd

Resistance, week 18:
minocycline < benzoyl peroxide < ery. od + BP od < oxytetracycline < ery. + BP bd

Patient global assessment by baseline tetracycline resistance status

Baseline tetracycline resistance was a significant factor in the analysis of patient global

TABLE 24 *Mean (with 95% CI) inflamed lesion counts by baseline erythromycin resistance status*

	Week 12		Week 18	
Erythromycin resistance: Treatment group	**Without (*n* = 347)**	**With (*n* = 300)**	**Without (*n* = 347)**	**With (*n* = 300)**
Oxytetracycline	–14.9 (–19.6 to –10.3)	–15.7 (–20.8 to –10.6)	–17.5 (–22.7 to –12.3)	–19.3 (–24.4 to –14.2)
Minocycline	–25.2 (–29.8 to –20.6)	–20.2 (–25.4 to –15.0)	–24.1 (–29.3 to –18.9)	–19.7 (–24.9 to –14.5)
Benzoyl peroxide	–18.9 (–23.4 to –14.4)	–20.3 (–25.5 to –15.0)	–21.8 (–26.9 to –16.7)	–22.7 (–27.9 to –17.4)
Ery. + BP bd	–21.6 (–26.3 to –16.8)	–27.0 (–32.2 to –21.8)	–23.8 (–29.2 to –18.5)	–28.3 (–33.5 to –23.1)
Ery. od + BP od	–24.3 (–29.0 to –19.6)	–24.5 (–29.5 to –19.4)	–28.0 (–33.3 to –22.6)	–26.1 (–31.1 to –21.1)

The confidence intervals in this table refer to changes from baseline for each treatment separately, not treatment comparisons.

improvement at week 18 ($p = 0.030$), but not at week 12 ($p = 0.124$), although there was a similar pattern of responses at both weeks (*Table 23*). For all treatment groups apart from benzoyl peroxide, there was a lower percentage success rate for participants with resistance than without resistance. The difference was most marked in the minocycline group, followed by the oxytetracycline group. Similar trends were seen for both lesion counts and Burke and Cunliffe grade (see following sections). It should be noted, however, that the numbers of participants with tetracycline resistance per group were small (around 20–25).

Treatment ranking with respect to patient global and tetracycline resistance at baseline:

No resistance, week 12:
benzoyl peroxide < oxytetracycline < minocycline < ery. od + BP od < ery. + BP bd
No resistance, week 18:
oxytetracycline < benzoyl peroxide < minocycline < ery. od + BP od < ery. + BP bd
Resistance, week 12:
minocycline < oxytetracycline < ery. od + BP od < ery. + BP bd < benzoyl peroxide
Resistance, week 18:
minocycline < oxytetracycline < ery. od + BP od < benzoyl peroxide < ery. + BP bd

Lesion counts by baseline erythromycin resistance status

Baseline erythromycin resistance was not a statistically significant factor in the analysis of lesion counts ($p = 0.513$ week 12, $p = 0.315$ week 18) (*Table 24*). There was little difference in counts between participants with resistance compared with those without for oxytetracycline, benzoyl peroxide and ery. od + BP od groups. In the minocycline group there was a greater drop in those without resistance, and in the ery. + BP bd group a greater drop in those with resistance.

Ranking of treatments with respect to inflamed lesion counts and erythromycin resistance:

No resistance, week 12:
oxytetracycline < benzoyl peroxide < ery. + BP bd < ery. od + BP od < minocycline
No resistance, week 18:
oxytetracycline < benzoyl peroxide < ery. + BP bd < minocycline < ery. od + BP od
Resistance, weeks 12 and 18:
oxytetracycline < minocycline < benzoyl peroxide < ery. od + BP od < ery. + BP bd

Lesion counts by baseline tetracycline resistance status

Baseline tetracycline resistance was a statistically significant factor in the analysis of lesion counts at week 12 ($p = 0.025$), but not at week 18 ($p = 0.185$) (*Table 25*). Decreases in lesion counts were less for those with resistance than those without, in both the oxytetracycline and minocycline groups, but the other way round in the topical groups. It should be noted that numbers were small in the tetracycline-resistant subset.

Ranking of treatments with respect to inflamed lesion counts and tetracycline resistance at baseline:

No resistance, week 12:
oxytetracycline < benzoyl peroxide < ery. + BP bd < ery. od + BP od < minocycline
No resistance, week 18:
oxytetracycline < benzoyl peroxide < minocycline < ery. + BP bd < ery. od + BP od
Resistance, weeks 12 and 18:
oxytetracycline < minocycline < benzoyl peroxide < ery. od + BP od < ery. + BP bd

TABLE 25 *Mean inflamed lesion counts by baseline tetracycline resistance status*

Tetracycline resistance: Treatment group	Week 12		Week 18	
	Without (n = 534)	With (n = 114)	Without (n = 534)	With (n = 114)
Oxytetracycline	–16.4 (–20.1 to –12.8)	–10.1 (–19.9 to –0.3)	–19.6 (–23.6 to –15.6)	–9.7 (–18.7 to –0.7)
Minocycline	–24.1 (–27.9 to –20.4)	–16.6 (–25.7 to –7.5)	–23.0 (–27.1 to –18.9)	–17.0 (–25.4 to –8.7)
Benzoyl peroxide	–19.1 (–22.7 to –15.4)	–23.6 (–34.2 to –13.0)	–21.5 (–25.5 to –17.6)	–27.1 (–36.8 to –17.3)
Ery. + BP bd	–23.6 (–27.6 to –19.6)	–28.2 (–36.1 to –20.3)	–24.0 (–28.3 to –19.6)	–32.8 (–39.6 to –26.0)
Ery. od + BP od	–24.0 (–27.7 to –20.3)	–24.2 (–33.3 to –15.1)	–26.1 (–30.2 to –22.0)	–29.8 (–38.1 to –21.4)

TABLE 26 *Prevalence of skin colonisation with viable and antibiotic-resistant propionibacteria at baseline*

No. of participants	% of participants colonised with propionibacteria				
	Any viable organisms	Clindamycin-resistant strains	Erythromycin-resistant strains	Minocycline-resistant[a] strains	Tetracycline-resistant strains
648	97.8	41.0	46.6	1.2	17.6

[a] Breakpoint needs redefining.

Burke and Cunliffe grade by baseline resistance status

As a less subjective and possibly more sensitive measure, Burke and Cunliffe grade was also analysed by resistance status. The results are given in Appendix 15. Again, there was little effect of erythromycin resistance on outcome, except possibly in the minocycline group, but outcomes with both tetracyclines were better in participants not colonised with tetracycline-resistant propionibacteria.

Prevalence of viable and antibiotic-resistant propionibacteria at baseline

The percentages of participants colonised with any viable propionibacteria and with isolates resistant to each antibiotic at week 0 are given in *Table 26*.

Time-related changes in the prevalence and population density (growth score) of antibiotic-resistant propionibacteria

The percentage of participants colonised by viable propionibacteria (total load) decreased slightly in all groups over time, but more markedly in the ery. + BP bd and ery. od + BP od groups, where the percentages decreased from 96% and 99% to 76% and 84%, respectively, at 6 weeks. All changes at 18 weeks from baseline were statistically significant. See Appendix 15 for standard deviations of differences.

The prevalence and population density of isolates resistant to clindamycin decreased with all three topical regimens over time, and also slightly in the minocycline group. Only the changes in the topical groups were statistically significant.

The prevalence and population density of propionibacteria resistant to erythromycin were lower at 18 weeks than at baseline for all treatment groups, but reductions were more marked with the three topical regimens. Only the changes in the topical groups were statistically significant.

At baseline, only 1.1% of participants were colonised with propionibacteria capable of growth in the presence of 5 mg l^{-1} of minocycline, and there was little change over the course of the study. The MIC of minocycline for these isolates was determined and found to be 8 mg l^{-1}. Minocycline MICs of this magnitude had not been recorded for UK isolates of propionibacteria before this study.

Neither oral regimen decreased the prevalence or population density of tetracycline-resistant propionibacteria. In contrast, all three topical regimens produced marked decreases in both parameters, which were statistically significant at 18 weeks.

TABLE 27 *Changes over time in total viable propionibacterial load*

	Mean (SD) growth scores on non-selective medium				% of participants colonised			
Week: **Treatment**	**0**	**6**	**12**	**18**	**0**	**6**	**12**	**18**
Oxytetracycline	4.2 (1.08)	3.7 (1.31)	3.8 (1.25)	3.7 (1.30)	98.5	94.7	96.2	96.2
Minocycline	4.2 (1.05)	3.6 (1.30)	3.4 (1.44)	3.4 (1.33)	97.7	96.9	93.8	95.3
Benzoyl peroxide	4.0 (1.01)	3.5 (1.20)	3.5 (1.24)	3.2 (1.34)	98.5	96.2	96.9	93.8
Ery. + BP bd	4.0 (1.22)	2.5 (1.80)	2.5 (1.80)	2.5 (1.68)	96.1	76.4	74.8	80.3
Ery. od + BP od	4.1 (0.97)	2.9 (1.63)	2.7 (1.51)	2.8 (1.55)	98.5	84.0	84.7	85.5

TABLE 28 *Changes over time in population density and prevalence of clindamycin-resistant propionibacteria*

	Mean (SD) growth scores				% of participants colonised			
Week: **Treatment**	**0**	**6**	**12**	**18**	**0**	**6**	**12**	**18**
Oxytetracycline	1.2 (1.70)	1.2 (1.69)	1.3 (1.79)	1.2 (1.69)	42.0	40.5	41.2	39.7
Minocycline	1.3 (1.76)	1.1 (1.69)	1.2 (1.72)	1.1 (1.69)	40.3	34.9	38.0	34.1
Benzoyl peroxide	1.1 (1.64)	0.8 (1.43)	0.7 (1.37)	0.6 (1.23)	37.7	26.9	26.2	22.3
Ery. + BP bd	1.2 (1.70)	0.8 (1.43)	0.9 (1.52)	0.8 (1.31)	40.2	28.3	33.1	31.5
Ery. od + BP od	1.4 (1.71)	0.8 (1.43)	0.7 (1.27)	0.8 (1.39)	45.0	29.8	26.7	30.5

TABLE 29 *Changes over time in population density and prevalence of erythromycin-resistant propionibacteria*

	Mean (SD) growth scores				% of participants colonised			
Week: **Treatment**	**0**	**6**	**12**	**18**	**0**	**6**	**12**	**18**
Oxytetracycline	1.4 (1.74)	1.3 (1.77)	1.4 (1.75)	1.2 (1.69)	47.3	42.7	46.6	42.7
Minocycline	1.5 (1.84)	1.3 (1.76)	1.4 (1.76)	1.2 (1.75)	45.7	42.6	46.5	39.5
Benzoyl peroxide	1.3 (1.76)	1.0 (1.54)	0.9 (1.54)	0.8 (1.41)	43.8	35.4	32.3	27.7
Ery. + BP bd	1.5 (1.78)	1.0 (1.51)	1.1 (1.60)	1.0 (1.39)	48.0	35.4	39.4	38.6
Ery. od + BP od	1.5 (1.80)	1.0 (1.57)	0.9 (1.41)	1.0 (1.48)	48.1	36.6	35.9	36.6

TABLE 30 *Changes over time in population density and prevalence of minocycline-resistant[a] propionibacteria*

	Mean (SD) growth scores				% of participants colonised			
Week: **Treatment**	**0**	**6**	**12**	**18**	**0**	**6**	**12**	**18**
Oxytetracycline	0.0 (0.35)	0.0 (0.26)	0.0 (0.26)	0.0 (0.35)	0.8	0.8	0.8	0.8
Minocycline	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0	0	0	0
Benzoyl peroxide	0.0 (0.39)	0.0 (0.35)	0.0 (0.00)	0.0 (0.35)	1.5	0.8	0	0.8
Ery. + BP bd	0.1 (0.44)	0.0 (0.37)	0.0 (0.27)	0.0 (0.00)	1.6	1.6	0.8	0
Ery. od + BP od	0.1 (0.56)	0.1 (0.51)	0.1 (0.56)	0.0 (0.44)	2.3	1.5	1.5	0.8

[a] This breakpoint was shown during the study to be invalid.

The percentages of participants from whom viable propionibacteria were recovered, together with mean growth scores, are given in *Tables 27–31*. Scores are on a scale of 0–5, where the higher the score the greater the population density. The biggest changes were recorded in the first 6 weeks, and are thus consistent with changes in acne severity and quality of life in this regard.

TABLE 31 *Changes over time in population density and prevalence of tetracycline-resistant propionibacteria*

	Mean (SD) growth scores				% of participants colonised			
Week: **Treatment**	**0**	**6**	**12**	**18**	**0**	**6**	**12**	**18**
Oxytetracycline	0.5 (1.32)	0.6 (1.44)	0.6 (1.39)	0.5 (1.34)	14.5	18.3	18.3	13.7
Minocycline	0.5 (1.29)	0.6 (1.35)	0.6 (1.28)	0.5 (1.29)	17.1	20.2	19.4	16.3
Benzoyl peroxide	0.4 (1.23)	0.3 (1.00)	0.3 (0.88)	0.2 (0.77)	12.3	9.2	10.0	5.4
Ery. + BP bd	0.9 (1.59)	0.5 (1.17)	0.6 (1.28)	0.4 (1.04)	26.8	15.0	19.7	18.1
Ery. od + BP od	0.6 (1.32)	0.4 (1.07)	0.3 (0.89)	0.2 (0.80)	17.6	11.5	8.4	7.6

TABLE 32 *Participants gaining and losing resistant propionibacteria during the study*

Resistant organism	Treatment group	Gained resistance	%	Lost resistance	%
Clindamycin	Oxytetracycline	12 (of 76)	16	15 (of 55)	27
	Minocycline	9 (of 77)	12	17 (of 52)	33
	Benzoyl peroxide	3 (of 81)	4	23 (of 49)	47
	Ery. + BP bd	14 (of 76)	18	25 (of 51)	49
	Ery. od + BP od	5 (of 72)	7	24 (of 59)	41
Erythromycin	Oxytetracycline	12 (of 69)	17	18 (of 62)	29
	Minocycline	12 (of 70)	17	20 (of 59)	34
	Benzoyl peroxide	4 (of 73)	5	25 (of 57)	44
	Ery. + BP bd	14 (of 66)	21	26 (of 61)	43
	Ery. od + BP od	10 (of 68)	15	25 (of 63)	40
Tetracycline	Oxytetracycline	5 (of 112)	4	6 (of 19)	32
	Minocycline	8 (of 107)	7	9 (of 22)	41
	Benzoyl peroxide	2 (of 114)	2	11 (of 16)	69
	Ery. + BP bd	9 (of 93)	10	20 (of 34)	59
	Ery. od + BP od	2 (of 108)	2	15 (of 23)	65

Although benzoyl peroxide is a recognised antiresistance agent, the authors were surprised to find that population densities of viable propionibacteria, and variants resistant to erythromycin, fell by a larger amount when the regimen contained topical erythromycin than for benzoyl peroxide alone. In the very small sample ($n = 20$) given topical erythromycin alone, reductions were not as large as those in the combination group (see Appendix 18).

There was considerable within- and between-group variability in both the population density and prevalence of isolates resistant to tetracycline even at baseline, probably a reflection of the lower population densities and the inability to detect small numbers reliably. By week 18, only two of the eight patients with propionibacteria resistant to 5 mg l^{-1} of minocycline pretreatment remained colonised. One had received oxytetracycline and the other benzoyl peroxide.

Participants gaining and losing resistant propionibacteria

A number of participants who had resistant propionibacteria at baseline had lost them by week 18, and others who had no resistant isolates at baseline had gained them. These numbers are summarised in *Table 32*.

More people lost than gained resistant organisms in all treatment groups, but particularly in the benzoyl peroxide group. A slightly higher percentage of participants lost resistance in the topical groups than in the oral groups. The lowest percentages of participants gaining resistant organisms or colonised with higher numbers of resistant organisms compared with baseline were in the benzoyl peroxide group (the only one with no selective pressure) (*Table 33*).

Efficacy by resistance status at week 18

The same analyses as above were performed for efficacy by baseline resistance status, this time for resistance status at week 18. The results for week 18 status were very similar to those obtained for baseline status.

Summary of microbiology results

Carriage rates for antibiotic-resistant propionibacteria in the community (*Table 34*) were slightly lower than among outpatients

TABLE 33 *Participants[a] who became colonised with increased numbers of resistant propionibacteria (higher growth score) during the active treatment phase*

Resistance	Treatment group	Increased growth score (*n*)	%
Clindamycin	Oxytetracycline	23 (of 122)	19
	Minocycline	16 (of 118)	14
	Benzoyl peroxide	7 (of 124)	6
	Ery. + BP bd	16 (of 120)	13
	Ery. od + BP od	10 (of 126)	8
Erythromycin	Oxytetracycline	22 (of 121)	18
	Minocycline	21 (of 115)	18
	Benzoyl peroxide	8 (of 120)	7
	Ery. + BP bd	22 (of 117)	19
	Ery. od + BP od	13 (of 123)	11
Tetracycline	Oxytetracycline	9 (of 128)	7
	Minocycline	13 (of 125)	10
	Benzoyl peroxide	2 (of 127)	2
	Ery. + BP bd	11 (of 122)	9
	Ery. od + BP od	3 (of 130)	2

[a] (Of those who didn't already have confluent growth.)

TABLE 34 *Baseline prevalence of skin colonisation with resistant propionibacteria among all participants (n = 760)*

% of participants colonised with propionibacteria				
Any viable organisms	**Clindamycin-resistant strains**	**Erythromycin-resistant strains**	**Minocycline-resistant[a] strains**	**Tetracycline-resistant strains**
98.0	42.1	47.5	1.1	17.6

[a] Breakpoint needs redefining.

attending the dermatology clinic in Leeds over the same period,[32] but still high, with no difference between the Leeds and Nottingham centres in the present study. Population densities (growth scores) were also lower in this community sample compared with outpatients (mean 1.5 for erythromycin-resistant isolates in the trial at baseline compared with >3.0 for outpatients).

Although all five treatments reduced total propionibacterial numbers, both erythromycin-containing regimens worked best. These same two regimens reduced the prevalence of skin colonisation with propionibacteria by 16% (ery. + BP bd) and 13% (ery. od + BP od); 20% and 14% of participants, respectively (compared with around 5% in the other groups), yielded no viable organisms at all.

Both erythromycin-containing regimens and benzoyl peroxide alone reduced the extent of skin colonisation with erythromycin-resistant and tetracycline-resistant propionibacteria in terms of mean growth scores and prevalence. In comparison, the tetracyclines had minimal effect on the prevalence or population density of propionibacteria resistant to erythromycin or tetracycline. This may, however, be explained by their overall weak antibacterial effect *in vivo* compared with the other regimens.

Resistance in cutaneous propionibacteria did not compromise outcomes on any of the three benzoyl peroxide-containing regimens, although efficacy was reduced in groups with tetracycline resistance for both tetracyclines, but minocycline in particular (according to patients' self-assessment). With only around 20–25 participants with tetracycline resistance per treatment group, some caution is advised in interpretation of these results.

Cost-effectiveness of treatments for facial acne

Cost effectiveness data are shown in *Tables 35–39*. Treatment ranks are based on means, with ranks for medians in parentheses if these differ. Both

TABLE 35 *Cost-effectiveness at week 18 based on the ratios of patient global assessment (at least moderately improved) to the cost of treatment*

Treatment group	*n*	Mean	Median	SD	Min.	Max.	Rank
Oxytetracycline	131	0.0240	0.0307	0.0257	0.00	0.07	3
Minocycline	130	0.0045	0.0072	0.0043	0.00	0.01	5
Benzoyl peroxide	130	0.0554	0.0421	0.0676	0.00	0.17	1
Ery. + BP bd (3)	127	0.0117	0.0157	0.0089	0.00	0.02	4
Ery. od + BP od	131	0.0319	0.0329	0.0315	0.00	0.08	2
Ery. + BP bd (2)	127	0.0164	0.0206	0.0129	0.00	0.03	4

(3), three packs; (2), two packs. The requirement for 18 weeks of treatment with benzoyl peroxide once daily exceeded two packs by a small amount. Hence, ratios were also calculated based on the assumption that two packs may be sufficient in some cases.

TABLE 36 *Confidence intervals for differences between treatments, and ratios of means, in cost-effectiveness at week 18 based on the ratios of patient global assessment (at least moderately improved) to the cost of treatment*

Treatment comparison	Difference	Lower 95% CL	Upper 95% CL	Ratio of means[a]	Inverse of ratio
Minocycline vs oxytetracycline	–0.0195	–0.0240	–0.0150	0.188	5.333
Ery. + BP bd vs oxytetracycline	–0.0123	–0.0170	–0.0076	0.489	2.051
Ery. + BP bd vs minocycline	0.0072	0.0055	0.0089	2.600	0.385
Ery. od + BP od vs ery. + BP bd	0.0202	0.0146	0.0258	2.727	0.367
Benzoyl peroxide vs oxytetracycline	0.0314	0.0190	0.0438	2.308	0.433
Benzoyl peroxide vs minocycline	0.0509	0.0393	0.0625	12.311	0.081
Benzoyl peroxide vs ery. + BP bd	0.0437	0.0320	0.0554	4.735	0.211
Ery. od + BP od vs oxytetracycline	0.0079	0.0009	0.0149	1.329	0.752
Ery. od + BP od vs minocycline	0.0274	0.0220	0.0328	7.089	0.141
Ery. od + BP od vs benzoyl peroxide	–0.0235	–0.0363	–0.0107	0.576	1.737

[a] Confidence intervals for the ratios are not available because some individual values are negative, and hence cannot be logged for the calculations.

means and medians are given. Although medians are probably more robust for this type of data, means may be more useful for considering costs, and comments on relative cost-effectiveness in the text refer to means.[48] Costs of 18 weeks of treatment and other cost components are given in Appendix 3.

The same rank order is produced by each of the four analyses irrespective of the use of medians or means, except when median ratios of patient global assessment at week 12 were used. Additional analyses (patient global, change in lesion count, WTP and WTA versus cost in weeks) show the same ordering, except for lesion change medians and WPT means; however, benzoyl peroxide (the most cost-effective) and minocycline (the least cost-effective) remain in the same positions for all analyses (see Appendix 14 for details).

The WTP (question 1; summarised over treatments) at baseline did not appear to be dependent on initial acne severity. WTP at week 18 (for the treatment received) generally increased with degree of improvement (participant assessed), except for the category 'worse', for which there was a higher mean and median than for 'no improvement', although numbers were small in these categories (see Appendix 14).

Concomitant medications

See Appendix 16 for a list of these.

TABLE 37 *Cost-effectiveness at week 18 based on the ratios of change in lesion count to the cost of treatment*

Treatment group	*n*	Mean	Median	SD	Min.	Max.	Rank
Oxytetracycline	131	–0.794	–0.460	1.265	–5.42	2.33	3
Minocycline	130	–0.187	–0.142	0.251	–1.35	0.36	5
Benzoyl peroxide	129	–1.684	–1.052	2.699	–15.10	2.95	1
Ery. + BP bd (3)	127	–0.422	–0.392	0.559	–3.75	1.99	4
Ery. od + BP od	131	–1.286	–0.804	1.562	–7.15	0.66	2
Ery. + BP bd (2)	127	–0.582	–0.524	0.786	–5.63	2.62	4

(3), three packs; (2), two packs. See footnote to *Table 35* for explanation.

TABLE 38 *Cost-effectiveness at week 12 based on the ratios of patient global (at least moderate improvement) to the cost of treatment*

Treatment group	*n*	Mean	Median	SD	Min.	Max.	Rank (median)
Oxytetracycline	131	0.0268	0.0000	0.0361	0.00	0.10	3 (5)
Minocycline	130	0.0061	0.0071	0.0061	0.00	0.01	5 (3)
Benzoyl peroxide	130	0.0604	0.0067	0.0953	0.00	0.26	1 (4)
Ery. + BP bd	127	0.0148	0.0206	0.0123	0.00	0.03	4 (2)
Ery. od + BP od	131	0.0320	0.0351	0.0364	0.00	0.10	2 (1)

TABLE 39 *Cost-effectiveness at week 12 based on the ratios of change in lesion count to the cost of treatment*

Treatment group	*n*	Mean	Median	SD	Min.	Max.	Rank
Oxytetracycline	131	–0.890	–0.433	1.578	–6.89	4.12	3
Minocycline	130	–0.274	–0.220	0.315	–1.35	0.47	5
Benzoyl peroxide	129	–2.062	–0.916	3.989	–23.18	4.43	1
Ery. + BP bd	127	–0.536	–0.458	0.737	–5.44	2.62	4
Ery. od + BP od	131	–1.313	–0.807	1.638	–7.60	0.84	2

Ancillary analyses

The primary end-points were examined separately for participants recruited from surgeries and colleges, and also for each assessor.

Patient global improvement was generally better in college- than in surgery-recruited participants, although lesion counts were fairly similar, except for the benzoyl peroxide and ery. od + BP od groups, for which the results were better in college students. Perhaps a higher level of education enabled students to better comply with treatment regimens, and may also have led to different expectations and hence different global assessments. In terms of the measured baseline characteristics, there was little difference in ages (college: n = 82, mean = 18.9, range 14–25 years; surgery: n = 566, mean = 19.8, range 11–42 years). There was a lower reported previous use of prescription medication for acne in college students (70% versus 93%) and topical medications (63% versus 85%), but not in oral medications (56% versus 60%) or OTC medications (84% versus 88%). These differences should be taken in context, however, as only 13% (83) of study participants were recruited from colleges.

There were differences in baseline lesion counts and changes between the assessors. Monitoring sessions showed that the assessors counted different numbers of spots on the same people; however, intra-assessor (within) variation was less than interassessor (between) variation (data only part analysed), and each participant was assessed by the same assessor at each visit. The ordering of treatments was generally similar. For both the patient and the assessor global, success rates were generally smaller for participants of assessor 3 than the others. Patient global treatment rankings were generally similar for each assessor (except for assessor 1, who was responsible for only four or

TABLE 40 *Number of participants with adverse events by visit*

	Week 6				Week 12				Week 18			
Treatment group	**GI**	**CNS**	**Skin**	**M/S**	**GI**	**CNS**	**Skin**	**M/S**	**GI**	**CNS**	**Skin**	**M/S**
Oxytetracycline	22	11	5	0	4	0	3	0	1	1	1	0
Minocycline	14	12	5	0	8	5	4	3	2	2	2	5
Benzoyl peroxide	8	2	17	0	3	2	2	1	0	1	3	0
Ery. + BP bd	8	4	11	0	6	3	3	1	4	2	2	2
Ery. od + BP od	8	2	11	0	4	1	4	1	1	3	1	2

GI, gastrointestinal; CNS, central nervous system; M/S, musculoskeletal.

five participants per treatment group); however, treatment rankings for assessor global differed between the assessors (particularly assessor 2, for whom minocycline ranked higher and ery. + BP bd ranked lower than for the other assessors; this was probably a chance finding due to small sample variability, as assessors were blinded to treatment, all of which were active anyway). Assessor 3 also gave lower CASS values. Burke and Cunliffe grades were higher for assessor 2. Again, there are inherent difficulties in looking at results for subsets of participants, as the sample size is too small for reasonable treatment comparisons. Assessor was included as a covariate in all analyses.

Adverse events and side-effects

Adverse events

Overall, 28% of participants reported at least one adverse event in the study. The number of participants reporting an adverse event at week 6 was 164/581 (28%), with slightly more in the oral groups, decreasing to 78/514 (15%) at week 12 (similar numbers per group) and 66/475 (14%) at week 18.

Sometimes the same adverse event was ongoing at more than one visit, and sometimes more than one episode of the same adverse event occurred during the same visit period. In *Table 40*, participants are only counted once within a category at a visit, but the same adverse event may be counted at more than one visit if it is of long duration; thus, this represents the number of participants who experienced any adverse event in that body system category at that visit.

The adverse events (by classification) for which the largest between-group differences in incidence were reported are summarised in *Table 40*.

Gastrointestinal (GI) adverse events consisted mainly of upset stomachs and nausea, CNS events were mostly headaches, and skin conditions were mostly severe irritation. By week 12 the incidence of these adverse events had decreased, although GI and CNS adverse events were still slightly higher in the minocycline group.

The number of musculoskeletal adverse events in the minocycline group rose from none at week 6 to three at week 12 (two incidences of and one exacerbation of joint pain) and five at week 18 (one sprained ankle, one possible fractured wrist, one exacerbation of ankle injury, one knee burning/aching sensation and one joint pain). The incidence of such events was lower in the other groups. Also, in the minocycline group there were two transient cases of skin pigmentation one each at week 6 and week 12.

Vaginal candidosis (included under infections as either thrush or *Candida*) occurred in six people in the oxytetracycline group (one patient had several episodes), three people in the minocycline group (one patient had several episodes), two people in the benzoyl peroxide group, one person in the ery. + BP bd group and two people in the ery. od + BP od group. Details can be found in Appendix 17.

Local irritation

Participant assessment of local irritation

A majority of participants experienced local symptoms pretreatment and many appeared to find it hard to distinguish between symptoms of acne and symptoms of intolerance. Despite higher than expected baseline incidences, treatment-related changes over time were detected (*Table 41*).

Participant-reported stinging

In the topical groups there was an increase in incidence from 27–36% to 39–46% in the first 2 weeks, but then a return to baseline levels,

TABLE 41 *Number (percentage) of participants reporting local irritation of any severity (mild, moderate or severe)*

		Week					
Treatment group		**0**	**0–2**	**2–4**	**4–6**	**12**	**18**
Stinging	Oxytetracycline	46 (35.4)	34 (26.2)	22 (16.9)	16 (12.3)	25 (19.2)	16 (12.3)
	Minocycline	37 (28.5)	35 (26.9)	22 (16.9)	14 (10.8)	19 (14.6)	15 (11.5)
	Benzoyl peroxide	35 (26.9)	51 (39.2)	33 (25.4)	21 (16.2)	26 (20.0)	21 (16.2)
	Ery. + BP bd	39 (30.7)	50 (39.4)	36 (28.3)	24 (18.9)	20 (15.7)	19 (15.0)
	Ery. od + BP od	47 (35.9)	60 (45.8)	38 (29.0)	21 (16.0)	26 (19.8)	21 (16.0)
Burning	Oxytetracycline	15 (11.5)	21 (16.2)	11 (8.5)	7 (5.4)	15 (11.5)	10 (7.7)
	Minocycline	15 (11.5)	15 (11.5)	13 (10.0)	10 (7.7)	11 (8.5)	8 (6.2)
	Benzoyl peroxide	22 (16.9)	48 (36.9)	24 (18.5)	17 (13.1)	24 (18.5)	18 (13.8)
	Ery. + BP bd	15 (11.8)	34 (26.8)	20 (15.7)	13 (10.2)	9 (7.1)	10 (7.9)
	Ery. od + BP od	14 (10.7)	45 (34.4)	25 (19.1)	12 (9.2)	16 (12.2)	15 (11.5)
Dryness	Oxytetracycline	80 (61.5)	67 (51.5)	55 (42.3)	45 (34.6)	59 (45.4)	52 (40.0)
	Minocycline	89 (68.5)	66 (50.8)	55 (42.3)	50 (38.5)	57 (43.8)	50 (38.5)
	Benzoyl peroxide	82 (63.1)	102 (78.5)	85 (65.4)	85 (65.4)	83 (63.8)	81 (62.3)
	Ery. + BP bd	88 (69.3)	107 (84.3)	90 (70.9)	75 (59.1)	93 (73.2)	72 (56.7)
	Ery. od + BP od	83 (63.4)	97 (74.0)	84 (64.1)	72 (55.0)	66 (50.4)	71 (54.2)
Erythema	Oxytetracycline	104 (80.0)	66 (50.8)	55 (42.3)	48 (36.9)	69 (53.1)	64 (49.2)
	Minocycline	102 (78.5)	76 (58.5)	63 (48.5)	56 (43.1)	55 (42.3)	55 (42.3)
	Benzoyl peroxide	102 (78.5)	98 (75.4)	77 (59.2)	65 (50.0)	73 (56.2)	71 (54.6)
	Ery. + BP bd	96 (75.6)	80 (63.0)	74 (58.3)	59 (46.5)	71 (55.9)	58 (45.7)
	Ery. od + BP od	100 (76.3)	85 (64.9)	65 (49.6)	57 (43.5)	63 (48.1)	56 (42.7)
Scale	Oxytetracycline	81 (62.3)	50 (38.5)	39 (30.0)	30 (23.1)	42 (32.3)	38 (29.2)
	Minocycline	72 (55.4)	46 (35.4)	37 (28.5)	33 (25.4)	35 (26.9)	37 (28.5)
	Benzoyl peroxide	73 (56.2)	77 (59.2)	62 (47.7)	57 (43.8)	61 (46.9)	56 (43.1)
	Ery. + BP bd	80 (63.0)	67 (52.8)	57 (44.9)	45 (35.4)	54 (42.5)	49 (38.6)
	Ery. od + BP od	64 (48.9)	64 (48.9)	51 (38.9)	34 (26.0)	47 (35.9)	35 (26.7)
Itching	Oxytetracycline	72 (55.4)	59 (45.4)	43 (33.1)	38 (29.2)	52 (40.0)	43 (33.1)
	Minocycline	74 (56.9)	54 (41.5)	41 (31.5)	40 (30.8)	47 (36.2)	45 (34.6)
	Benzoyl peroxide	76 (58.5)	71 (54.6)	58 (44.6)	50 (38.5)	60 (46.2)	54 (41.5)
	Ery. + BP bd	75 (59.1)	66 (52.0)	54 (42.5)	46 (36.2)	51 (40.2)	43 (33.9)
	Ery. od + BP od	66 (50.4)	59 (45.0)	45 (34.4)	42 (32.1)	44 (33.6)	39 (29.8)

followed by a decrease to below baseline (around 16%). Moderate or severe stinging virtually doubled from 9–12% to 15–22% in the first 2 weeks, then returned to baseline levels (see Appendix 17 for details of moderate or severe symptoms). In the oral groups incidence decreased over the first 4 weeks from 35%/29% to 17%.

Participant-reported burning

In the topical groups incidence more than doubled to around 27–37% in the first 2 weeks, but then returned to baseline levels. Moderate or severe burning increased from around 1–4% to 10–18% in the first 2 weeks, then dropped to 3–8% during 2–4 weeks. It remained slightly raised throughout the study in the benzoyl peroxide group. There was little change over time in the oral groups.

Participant-reported dryness

In the topical groups incidence increased in the first 2 weeks from 63–69% to 74–84%, but then returned to baseline levels in the benzoyl peroxide group and below baseline in the other groups. Moderate/severe dryness increased from 18–22% to 41–54% in the first 2 weeks, then decreased to 23–32% at 2–4 weeks and further to 15–24% at 4–6 weeks. In the oral groups dryness incidence decreased from 62%/69% to 39%/40% by the end of the study; moderate/severe dryness decreased from 15%/17% to 4%/7%. This could be a result of increased use of moisturiser from around half of participants at baseline to two-thirds in the oral groups and four-fifths in the topical groups.

Participant-reported erythema

In all groups incidence decreased over the study from 76–80% to 42–55%, with slightly less of an

increase in the benzoyl peroxide group. Moderate/severe erythema decreased from 41–47% to 23–29% at 0–2 weeks for all groups, except for benzoyl peroxide where there was little change (44%), and from then on decreased for all groups, with benzoyl peroxide remaining the highest of the groups. By week 18 moderate/severe erythema was reported in 15–21% of participants.

Participant-reported scale
The incidence decreased in all groups from around 55–63% to 27–43% by week 18, with the greater decreases in the oral groups. Moderate/severe scale was reported in 9–15% of participants at baseline, and decreased over the study in the oral groups, but increased in the active topical regimens at 0–2 weeks, thereafter decreasing to less than baseline.

Participant-reported itch
The incidence decreased in all groups from around 55–59% to one-third by the end of the study. Moderate/severe itch was reported in 15–20% of participants at baseline. It decreased over time in the oral groups. In the topical groups it increased at 0–2 weeks, but then decreased to below baseline levels.

Severe irritation
This generally had a higher incidence in the topical groups than in the oral groups, particularly with benzoyl peroxide (see Appendix 17).

It is worth noting that ITT analysis is likely to have resulted in smaller peak incidences over the first 6 weeks and greater irritation in later weeks than would probably have occurred if there had been no withdrawals. This is because very early withdrawals dilute the peak effect by minimal baseline irritation carried forward, and later withdrawals result in an increase in later irritation owing to peak irritation carried forward.

Assessor appraisal of local irritation
Applying a moisturiser makes assessment of dryness and scaling by a third party difficult. This may lead to differences between assessor and participant scores for these aspects of local irritancy. In this study, where there was a difference, assessor scores tended to be higher (*Table 42*) (see paragraph on comparison, after discussion of assessor-reported irritation).

Assessor-recorded dryness
The incidence increased in the benzoyl peroxide and ery. + BP bd groups at 6 weeks to 82% and 78%, respectively, with no change in the ery. od + BP od group, and a decrease in the oral groups to 64% and 60% for oxytetracycline and minocycline, respectively. There was little change at week 12, but at week 18 dryness had decreased in all groups to 56–58% in the oral groups and 60–69% in the topical groups. Moderate/severe dryness occurred in 11–19% of participants at baseline (see Appendix 17). In the oxytetracycline group this halved at week 6, and remained similar for the rest of the study. It changed little in the minocycline group throughout. Moderate/severe dryness increased in the topical groups at week 6, particularly in the benzoyl peroxide (28%) and

TABLE 42 *Assessor-reported local irritation of any severity*

		Week			
Treatment group		**0**	**6**	**12**	**18**
Dryness	Oxytetracycline	95 (72.5)	84 (64.1)	85 (64.9)	76 (58.0)
	Minocycline	92 (70.8)	78 (60.0)	87 (66.9)	73 (56.2)
	Benzoyl peroxide	93 (71.5)	106 (81.5)	96 (73.8)	90 (69.2)
	Ery. + BP bd	91 (71.7)	99 (78.0)	98 (77.2)	87 (68.5)
	Ery. od + BP od	94 (71.8)	92 (70.2)	96 (73.3)	79 (60.3)
Erythema	Oxytetracycline	110 (84.0)	93 (71.0)	95 (72.5)	85 (64.9)
	Minocycline	107 (82.3)	92 (70.8)	90 (69.2)	78 (60.0)
	Benzoyl peroxide	107 (82.3)	101 (77.7)	95 (73.1)	88 (67.7)
	Ery. + BP bd	105 (82.7)	97 (76.4)	89 (70.1)	79 (62.2)
	Ery. od + BP od	103 (78.6)	87 (66.4)	82 (62.6)	68 (51.9)
Scale	Oxytetracycline	57 (43.5)	49 (37.4)	49 (37.4)	37 (28.2)
	Minocycline	60 (46.2)	55 (42.3)	53 (40.8)	49 (37.7)
	Benzoyl peroxide	66 (50.8)	69 (53.1)	70 (53.8)	59 (45.4)
	Ery. + BP bd	62 (48.8)	68 (53.5)	66 (52.0)	58 (45.7)
	Ery. od + BP od	68 (52.3)	61 (46.9)	57 (43.8)	45 (34.6)

ery. + BP bd (26%) groups, less so in the ery. od + BP od group (18%).

Assessor-recorded erythema
The incidence of erythema decreased by week 6, and again between weeks 12 and 18 in all treatment groups. Moderate/severe erythema was recorded in 28–36% of participants at baseline, decreasing in all groups at week 6, although less so in the benzoyl peroxide group (see Appendix 17). Decreases in the incidence of moderate/severe erythema continued in all but the oxytetracycline and ery. od + BP od groups at 12 and 18 weeks.

Assessor-recorded scale
The incidence was 44–52% at baseline. It increased slightly in the benzoyl peroxide and ery. + BP bd groups and decreased slightly in the other groups at week 6, was unchanged at week 12, and then decreased in all groups to 28–46% at week 18. Moderate/severe scale was recorded in only 4–7% of participants at baseline, decreasing slightly in the oral groups and rising slightly in the topical groups, particularly benzoyl peroxide (from 5% to 11% at week 6; see Appendix 17).

Severe irritation
Overall, there was a higher incidence of severe irritation in the active topical groups, particularly in the benzoyl peroxide-treated group (see Appendix 17).

Differences between assessor and patient severity rating
For the three categories assessed by both the assessor and participant, the same severity was recorded in 50%, 56% and 59% of cases for dryness, erythema and scale, respectively. The assessor recorded greater severity in 31%, 28% and 23% of cases, and the participant recorded greater severity in 19%, 16% and 18% of cases for dryness, erythema and scale, respectively. The discrepancy was by two or three categories in only 4%, 6% and 4% of cases, respectively.

Early withdrawal versus irritation
Perhaps not surprisingly more severe side-effects (those with a moderate or severe rating) within the first 6 weeks were related to greater likelihood of not completing the study, in particular where the participant rated erythema, stinging or burning as severe.

Plots of irritation
Nested plots (one per irritation per week, with nested severity) gave a good visual impression of the differences between treatments, but with 48 plots in total, only plots of participant-assessed burning, stinging and dryness at week 2 have been presented (*Figures 5–7*). These showed the most marked differences between treatment groups.

Worst case analysis of irritation scores
A between-treatment comparison of the percentage of participants with at least moderate severity irritation at some point of the study again indicated worse irritation in the topical treatment groups which, for all but erythema and itching, was statistically significant (*Table 43*).

Overall irritation index
Maximum possible scores were reached in some patients for the patient six-scale index from 0–2 weeks onwards in the benzoyl peroxide and ery. od + BP od groups, and for the assessor scale for minocycline at week 0, benzoyl peroxide & ery. od + BP od from weeks 0–2 onwards, and ery. + BP bd at week 12 (*Tables 44* and *45*).

The differences in change from baseline between the two oral groups were similar (and not statistically significant) for all three indices at any week. In the first two weeks (0–2 weeks) irritation was significantly higher in the topical groups than

Table 43 *Percentage of participants whose worst case irritation score over the study was either moderate or severe*

	Assessor			Patient					
Treatment group	**Dryness**	**Erythema**	**Scale**	**Stinging**	**Burning**	**Dryness**	**Erythema**	**Scale**	**Itching**
Oxytetracycline	18.3	29.8	5.3	10.0	4.6	27.7	32.3	15.4	14.3
Minocycline	15.4	28.5	5.4	10.8	5.4	25.4	37.7	9.2	16.2
Benzoyl peroxide	37.7	33.1	16.9	26.2	20.8	63.9	49.2	34.6	24.6
Ery. + BP bd	31.5	27.6	14.2	20.5	11.8	55.9	38.6	28.4	22.1
Ery. od + BP od	26.0	24.4	11.5	20.6	15.3	50.4	36.6	22.9	22.9
Cochran–Mantel–Haenszel test for difference between treatment groups									
p-Value:	0.001	0.637	0.005	0.002	0.001	0.001	0.073	0.001	0.230

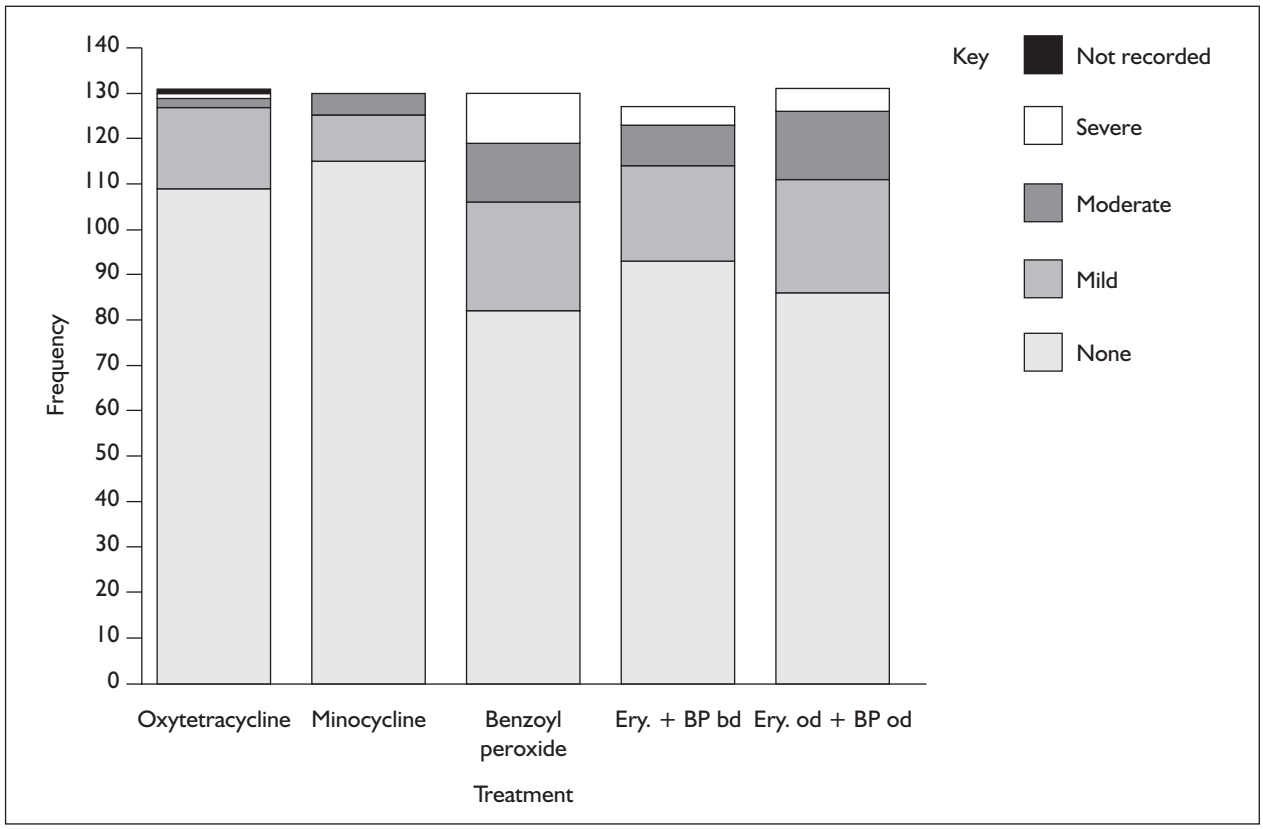

FIGURE 5 *Participant-reported burning, ITT analysis for weeks 0–2*

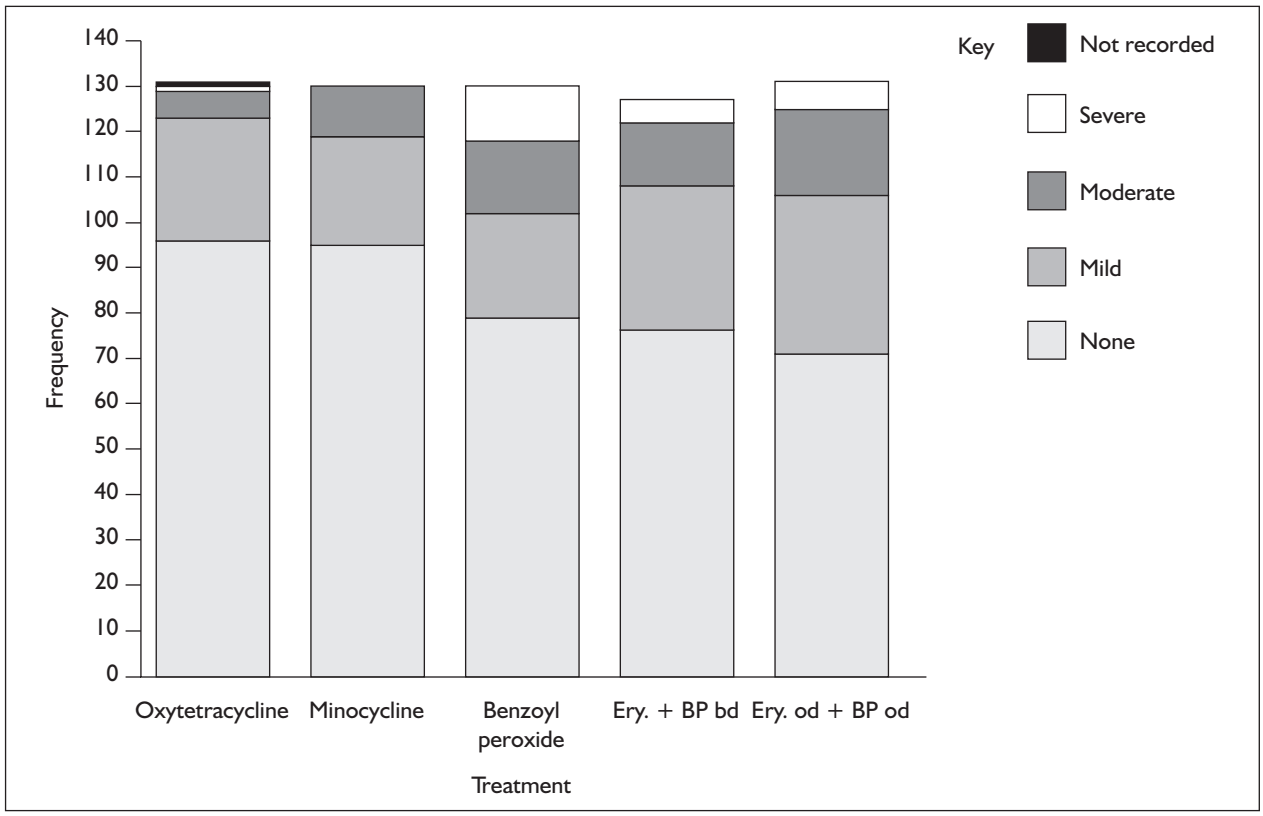

FIGURE 6 *Participant-reported stinging, ITT analysis for weeks 0–2*

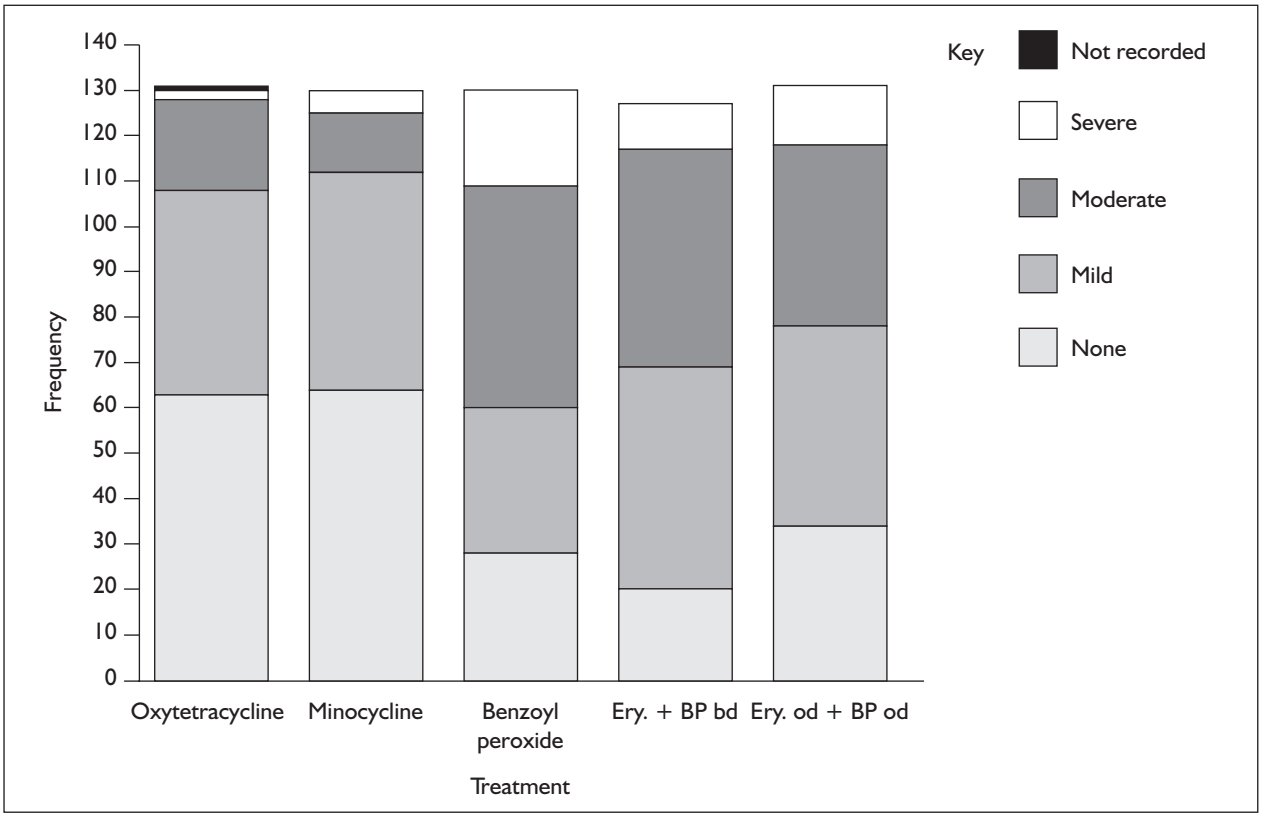

FIGURE 7 *Participant-reported dryness, ITT analysis for weeks 0–2*

TABLE 44 *Overall irritation index: mean scores*

Treatment group		Week 0	0–2	2–4	4–6	12	18
Patient index (max. = 18)	Oxytetracycline	4.3	3.0	2.1	1.7	2.6	2.1
	Minocycline	4.1	3.0	2.2	2.0	2.1	2.0
	Benzoyl peroxide	4.2	5.9	3.8	3.2	3.6	3.3
	Ery. + BP bd	4.2	4.8	3.4	2.6	3.0	2.6
	Ery. od + BP od	4.0	4.9	3.2	2.4	2.7	2.5
Assessor index (max. = 9)	Oxytetracycline	2.6	–	–	2.0	2.2	1.8
	Minocycline	2.5	–	–	2.0	2.1	1.9
	Benzoyl peroxide	2.6	–	–	2.8	2.6	2.4
	Ery. + BP bd	2.5	–	–	2.6	2.4	2.2
	Ery. od + BP od	2.5	–	–	2.3	2.2	1.8
Patient index (max. = 9)	Oxytetracycline	2.9	1.9	1.5	1.1	1.7	1.4
	Minocycline	2.8	2.0	1.5	1.3	1.4	1.4
	Benzoyl peroxide	2.8	3.8	2.6	2.3	2.4	2.2
	Ery. + BP bd	2.9	3.0	2.3	1.8	2.2	1.8
	Ery. od + BP od	2.7	3.0	2.2	1.7	1.8	1.7

The assessor index was not recorded at weeks 0–2 and 2–4.

TABLE 45 *Standard deviations for mean overall irritation scores*

Treatment group		Week 0	0–2	2–4	4–6	12	18
Patient index (max. = 18)	Oxytetracycline	2.41	2.75	2.45	2.08	2.66	2.26
	Minocycline	2.52	2.79	2.34	2.39	2.14	2.19
	Benzoyl peroxide	2.52	4.46	3.67	3.35	3.60	3.35
	Ery. + BP bd	2.33	3.30	2.98	2.74	2.54	2.56
	Ery. od + BP od	2.69	3.87	3.13	2.90	2.96	2.98
Assessor index (max. = 9)	Oxytetracycline	1.58	–	–	1.42	1.61	1.56
	Minocycline	1.51	–	–	1.34	1.47	1.64
	Benzoyl peroxide	1.53	–	–	1.68	1.63	1.78
	Ery. + BP bd	1.37	–	–	1.49	1.47	1.63
	Ery. od + BP od	1.56	–	–	1.63	1.54	1.52
Patient index (max. = 9)	Oxytetracycline	1.59	1.83	1.63	1.40	1.64	1.46
	Minocycline	1.64	1.76	1.49	1.52	1.45	1.54
	Benzoyl peroxide	1.57	2.33	2.10	2.02	2.12	1.91
	Ery. + BP bd	1.63	1.91	1.78	1.71	1.67	1.69
	Ery. od + BP od	1.68	2.22	2.03	1.81	1.87	1.85

The assessor index was not recorded at weeks 0–2 and 2–4. Indices were not normally distributed, but changes from baseline (see Appendix 17) were.

in the oral groups, particularly in the benzoyl peroxide group. Over the following weeks mean irritation was generally higher in the topical groups (particularly benzoyl peroxide) than in the oral groups, although for all five groups the mean score was nearly always lower (i.e. less irritation) than at baseline, and differences diminished over time. This may have been a result of using a moisturiser, or the spots causing fewer symptoms. [*Table 157* in Appendix 17 (p. 180) shows the mean differences, and standard deviations of the differences, to enable individual treatment comparisons, although readers should beware spurious significant values from multiple testing.]

Summary of irritation and side-effects

In the first few weeks after starting treatment there were more gastrointestinal and CNS side-effects in the oral groups, and more skin irritation in the topical groups, particularly with benzoyl peroxide. In most participants these soon settled. There was some residual dryness in the benzoyl peroxide group that could usually be controlled by the use of a moisturiser or by reducing the application frequency to once daily until the condition settled.

Overall summary

Differences between treatments were small and only a few comparisons were statistically significant, but in terms of efficacy, the topical treatments generally performed at least as well as the oral treatments and reduced propionibacterial counts by a greater amount (*Table 46*). The efficacy of both tetracyclines was compromised to an extent in participants colonised by tetracycline-resistant propionibacteria. In terms of quality of life, minocycline ranked higher than for efficacy and benzoyl peroxide ranked lower (*Table 47*). There was little difference between treatments for any of the utility questions and none was regarded as highly as a cure.

In the first few weeks after starting treatment there was a greater number of gastrointestinal and CNS side-effects in the oral groups, and more skin irritation in the topical groups, particularly with benzoyl peroxide. However, these soon settled in most participants.

Discontinued groups

Results for discontinued groups are shown in Appendix 18. The combination of benzoyl peroxide with oxytetracycline appeared to be the most efficacious but also had the highest incidence of skin irritation. Oral erythromycin was the least effective. With only small numbers of participants in each group (between 17 and 20), the authors caution against placing too much reliance on these findings.

TABLE 46 *Efficacy parameters: treatments ranked by improvement in facial acne from baseline at week 18*

Treatment group	Patient global	Inflamed lesion count[a]	B&C grade[a]	Assessor global	CASS	Worst aspect
Oxytetracycline	4	5	5	5	5	3
Minocycline	5	4	3	4	3	5
Benzoyl peroxide	3	3	4	3	4	4
Ery. + BP bd	1	2	2	2	=1	1
Ery. Od + BP od	2	1	1	1	=1	2

5 = worst to 1 = best.
[a] Ranks differ when split by baseline severity (see main results for details).
Ranks are based only on the means/ORs, and do not necessarily imply a statistically significant difference.

TABLE 47 *Quality of life: treatments ranked by improvement from baseline at week 18*

Treatment group	SF-36							
	Physical functioning	Role – physical	Bodily pain	General health	Vitality	Social functioning	Role – emotional	Mental health
Oxytetracycline	1	5	2	2	1	4	5	2
Minocycline	=3	2	3	1	=4	2	4	4
Benzoyl peroxide	2	4	5	5	=4	5	1	5
Ery. + BP bd	5	1	1	4	3	1	2	1
Ery. od + BP od	=3	3	4	3	2	3	3	3

Treatment group	DLQI	CDLQI	DQOLS		
			Psychosocial	Activities	Symptoms
Oxytetracycline	4	5	4	4	4
Minocycline	1	2	2	3	1
Benzoyl peroxide	5	1	5	5	5
Ery. + BP bd	2	=3	1	2	3
Ery. od + BP od	3	=3	3	1	2

5 = worst to 1 = best.
Ranks are based only on the means/ORs, and do not necessarily imply a statistically significant difference.

Chapter 4
Discussion

Interpretation

Efficacy and cost-effectiveness for managing facial acne

Even under the controlled conditions of a clinical trial, it seems that managing mild to moderate inflammatory acne of the face with antimicrobial therapy alone is unsatisfactory. Only half to two-thirds of participants showed at least moderate improvement (primary outcome measure, patient global assessment) by 18 weeks of treatment, and total clearance was rare. The inflamed lesion count fell by an average of 44% over this time. Fifty-five per cent of participants sought further treatment within 3 months of the end of the study, further suggesting that the degree of improvement was either inadequate or unsustained, or the participant was concerned about a relapse. In terms of global assessment and total inflamed lesion counts, the topical therapies studied were at least as effective as oral treatment with oxytetracycline or minocycline. [All topicals ranked higher than both orals, but differences were mostly not statistically significant, e.g. global assessment OR of the worst topical, benzoyl peroxide (60% moderately improved), to the best oral, oxytetracycline (55%), was 1.19, 95% CI 0.72 to 1.96. The difference between the best topical and the worst oral was statistically significant.] This is a finding of huge importance given that topical therapy has minimal systemic side-effects, and there is less potential to promote bacterial resistance at non-skin sites.

Since efficacy differences were small and by and large not statistically significant, it is important to consider cost. The most expensive oral antibiotic (minocycline, £106 for 18 weeks of treatment) worked no better than the cheapest (oxytetracycline, £15 for 18 weeks of treatment) based on the primary outcome measures (patient global 54% versus 55%, OR 0.95, 95% CI 0.58 to 1.55; change in lesion count –22 versus –18, difference in LSmeans –3.5, 95% CI –8.7, 1.6). This agrees with a recent Cochrane systematic review of minocycline trials, which found no good evidence of the drug's superiority against a wide range of comparators.[34]

The individual components of erythromycin and benzoyl peroxide each given once daily worked just as well as the combined product at one-third of the cost. Benzoyl peroxide was the most cost-effective treatment, and minocycline the least cost-effective for facial acne (ratio of means 12.3, difference in means –0.051 units/£, 95% CI –0.063 to –0.039). There are, however, some drawbacks associated with the use of benzoyl peroxide alone. In this study it was associated with the least improvement in quality of life, and the highest incidence and severity of local irritant effects, although these were mostly transient. For patients with significant truncal acne topical application may be problematic (the back is difficult to treat) and the cost-effectiveness of topical therapy will decrease as the area of involvement increases. Sixty-five per cent of participants in this study had some degree of truncal acne, suggesting that the number of patients who may require treatment at sites in addition to the face may be considerable. Improvement in truncal acne, together with the once-daily dosage, may at least in part explain why quality of life scores enhanced the relative ranking of minocycline. The additional benefit in terms of life quality was smaller for oxytetracycline, perhaps because the gains in terms of truncal acne were offset by the inconvenience of the dosing regimen. Assuming (rightly or wrongly) that relative responses do not differ markedly between skin sites, oxytetracycline is likely to be more cost-effective than minocycline or topical antimicrobials for managing extensive truncal acne. Local irritancy might have contributed to the poor performance of benzoyl peroxide in terms of quality of life changes. Concomitant use of erythromycin seemed to reduce the irritancy of benzoyl peroxide, as did reduced frequency of application (as in the group using separate formulations of erythromycin and benzoyl peroxide once daily). In the former case, reduced irritancy may be dependent on the composition of the base of the combined product rather than a direct effect of erythromycin. These observations suggest that compliance and quality of life may be improved by prescribing benzoyl peroxide in combination with erythromycin.

For many participants the onset of effect was seen quite early, with 47% of participants gaining at least moderate improvement by 6 weeks of treatment and 78% gaining at least slight improvement. The biggest reductions in propionibacterial counts and quality of life (as assessed using the DQOLS) were also recorded in the first 6 weeks. Of the 22% showing no improvement in facial acne at 6 weeks, nearly a quarter had shown at least moderate improvement by 18 weeks. As expected, there was large interparticipant variability in both speed and magnitude of response in this study. Therefore, the authors would advise that therapy be discontinued, not at a fixed point, but as soon as the patient and doctor agree the acne is under control, with review and hence decision points at 6-weekly intervals for up to 18 weeks. Both the Acne Support Group and the National Institute for Clinical Excellence currently recommend review of treatment after 2–3 months, but the present findings suggest that 3 months is too long to wait for the first review. Continuing therapy beyond 18 weeks is likely to result in little further improvement in the majority of cases. Patients who are unhappy about stopping therapy altogether can be switched to a non-antibiotic-based maintenance regimen after 6, 12 or 18 weeks of antibiotic treatment. Such a strategy is in line with the Department of Health action plan to encourage prudent antimicrobial prescribing.[49]

Participants were only prepared to pay around £25 for the degree of improvement seen in this trial, but were prepared to pay around £100 for a complete cure. It is possible that the monetary value categories used were not sufficiently discriminating at the lower end to identify treatment differences. WTA was predictably greater than WTP, although the order of magnitude was greater than expected (more usually two to four times greater). There was an increase in the amount that the participant would be willing to pay for a cure after treatment. This may relate to hopes having been dashed or a better appreciation of what a cure is worth, that is, a learning experience. The similarity in WTP/WTA across treatments before and after the intervention may suggest that what the individual is interested in is a cure, not how that cure is achieved in terms of the treatment they have to take. Taking median values, these patients were prepared to pay only a quarter as much for a cure at the start of the trial as were outpatients with acne in a 1988 study[43] and in pilot testing for the present study (also with outpatients). Outpatients may not be representative of acne patients in the community in that they value treatment differently. In addition, young people whose only income is pocket money may be willing to pay considerably less than wage earners.

Measured by conventional quality of life scales, it may appear that the mild to moderate acne seen in the community does not bother the majority of people very much. If this is the case, why did people take part in the study, and why do so many people consult their doctor or pharmacist for treatment? An alternative explanation is that none of the scales used adequately captures the effects of acne on quality of life and/or that dermatology-specific scales developed using outpatients with a variety of skin diseases are not appropriate for use in the community (see section 'Outcome measures', p. 52). Once patients are in a clinical trial this may have an immediate effect on their quality of life scores on any scale, given that they have the security of knowing that both treatment and support will be offered.

One aspect not explored in this study was patient satisfaction. Satisfaction in this context could be defined as willingness to stop the treatment altogether or to switch to a preventive non-antibiotic-based regimen (recognising that some patients do not wish to be without treatment). It would also be helpful to explore how much residual acne (as a percentage of baseline severity using a grading scale or as an absolute number of spots) is present in patients who are satisfied with the degree of improvement achieved. For instance, would a patient with grade 3 acne at baseline be as satisfied as someone with grade 1.0 acne that fell to grade 0.5 after treatment (50% reduction) if their grade fell to 1.5 (a similar percentage reduction) or 0.5 (a similar severity but an 83% reduction)? This information could be used to define more meaningful end-points for future clinical trials.

While this study was being conducted, a very large systematic review of all acne trials published in English (a limitation since many acne trials have been published in other languages) was carried out by the Evidence-Based Practice Center at Johns Hopkins University.[50] This confirmed the conclusions from the previous two systematic reviews of acne trials[34,35] that heterogeneity of outcome measures and poor methodological quality[51] have severely compromised the evidence base so that comparative data on efficacy cannot be relied upon. There is thus no reasonable justification to compare the present findings with published trials of the same interventions.

Patient preference

Even if a treatment is cost-effective, there is little point in prescribing medication that patients do not want to use. Each treatment has its own drawbacks, and it may be prudent to discuss with patients what might deter them from taking or applying it. For instance, some (especially males) found applying creams and lotions a chore, whereas others disliked taking tablets (difficulty in swallowing them, worry about long-term effects of oral antibiotics, inconvenience of the dosing or application regimen). Keeping Benzamycin in the fridge is not ideal, and may lead to reduced use of the medication. However, a new dual-pouch packaging system (Benzamycin PAK) has been developed that does not require refrigeration: the two active agents are extruded separately and mixed by the patient in the palm of the hand. The new delivery system has undergone extensive trials in the USA,[52] but is not yet available in the UK.

Worries about local and systemic side-effects of acne treatments can be lessened if patients know what to expect and how to deal with them. Without adequate advice patients may be reluctant to accept a therapy such as minocycline, associated with a rare but serious side-effect, while initially accepting one with a high probability of local irritant effects, only to reject it later after a few days of over-zealous use.

Many patients will have purchased one or more formulations of benzoyl peroxide OTC and already made up their minds about the efficacy and acceptability of these. Presumably the very fact that they seek medical help indicates at least some degree of dissatisfaction with the OTC remedies that they have tried. It may be difficult for doctors to persuade a patient (or a parent) disillusioned with some OTC formulations of the drug to leave the surgery with a prescription for more of the same. It is essential that doctors spend a few minutes telling patients how to use any product containing benzoyl peroxide properly to maximise efficacy and minimise irritation. There is evidence that a combination of verbal and written instructions is preferred by patients.[53] There is also a clear role for pharmacists here.

Several formulations of 5% benzoyl peroxide are available both on prescription and OTC. This trial has shown the relative efficacy of only one of these and it may be wrong to assume that all benzoyl peroxide formulations are the same. Products containing benzoyl peroxide may also differ with respect to tolerability and at least one formulation is marketed on the basis of reduced irritancy. In addition, better tolerated formulations are under development and likely to be available soon.

As well as cost to the healthcare provider, cost to the patient should be considered. For those who pay prescription charges, this will depend on what is included as a single prescription, and the size of the pack or number of tablets.

During an informal discussion group with GPs to explore factors influencing their prescribing habits, it emerged that patients were often the strongest drivers in determining choice of treatment, and that dissemination of information should target user groups, for example the Acne Support Group or teenage magazines, as well as medical practitioners and pharmacists. To this end, the implications for each type of user group are listed separately (see section 'Implications for user groups', p. 55).

Antibiotic resistance

Although not a classical infection, acne responds to antimicrobial treatment aimed at reducing the total propionibacterial load. All five regimens reduced the numbers and prevalence of viable propionibacteria on the skin, but the topical ones were more effective than the oral ones. Oxytetracycline was the least effective, with a mean decrease in propionibacterial growth score by week 18 of only 0.5 (although the difference was still statistically significant, $p < 0.001$). The number and prevalence of resistant organisms on skin also fell during topical antimicrobial therapy, and to a greater extent when the regimen contained both erythromycin and benzoyl peroxide. Changes for all resistant organisms for all the topical regimens were highly statistically significant (largest p-value of 0.006); changes, if any, were small and not statistically significant for the oral regimens. There is some evidence from an independent study that erythromycin and benzoyl peroxide works synergistically against some but not all erythromycin-resistant propionibacterial strains.[54] This may be due to increased radical formation by benzoyl peroxide in the presence of erythromycin.[55] In the absence of resistance, the effects of antimicrobial treatment regimens on propionibacterial numbers can be used as an indirect estimate of compliance in individual people, with those in whom numbers do not fall being obviously non-compliant. Although falling bacterial numbers cannot reveal the degree of compliance, rising numbers after an initial fall suggest that compliance has deteriorated (and/or may be associated with resistance gain).

No regimen was shown to promote an overall increase in the prevalence or population density of resistant propionibacteria during the 18-week treatment period. Despite this, some participants were colonised *de novo* by resistant strains during therapy. The relationship between compliance and resistance is a complex one. Resistance gain might be expected in poorly compliant patients on active topical therapy as a result of selection at the periphery followed by recolonisation of the treated site. The results indicate that combined use of an antibiotic with benzoyl peroxide is a sensible option to avoid the selection and overgrowth of resistant skin bacteria. They also suggest that treatment courses of up to 18 weeks' duration have minimal selectivity. They do not show that antibiotic therapy for acne is always non-selective, but only under the conditions of this study. Evidence from a separate study shows that propionibacterial resistance is driven by antibiotics prescribed for acne.[36]

Under the conditions of this study, resistance in cutaneous propionibacteria did not compromise outcomes on any of the three benzoyl peroxide-containing regimens. In contrast, tetracycline resistance reduced the efficacy of both tetracyclines, but minocycline in particular. It is not known why the effects of resistance were greater for minocycline than for oxytetracycline. Possibilities include different skin levels of the two drugs at the standard doses, and differences in residual anti-inflammatory activity. It has been shown[56] that serum minocycline levels of 100 mg per day (the BNF recommended dose for acne) are insufficient to inhibit some propionibacterial strains with reduced susceptibility to the drug. Increasing the dose of minocycline would increase costs and the risk of some adverse events, but may overcome the effects of resistance on outcomes, especially in patients of high body weight.

Resistance to tetracycline (defined as ability to grow at a concentration of 5 mg l^{-1} of the drug) was better correlated with inadequate response to minocycline than ability to grow at the same concentration of minocycline. This indicates that the breakpoint used here for minocycline is not an accurate predictor of clinical resistance and that some clinically resistant strains will not be detected. Propionibacteria capable of growth on 5 mg l^{-1} of tetracycline are inhibited *in vitro* by concentrations of minocycline between 0.25 and 4 mg l^{-1} (depending on the strain),[57] suggesting that clinical resistance and hence follicular drug levels lie at some point between these two concentrations.

Carriage rates for antibiotic-resistant propionibacteria in the community were found to be slightly lower than in a leading outpatient clinic,[32] but still high (approaching 50% for erythromycin and over 40% for clindamycin at baseline), and similar for Leeds and Nottingham. However, population densities were generally lower. Colonisation with resistant propionibacteria is thus common among acne patients managed in the community and may influence outcomes to varying extents depending on the antibiotic, route of administration and compliance. Prescribers should consider resistance as an explanation for inadequate response to, or relapse during, antimicrobial therapy, especially when benzoyl peroxide is not co-prescribed. The relative efficacy of different antibiotic regimens may depend on the local prevalence of antibiotic-resistant propionibacteria. Where the prevalence of resistant strains is markedly different from the UK,[36] outcomes of similar treatment comparisons to the one reported here may differ.

In summary, antibacterial potency rankings put topical regimens including erythromycin and benzoyl peroxide ahead of oral tetracyclines and mirror the results obtained for clinical efficacy.

Outcome measures

The experiences with this trial reinforced the dangers of including too many outcome measures. The more that are included, the more likelihood there is of conflicting results between different measures, and the collection and processing time of additional data can be significant. In general, it is best to include a few well-chosen outcome measures rather than trying to cover every area of interest. The intention was to inform this choice with supporting data. Recommendations for those who may be involved in the design or conduct of acne trials in the future are given later in this chapter (section 'Implications for trialists', p. 56).

Despite the use of several measures of clinical efficacy, the treatment ranks generated were generally similar, with oxytetracycline ranked worst by four out of five measures and erythromycin plus benzoyl peroxide twice daily ranked best by four out of five measures. Discrepancies arose when comparing outcomes as estimated by clinical measures of efficacy with those generated by quality of life questionnaires. The reasons why such differences might have occurred have already been discussed at length. Greater reliance has been placed on the subjective measures than on quality of life changes, for several reasons. These types of outcome have been

widely used in acne trials and their utility is widely accepted by trialists and regulators. In contrast, quality of life estimation has been rarely used in acne trials and the problems encountered here are not unique to this study. Moreover, it was hard to identify consistent trends in the quality of life data. Benzoyl peroxide tended to be ranked worst using several of the SF-36 scales, the DLQI and the DQOLS, but ranked best on the children's version of the DLQI. Although minocycline tended to rank higher using quality of life scores, its actual rank varied from first to fourth depending on the instrument and scale. Follow-up after the end of a trial may be necessary to detect the overall change in quality of life resulting from the medication received: it may take individuals a while to notice how different they feel and for their self-esteem to adjust.

The extra information gained from the inclusion of quality of life estimation has to be offset against the time taken for the participant to complete the questionnaires (some people complained), for assessors to chase up missing questionnaires, and for data processing (database building, data entry and analysis). In retrospect, a simple acne-specific questionnaire may have been more suitable for capturing quality of life changes in this population and would have required minimal effort. Of the three scales used, the DQOLS were probably the most sensitive to change in this setting and SF-36 was the least. Even using the dermatology-specific instruments, the level of disability measured in many participants was small. These scales were developed to cope with eczema and psoriasis as well as acne, even though the major influencers on quality of life differ markedly between them. Baseline mean scores using the DLQI were similar to the mean score (4.3/30) reported by the original authors for patients with acne.[40] Using the children's version, baseline scores recorded here were somewhat lower than reported for under-16-year-old outpatients (mean 5.7/30).[41] The DQOLS (intended by the original authors to supplement the DLQI) proved the most informative of the quality of life questionnaires. Baseline scores on the DQOL symptoms scale were closely similar to those reported by Morgan and colleagues for outpatients at a hospital dermatology clinic, indicating that initial disease severity was comparable.[42] In contrast, scores on the psychosocial and activities scales were markedly lower, suggesting that participants in the present study were less affected by their disease than the outpatients. Several dermatology-specific instruments have been found to be responsive to change mediated by therapeutic intervention, including at least one new one not available when this study began.[58–60] However, few have been put to the test within formal RCTs.[61,62] With the SF-36, baseline values were high, leaving little capacity to estimate or compare beneficial treatment effects. The lack of sensitivity of generic measures to treatment effects in acne has been observed before.[59] Despite this, baseline scores on the social functioning, role – emotional and the mental health scales for women aged 16–34 years were lower than published UK population norms from three separate studies.[46] Baseline scores using the SF-36 in outpatients with acne were reportedly much lower than those recorded in this study for acne patients in the community.[63] Inferring the effects on life quality of skin diseases such as acne, managed primarily in the community, from studies in outpatients may be misleading. Acne patients who are referred to secondary care may not simply have more severe disease, but a more severe burden of disease. Others have also found poor correlation between clinical outcomes and improvement in quality of life scores.[64] However, this is not simply a reflection of differences in subjective impairment of functioning, but also of real differences between treatments that affect patient acceptability and satisfaction.

The authors are not aware of the use of utility measures in previous acne trials. The similarity of WTP and WTA values across treatment groups suggests that what the individual is interested in is getting better, not how that benefit is achieved. Thus, process utility may not apply in the case of acne treatments. The range of monetary values used here in the utility questionnaire was based on that previously used by Motley and Finlay[43] with outpatient referrals, and followed pilot testing for this study with an outpatient population. In view of the age of the Motley and Finlay's original paper, the upper end of the range was extended by two additional categories (£10,000 and >£10,000). In fact, the questionnaire might have been more discriminatory had the upper bound been left at £5000, but the number of categories in the middle of the range increased. It may be concluded that the use of a utility questionnaire was informative, although the questionnaire needs refinement before it can be used routinely in acne trials.

Counting of spots may not always be necessary. Spot counting is very time consuming, and some people find such close inspection of their faces embarrassing. It also takes considerable time to learn. Although this is an objective outcome measure, it still suffers from large between-assessor

variation, as reported previously[65] and noted in the monitoring sessions. In this study, patient and assessor global measures gave similar results to the lesion counts, and were much quicker to perform. One disadvantage of the global measures was taking photographs, in terms of the time needed to take and develop them, the expense of equipment (camera, slide-projector, film and developing), and equipment transportation difficulties if the participants are assessed at different centres. Overall severity was assessed at each visit using both the Burke and Cunliffe grade and the new CASS. Both gave similar results, and the authors hope to compare the outcomes from these scales in more detail. The new scale collects more information than the Burke and Cunliffe grade, and it is not much more time-consuming to use.

Duration of treatment

How long should a course of treatment be? The incremental differences in improvement between 12 and 18 weeks are small, but are they worth paying up to 50% more for (depending on treatment pack size; see Appendix 3)? Improvement was not brilliant over the 12 or 18 weeks, and may not meet patients' expectations. Given that 55% of participants either carried on with treatment after 18 weeks, or sought more within 3 months of the end of the study, they may well have regarded the degree of improvement to be inadequate, or were concerned about relapse and wanted to stop the spots recurring. Such concern is valid given the chronicity of acne during adolescence and early adulthood.

This trial was unusual in that treatment was continued for 18 weeks compared with a norm in most acne trials of 8–12 weeks. Despite the multitude of previous trials of antibiotics for acne, the shape of response curves for any of the commonly used agents is unknown and hence predictions cannot be made about how long individual courses of treatment should be to maximise both efficacy and cost-effectiveness. A related issue is whether the efficacy of antimicrobial therapy can be boosted by adding another antiacne drug with a different mode of action to the regimen. Adding, say, a comedolytic agent would increase costs significantly and would only be cost-effective if the overall degree of response were greater and the time to achieve it reduced.

It seems that further research is needed both to define the optimum duration of treatment with single agents, and to ascertain whether combination therapy alters the shapes of response curves, either to lessen the time to optimal improvement and/or to increase the magnitude of response. In the meantime, prescribers should consider revising treatment strategies to think more about long-term management and to avoid the use of prolonged courses of antibiotics. Some suggestions are given below (see section on 'Future research', p. 58).

Generalisability: strengths and limitations of the study

This study simultaneously tested five of the most commonly used antimicrobial treatments for mild to moderate inflammatory acne of the face in a representative community sample. Several outcomes measuring different aspects of acne were used together with a cost-effectiveness analysis, and produced broadly similar results. In addition, bacterial resistance data were collected before and after treatment and helped to explain some of the response variation. The study was industry independent, hence removing a potential source of bias. Also, each participant was seen by the same one of four assessors at all visits, helping to reduce variability. The assessors were not dermatologists and hence had no preconceived ideas about how well the test treatments might work.

Limitations of the study include the overall low accrual rate, suggesting that the outcomes may not be generalisable to all acne sufferers managed in primary care. However, baseline characteristics of the study population were typical of acne trials in general. The response rate is perhaps not surprising given that the study dealt with a predominantly adolescent population and patients' own doctors were not directly involved in the recruitment procedure. In addition, participants were required to stop all active acne treatment for a washout period of 4 weeks (unwillingness to stop current treatment was the second most common reason for non-participation given by those showing an initial interest), and the commitment in terms of the number and duration of study visits was considerable. These were all issues raised by focus group participants as likely to affect their willingness to take part. The external validity of the study is also limited in that only effects of treatment on facial acne were evaluated. Although this is the area that usually causes most problems, some of the cost-effectiveness rankings between oral and topical treatment might have been reversed if truncal acne had been considered, since the usage of orals

is unchanged but that of topical increases. It is also difficult to generalise from this study of mild to moderate acne sufferers to those with severe disease treated in secondary care. Such patients will normally be expected to receive early intervention with oral isotretinoin, although (oral) antibiotics are likely to be prescribed while patients are on waiting lists.

Allocation concealment was thorough, but only assessors and investigators were completely blinded as to the type of intervention dispensed. Participants were not blinded because of the prohibitive costs of manufacturing identical placebos and reformulating the active treatments to make all five interventions look the same; however, it was estimated that around half of the participants were unsure of which of their treatments was active (see Appendix 2). Some of the participants' evaluations might have been coloured by their previous perceptions if they had already received one of the treatments before. Then again, perhaps it is important to capture treatment history effects in a pragmatic study such as this, as most acne sufferers' experience using several treatments and their preferences may be important in influencing outcomes. Ranking of treatment efficacy was similar regardless of whether participant or assessor ratings were used, suggesting that biased assessment of outcome was unlikely.

Implications for user groups

Implications for prescribers

Expert opinion continues to endorse long courses of antimicrobial treatment.[66] Although most improvement occurred in the first 6 weeks, the majority of participants were left with residual facial lesions after 12 and 18 weeks of treatment. In consequence, many sought to remain on treatment after the trial had ended. Although acne is a chronic, relapsing condition and patients should be offered treatment for as long as they need it, if an antimicrobial treatment does not appear to be working adequately for facial acne after 6 weeks, then a change may be considered, rather than waiting for several months. If antimicrobial therapy is working, it may be continued for up to 18 weeks until adequate control is achieved, accepting that different patients will need treatment for different durations. In the case of antibiotics, improvement should be reviewed at least every 6 weeks so that therapy can be stopped at the earliest opportunity, thus minimising the selection and overgrowth of resistant bacteria. The 6/18-week rule need not apply to non-antibiotic-based therapeutic or maintenance regimens, which can be continued indefinitely, although there are still issues relating to use of benzoyl peroxide (see section 'Implications for pharmacists', p. 55).

A key question for prescribers is whether antibiotics should remain first line treatments for acne given the limited efficacy and concerns about prudent antimicrobial prescribing.[49] Although alternative types of treatment were not tested in this study, prescribers may wish to consider non-antibiotic-based treatment regimens (such as comedolytics) before resorting to antibiotics.

Doctors also need to be aware that resistance in the target organism may be a cause of inadequate response or relapse, especially on oral antibiotic regimens, and that switching between agents within the same class (e.g. from one tetracycline to another) is unlikely to be beneficial. Conversely, resistance may not always result in lack of response. It has been observed before that topically administered erythromycin may be capable of inhibiting erythromycin-resistant propionibacteria *in vivo*;[67] adding benzoyl peroxide can prevent the emergence and spread of resistant organisms.

Implications for the NHS

The cost-effectiveness and resistance data do not support the use of minocycline as a first line treatment for facial acne. Instead, it is best used to improve compliance in patients for whom compliance is a recognised or likely problem.

The data on cost-effectiveness further support the use of topical in preference to oral antimicrobial therapy for mild to moderate inflammatory acne of the face. Indications for oral therapy should continue to include extensive truncal acne, since topical therapy is unlikely to be cost-effective when large areas of skin are involved.

It is recommended that sources of advice for dermatologists and primary care physicians (e.g. the BNF) are updated to reflect the new evidence.

The authors hope that they have demonstrated the value of industry-independent trials of acne therapies, and urge the NHS to consult widely with a view to publishing a list of key unanswered questions for patients and prescribers.

Implications for pharmacists

The pharmacist has three main roles:

- to advise patients on the selection of treatment
- to advise patients on the appropriate use of treatment to maximise efficacy and reduce irritancy
- to advise patients when they should seek medical help.

The outcomes of this study suggest that mild to moderate inflammatory acne can be controlled with 5% benzoyl peroxide that is available OTC. However, patients should ideally be given verbal instructions about how to use the product before purchase. These are the key messages:

- Warn patients that the product will bleach clothes, towels and/or bedlinen, and hair, and thus to rub it well in and to wash their hands thoroughly afterwards.
- The product should be applied to the whole of the affected area, not just the spots. For spots on the face, the entire face should be treated.
- Tell patients that they can use the product for acne spots on sites other than the face.
- For patients with sensitive skin, it is best to apply the product sparingly at first and to use it once a day or every other day, building up gradually to a more liberal application twice a day. Application of a moisturiser (30–60 minutes after the product) will help to minimise irritancy.
- Tell patients not to expect much improvement in the first week or two and gradual improvement thereafter. Make it clear that they may need to use the product for several months.

Many patients with acne buying OTC medications should find them of help if properly used. If the patient sees no obvious improvement after 6 weeks, he or she is likely to need medical help. Some patients with quite severe disease may initially purchase OTC remedies: pharmacists should prompt anyone with numerous large red spots, obviously deep lesions or evidence of scarring, or who seems overly anxious about their spots, to see their doctor straightaway.

Implications for patients

The data suggest that mild to moderate papulopustular acne of the face can be controlled as well using benzoyl peroxide as by the use of oral antibiotics. The product tested in the current study (Panoxyl Aquagel) is available OTC and on prescription. It should be stressed that this study has no evidence about other formulations of benzoyl peroxide, but in principle there should be no major differences in efficacy between them. However, they may differ in irritancy (which is to some extent formulation dependent) and patients may need to try more than one product to find the best. Patients can improve their experience of benzoyl peroxide use by heeding the advice given to them by the doctor and/or pharmacist.

The purchase of acne treatments, whether OTC or on prescription, can be costly, especially if some end up in the bin after a few uses. The Acne Support Group pointed out that combination therapies that rely on separate formulations are twice as expensive for patients if both items are prescribed although, as with the two-product group in this study, they could last for twice as long. Doctors may advise patients that they can obtain benzoyl peroxide OTC to reduce costs.

The results suggest that the ideal time to make a follow-up appointment for patients prescribed an acne medication is 6–8 weeks following the start of therapy. No or minimal improvement after this time indicates that a change of treatment may be necessary.

It is suggested that when the acne is under control and the degree of improvement is satisfactory to the patient, treatment regimens based on antibiotics should be stopped. Thus, patients on such regimens should make a further appointment to see their doctor to discuss stopping treatment or a switch to a non-antibiotic-based maintenance regimen.

Implications for trialists

The inclusion of so many outcome measures was in part to inform the selection of such measures in future acne trials. The following suggestions are based on the findings of this study.

- Lesion counting provided no more information than the use of acne severity scales, suggesting that its routine use may not be necessary. Given that it is highly subjective and time consuming, and extensive training is required, perhaps lesion counting is more suitable for trials in which a primary objective is to ascertain whether a treatment is active against inflamed lesions, non-inflamed lesions or both. If properly validated, the CASS may replace lesion counting and other methods of acne grading.
- Although patients' self-assessment was used as one of the two designated primary outcome measures, the authors do not feel able to recommend it unreservedly as the main or only measure of clinical efficacy at present. High-quality colour images taken at baseline were

shown to participants at each visit, but there is no evidence to show whether this is better or worse than relying on recall. It does allow for some degree of standardisation between participants and clinical assessors, who also based their judgement of improvement on comparisons with baseline images. Balanced against this is the risk that participants will be influenced by assessors' rating and vice versa unless due care is taken to avoid this. The assessors were advised to record their rating without comment before asking participants to self-assess.

- None of the three quality of life scales used performed well in this setting, and there was no apparent correlation between quality of life changes and clinical improvement as estimated by participants or assessors. Although there are several reasons why this might have occurred, it is clear that use of quality of life as an outcome measure in acne trials is problematic. Of the three instruments used, the DQOLS were the most sensitive to change and other instruments should be compared with these before replacing them for routine use.
- Worst aspect as a simple patient-based outcome measure may capture improvement in a more focused way than global assessment by concentrating on the symptom that bothers the participant most. However, some participants found it difficult to identify precisely what bothered them, or did not realise at the start of the study that their acne bothered them. Provision of a simple checklist at the baseline visit may help individuals to pinpoint what it is about having spots that troubles them the most, responses to which may also inform the development of a better quality of life instrument.
- The inclusion of utility measures was helpful as it clearly showed that the treatments ranked similarly for cost-effectiveness compared with cost benefit. The utility questionnaires used undoubtedly need refining, but their routine use in future acne trials should be welcomed.
- Although the authors recommend the use of a simplified set of outcome measures, they did not, as hoped, obtain clear evidence on which measures to select in preference to others. However, in most circumstances, three or four measures will suffice – one or two for efficacy (perhaps a global estimate plus a severity scale for the time being), one for quality of life and one for utility (in addition to the collection of data on tolerance and adverse events).
- The routine reporting of cost-effectiveness in acne trials would help prescribers to choose between agents with similar efficacy.
- An omission in this study was not asking participants whether they were satisfied with the degree of improvement at each time-point. For instance, would they have been prepared to stop the trial medication altogether? This seems a crucial question to define the degree of residual acne with which patients are prepared to live with (as a proportion of baseline severity or as a defined severity grade) and to inform assessment points for future acne trials.
- Baseline disease status could be reported in three ways: in terms of mean and range of lesion counts for the whole face (or other specified site); as mean or median grade and grade range on a recognised severity scale; and as mild, moderate or severe, making sure to identify the grades to which these terms have been applied. Without this information the generalisability of trial findings cannot be properly assessed. Additional details important when assessing generalisability include age, gender, ethnicity or skin type, source (hospital or community, whether patients or volunteers), duration and type of acne, previous use of acne treatments and whether lesions extend to non-facial sites.
- Since resistance status can affect clinical outcome, it is essential for any trial of antibiotics in acne to know both whether participants are colonised with resistant propionibacteria at baseline, and the prevalence of resistant propionibacteria in the country in which the trial is being conducted.

Implications for regulators and licensing authorities

For any new antimicrobial products for acne, licensing authorities may wish to consider requesting evidence of efficacy in patients colonised with antibiotic-resistant propionibacteria. In the case of new antibiotic-based products, demonstration that the agent does not select for overgrowth of resistant propionibacteria during routine use may be considered as an additional requirement.

Until any other product is unequivocally shown to be superior, this research suggests that benzoyl peroxide be used as the gold standard against which other treatments for mild to moderate inflammatory acne are compared.

Early intervention with oral isotretinoin has been shown to be more cost-effective than long-term use of antibiotics for both moderate and severe acne,[68] and many dermatologists already prescribe the drug for the management of less severe forms

of the disease.[69] Regulators may wish to consider whether the disappointing results obtained in the current study with antimicrobial regimens alter the balance of evidence for and against the wider use of oral isotretinoin.[70] Perhaps the key issues to address here are, first, whether antibiotics or oral isotretinoin should have any place in the routine management of mild acne (accepting that there will always be exceptional cases where their use is justified) and, second, how best to manage mild to moderate and moderately severe papulopustular acne given that oral isotretinoin is more cost-effective, but risk–benefit assessment possibly favours antibiotics.

Future research

Although this trial has helped to inform the selection of antimicrobial treatment for mild to moderate inflammatory acne of the face, prescribers are still faced with a lack of good quality evidence to help them to make informed decisions about many other aspects of acne management, such as choosing between antimicrobials and other types of treatment, how to manage truncal acne, when and how to combine treatments, whether and when to refer for oral isotretinoin, and the extent to which patient characteristics such as ethnicity or social class modulate outcomes. A small number of high-quality acne trials is needed to address the key issues for prescribers and patients as opposed to manufacturers and regulators. There is a need for more research on trial methodology and agreement between those who fund trials upon some degree of standardisation with respect to the selection and use of outcome measures. This study has shown how difficult it is to capture all aspects of acne with a single measure, but also that the use of multiple measures is not an ideal solution. Three priority areas for clinical research in acne are:

- defining end-points in acne trials: what is a satisfactory outcome?
- developing and validating better patient based measures for assessing treatment effects on facial and truncal acne
- exploring patient characteristics that may modify treatment effects (efficacy and tolerability).

Specific suggestions for future research are listed in Appendix 5.

Chapter 5

Main findings and conclusions

- Topical antimicrobial therapy with benzoyl peroxide alone or in combination with erythromycin was at least as effective as oral tetracycline or minocycline for mild to moderate inflammatory facial acne.
- Although differences were small and mostly did not reach statistical significance, the two erythromycin-containing regimens consistently performed at least as well as the other three regimens over a range of outcomes.
- For all regimens, most of the observed improvement occurred within the first 6 weeks of treatment.
- None of the regimens was highly effective and most participants (95%) were left with residual acne (defined as more than five inflamed lesions) at 18 weeks.
- Irritancy was less with both erythromycin-containing regimens than with benzoyl peroxide alone, which may have accounted for the better quality of life changes with combination therapy.
- Benzoyl peroxide was the most and minocycline the least cost-effective therapy for people with mild to moderate inflammatory acne of the face.
- Quality of life scores rated minocycline higher and benzoyl peroxide lower, possibly reflecting patient acceptability and beneficial effects of minocycline on truncal acne.
- All the regimens produced a reduction in propionibacterial numbers. The magnitude of the reduction was greatest with either of the topical erythromycin-containing regimens.
- Pre-existing propionibacterial resistance did not compromise the efficacy of any topical regimen, but the efficacy of oxytetracycline and minocycline was lessened in participants colonised by propionibacteria with reduced susceptibility to tetracyclines.
- Under the conditions of this trial, none of the regimens resulted in a net increase in the prevalence of antibiotic-resistant propionibacteria; more participants lost resistant strains than gained them during treatment, especially in the topically treated groups.
- The biggest changes in quality of life scores and the biggest falls in propionibacterial numbers occurred during the first 6 weeks of treatment, mirroring the changes in acne severity.
- Taken together, these results suggest that minocycline should not be a first line treatment for acne and that most patients with mild to moderate inflammatory acne of the face can be managed as well with topical antimicrobial therapy as with oral antibiotics.
- The temporal data suggest that a patient starting new acne treatment should be reviewed at 6 weeks. If a negligible response is seen at that time, a switch to an alternative treatment should be considered.
- The separate formulations of benzoyl peroxide and erythromycin were as effective and well tolerated as the proprietary combined formulation, but three times more cost-effective.

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Appendix 1

Study medication dispensed

Cohort 1

Medication was dispensed at 0 and 12 weeks in cohort 1. At week 12 the dispensed amounts of some topicals were increased, as some participants ran out in the previous 12 weeks. Participants were asked to return part-finished packs.

Although 336 is the correct number of tablets to allow four per day for 12 weeks, an extra 20 tablets were included in the oxytetracycline bottles to allow for late visits (as for the other treatments). It is thought to be a mistake at the planning stage that extra tablets were not included in the erythromycin bottles. Minocin MR capsules came in packs of 56 that were not split, so only multiples of 56 could be dispensed. Originally, the amount of each topical required was based on 0.35 ml per day, as determined using syringes to deliver a solution, although requests for extra topical medication in the study had meant a revision of the amounts of some of the gels and creams supplied. To help with cost calculations for the cost-effectiveness analysis, the required amount of each topical was reassessed by either weighing the gels or using a syringe for the solution. Three aliquots were prepared, one to treat the forehead area, and the other two to treat the cheeks, nose and chin (to the midline). In this way it was found that 0.4 ml of the gels was a more reasonable estimate of the average amount used per application. The previous estimate of 0.35 ml remained sufficient to cover the whole face (avoiding the eyes and mouth) with the solution. Amounts of each topical dispensed were limited by pack size, and for some of them by the expiry time once opened.

Week 0:

- 356 × 250 mg oxytetracycline tablets (non-proprietary)
- 112 Minocin MR capsules
- 336 × 250 mg erythromycin tablets (non-proprietary)
- 2 × 40 g tubes Panoxyl Aquagel 5% (1 × 40 mg when in combination with Stiemycin)
- 2 × 50 ml Stiemycin solution (1 × 50 mg when in combination with Panoxyl Aquagel 5%)
- 2 × 30 ml Dalacin T solution
- 1 × 23.3 g + 1 × 46.6 g Benzamycin gel
- 3 × 30 ml Zineryt solution
- 2 × 70 ml Topicycline lotion
- 2 × 35 g topical placebo cream
- 88 oral placebo tablets.

Week 12:

- 356 × 250 mg oxytetracycline tablets (non-proprietary)
- 112 Minocin MR capsules
- 336 × 250 mg erythromycin tablets (non-proprietary)
- 2 × 40 g tube Panoxyl Aquagel 5% (1 × 40 mg when in combination with Stiemycin)
- 2 × 50 ml Stiemycin solution (1 × 50 ml when in combination with Panoxyl Aquagel 5%)
- 3 × 30 ml Dalacin T solution
- 2 × 46.6 g Benzamycin gel
- 3 × 30 ml Zineryt solution
- 2 × 70 ml Topicycline lotion
- 3 × 35 g topical placebo cream
- 88 oral placebo tablets.

Cohort 2

Dispensing was at 6-weekly intervals, to encourage visit attendance.

Weeks 0, 6 and 12:

- 200 × 250 mg oxytetracycline tablets (non-proprietary)
- 56 Minocin MR capsules
- 1 × 40 g tubes Panoxyl Aquagel 5%
- 1 × 50 ml Stiemycin solution
- 1 × 46.6 g (or 2 × 23.3 g) Benzamycin gel
- 2 × 35 g topical placebo cream
- 50 oral placebo tablets.

Extra medication requests

Forty-four participants requested extra medication during the study; still more reported to their assessor that they had run out of medication, although they had not asked for more despite being told that they could. Nineteen of the 44 ran out of ery. + BP bd gel (two participants asked for extra twice and one participant on three occasions), five of topical placebo, three oral placebo (at least one participant took two tablets

per day by mistake), three of benzoyl peroxide, two of clindamycin, one of topical erythromycin, one of tetracycline + oxtet., one of minocycline on two occasions (despite telephone calls to check how the participant was using it), one of erythromycin (again reason unknown). In addition, one participant lost their topical placebo, one lost the whole pack of benzoyl peroxide + oral placebo, one container of oral placebo was eaten by the participant's dog, one participant made up the Benzamycin incorrectly and another spilt the components. Requests for extra medication decreased after the amounts dispensed were increased in November 1998. Three participants carried on after week 18 until week 24 (as originally planned in the study), and hence needed extra medication: two on ery. od + BP od and one on benzoyl peroxide alone, although no extra tablets were requested for any of the three.

Appendix 2

Blinding/masking: additional information

The reported incidents of unblinding of treatments to the assessor are given in *Table 48*.

For the five main treatments, 481 participants were asked how many active treatments they thought they were on: 254/481 (53%) gave the correct number of active treatments, 91 (19%) did not know, and the remaining 28% guessed incorrectly. The minocycline group made the most correct guesses, and benzoyl peroxide group the fewest. Ten participants thought that none of their treatments was active, and one participant in the benzoyl peroxide group thought that three of their treatments were active (the participant was probably confusing the moisturiser with treatment).

For the discontinued treatments, of the 73 asked (out of 112) 32 (44%) gave the correct answer, eight (11%) did not know and 33 (45%) gave an incorrect answer; four participants thought that none was active.

Additional questionnaire on blinding at +3 months

Forty-five out of the 60 forms were returned. Participants were asked:

- Did you think the tablets/capsules were active? Why?
- How many *different* creams/solutions/gels did you have in each pack?
- If one, did you think it was active? Why?
- If two, did you think the solution was active? Why? The cream was active? Why?
- Is there anything you particularly liked or disliked about your treatments?

The results were as follows.

Oxytetracycline: nine forms returned.

- **Tablets**: all nine thought that the tablets were active; one because the container indicated it, and the rest because spots cleared.
- **Cream**: five thought that the placebo cream was active, again because it worked; three thought not: no irritation, behaved differently to previous medications, consistency/smell/moisturising effect was 'wrong', and one did not know.
- **Likes/dislikes**: one participant said that the tablets made them feel angry, another that they preferred using the cream, and a third that they learnt a lot.

Minocycline: ten forms returned.

- **Capsules**: nine thought that the capsules were active; five because their spots improved, one thought that they were supposed to help, two because of packaging/appearance, and one gave no reason. One did not know.
- **Cream**: three thought that the placebo cream was active because it cleared the spots. Five

TABLE 48 *Recorded incidence of treatment unblinding to assessor*

Date	Participant ID	Treatment group	What was revealed to assessor
Pre-27 Oct. 1998	0176	Benzoyl peroxide	Identity of oral, but not topical
Pre-27 Oct. 1998	0331	Ery. + zinc acetate	Identity of oral, but not topical
Oct. 1998	0018	Clindamycin	Identity of oral, but not topical
Sept.–Oct. 1998	0004	Benzoyl peroxide	Identity of oral, but not topical
Sept.–Oct. 1998	0006	Minocycline	Identity of oral, but not topical
6 Nov. 1998	0345	Ery. + BP bd	All treatments
5 Nov. 1998	0221	Oxytet. + BP	Identity of topical
13 Jan. 1999	0348	Erythromycin	All treatments
4 June 1999	0390	Minocycline	Identity of oral
21 June 1999	0419	Ery. od + BP od	Identity of oral (withdrawal)
5 July 1999	0100	Benzoyl peroxide	Knows oral (due to AE)
10 Nov. 1999 (T6)	0224	Tetracycline + oxytet.	Knows oral

thought not: one because of packaging, one smell/texture/packaging, one greasy and unlike other acne creams, two no reason. One said they did not know as the packet was not labelled.
- **Likes/dislikes**: two said that they did not like the cream making their skin look or feel greasy or oily. One commented on the size of the tablets (but not whether that was a like or a dislike), and another that tablets were easy to use, and no worry.

Benzoyl peroxide: ten forms returned.
- **Tablets**: five thought that the tablets were active, three because their spots cleared, one because it was "given with the cream", and the third because they had no reason to think otherwise. Four thought that they were not active, the reasons being: not that successful, did not look real, no label, knew cream was active from the packaging. One participant did not know.
- **Gel**: nine thought that the gel was active: three because of the label/packaging, three because their skin improved, one (/two) because it dried up their spots, one said because it was easy to put on, and one had had it before from their doctor. One participant did not know.
- **Likes/dislikes**: not time-consuming or messy, the gel worked well and was easy to apply, and stopped the skin being oily.

Ery. + BP bd: six forms returned.
- **Tablets**: two thought that the tablets were active; one because their skin improved, and one because they got a rash. Three thought they were not: one said they tasted like chalk, and two thought they were vitamin C (one mentioned taste). One participant did not know.
- **Gel**: all six thought that the gel was active; five because their spots improved and the sixth gave no reason.
- **Likes/dislikes**: disliked the treatment ruining T-shirts and bedspreads, but liked the way it improved their skin. It dried their face at first, but then it was fine. Disliked initial dryness/whiteness left on face, but very effective: felt more confident about skin. No dislikes, pleased with results.

Ery. od + BP od: nine forms returned.
- **Tablets**: four thought that the tablets were active, three because their spots improved (reason not known for the fourth: writing was illegible). Four thought that they were not active; one because spots did not seem to get better, one because it did not say on the bottle ("if real it would be labelled for interactions"), one because they did not seem to have any effect, and the fourth gave no reason. One participant did not know.
- **Solution/gel**: all participants thought that the cream was active. One participant indicated that they only had a gel that they thought was active because it made the skin very dry. Six participants thought that the solution was also active; two because it seemed to clear the skin, one felt they were working together, one that it made the face dry, one had had the gel before, and the other had illegible writing ("it worked"?). Two participants thought that the solution was not active: there was improvement and drying the morning after applying the gel the night before, but not after applying the solution. The second said that the gel seemed to form a skin over the spots. One participant did not know about the solution, and gave no reason.
- **Likes/dislikes**: disliked the gel: irritated the skin, the solution was good, but disliked the smell left on skin. The solution made the skin a bit greasy. It made the face a lot clearer/cleared acne. The gel made the skin very dry and flaky.

Codebreak envelopes

Unopened envelopes were received for 462 (61%) of the participants in the study (including discontinued groups). Thirty envelopes (4%) were returned opened and a further three were broken via the Leeds General Infirmary (LGI) list: only six were recorded as opened to help to manage patient care while the patient was on the study (including two broken via LGI):

- **0100** (benzoyl peroxide group) had code broken by GP owing to adverse event, week 6: maculopapular rash limbs and chest, severe and itchy. Participant withdrawn owing to adverse event.
- **0169** (Stiemycin group): code broken by GP because acne worsened and patient wanted alternative treatment and to stop trial. Withdrawn at week 6: reason for withdrawal was that participant did not like having photographs taken.
- **0261** (benzoyl peroxide group) hospitalised owing to vomiting, headaches and dizziness (not thought to be due to trial treatment; had received other unknown medication). Withdrawn at week 6 for adverse event.
- **1313** (minocycline group): code broken by GP and withdrawn at week 6 owing to adverse

event: headache, nausea and rash which returned after break in treatment and restart.
- **1063** (oxytetracycline group): code broken by GP via LGI: required treatment for pelvic infection (thrush). Participant completed study.
- 0411 (oxytetracycline group): code broken by GP via LGI. Patient complained of bad migraine. Withdrawn at week 6 owing to migraine.

Seven were opened after study completion to enable further prescribing of acne treatment (one via LGI who wanted further topical which was placebo), four were opened in error, and one owing to the curiosity of the GP. The reason for opening the remaining 15 envelopes is unknown; all except one were from surgeries allocated to one particular assessor, and it is known that there were delays sending out end-of-study reports to GPs from this assessor, so the assumption is that these codes were broken to enable poststudy prescribing. Surgeries were unable to find a further 111 envelopes (seven confirmed unopened, and three discarded post-trial). It is possible that some surgeries did not receive the envelopes from the assessor. Fifteen envelopes (2%) were apparently posted back, but not received by the authors, 24 participants (3%) had moved surgery and hence the record moved with them, and for 120 participants (16%) no response was received from the surgery. The distribution and collection of the codebreaks was a very time-consuming process, and would have benefited from even more time than could be devoted to it. However, even when envelopes were opened unnecessarily, it was not thought that the GP's knowledge of the participant's treatment was likely to influence their progress in the study.

Appendix 3

Statistical methods: additional information

Patient self-assessment

For each of the seven comparisons (although all ten are presented for completeness), the difference in proportion of participants responding with at least a moderate improvement (patient's assessment) was estimated. These estimates were converted to the NNT, where

NNT = 1 / (absolute difference in risk)
= 1 / (difference in proportions)

The 95% confidence intervals for NNT were calculated by taking reciprocals of the values defining the confidence interval for the absolute risk reduction and reversing their order.

The response rate was also analysed by logistic regression, to take account of covariates. Burke and Cunliffe grade at baseline and duration of acne were significant covariates in the analysis.

Speed of action was assessed by using the assessments over time to see when the first sign of improvement occurred and when the maximum benefit occurred. The initial approach looked at proportions of participants improving at each time-point. A possibility for further exploration would be to model the data with a smoothing function from which the first sign of improvement and maximum improvement would be estimated.

Lesion counts

These were summed over all four areas of the face for each patient visit. Where one area was not assessed at baseline, that area was also not included at future visits for that participant. If a different area was missing at a future visit, that assessment was treated as missing for the purposes of analysis.

Summary tabulations were made of the number of inflamed lesions at each time-point and the number cleared by each treatment by the end of the study, that is, the difference from baseline count. Nodule counts (zero for the majority of participants) were tabulated separately and not formally analysed; they were taken into consideration as part of the global assessments.

Inflamed lesion count (change from baseline) was analysed by ANCOVA. Significant covariates were baseline number of lesions, Burke and Cunliffe grade, and weight. Estimates were made of differences in total lesion counts between treatments. The binomial approximation to the normal distribution was used to calculate 95% confidence intervals for these differences. Assumptions of normality and heterogeneity of variance were checked with residual plots (residuals versus normal deviates, residuals versus fitted values). The change from baseline data were sufficiently normal not to require transformation.

Assessor global assessment

This parameter was analysed using the same methods as patient self-assessment. Duration of acne and previous use of OTC medications were significant covariates in the logistic regression.

Burke and Cunliffe grade

Data were treated as continuous, and changes from baseline were sufficiently normally distributed for a parametric analysis. ANCOVA was used to estimate average grade on each treatment, and difference between treatments, plus 95% confidence intervals. Baseline score, duration of acne and height were significant covariates.

Combined Acne Severity Score

The score was calculated by summing over the four areas of the face for each of inflamed lesions, non-inflamed lesions and redness, and then adding these three scores together. If one or more areas of face were not assessed, the overall score was taken as missing for that visit.

The data were analysed by ANCOVA, and 95% confidence intervals (binomial approximation to normal) were reported. Checks on normality and heterogeneity of variance were made as above. Baseline score, age and assessor were significant covariates in the model.

Local irritation

The actual analysis differed from the analysis plan in a few places, where the proposed presentation of data was found to be inappropriate. These changes were made before the treatment codes were broken.

The irritation scores were ordinal variables with possible values 0 (none), 1 (mild), 2 (moderate) or 3 (severe). There were six scales for patient assessment, and three scales for assessor assessment at each visit; the patient assessment for the first 6 weeks was split into three lots of 2 weeks. Each scale was summarised by frequency, percentage and cumulative percentages for each category.

The three scales in common between the assessor and patient (dryness, erythema and scaling) were tabulated with assessor against patient. At 6 weeks the patient 4–6-week assessment was used. It is recognised that the assessor's assessment is a snapshot on the day, whereas the patient's summarises the preceding weeks.

Side-effects at week 6 were compared descriptively between participants who completed the study and those who did not.

For each irritation parameter (nine in total) nested barcharts were plotted of the proportions for each grade, with one bar for each treatment and each week.

For each of the nine parameters a worst case analysis was carried out. This involved taking the worst category over on-treatment visits for every participant, then counting the number of participants per treatment with a worst category of moderate or severe. The Cochran–Mantel–Haenszel test was used to compare differences between treatments.

Overall irritation indices were calculated: for patient-assessed irritations (maximum score 18), for assessor-assessed irritations (maximum score 9), and for the three irritations in common, as assessed by the patient (maximum score 9). These were analysed at each visit by ANOVA.

Use of moisturiser

This was summarised only, and not formally analysed. Many participants did not use the moisturiser (did not like the E45 cream) and others may have used it whether they needed it or not, so the data are not considered that useful, although they were considered alongside the dryness irritation scores.

Quality of life

Quality of life data were analysed in the standard way for each questionnaire.

SF-36

The standard UK version 1.0 was used. Each question was given a precoded value in the database. Ten of the 36 items were then recoded as per the standard SF-36 analysis procedures, with programming in SAS. Raw scale scores were computed by summing across items in the same scale. These raw scores were then transformed to a 0–100 scale (transformed scores). Details of the SF-36 precoded and final values are given in the SF-36 Health Survey Manual.

The eight scales were:

- physical functioning (items 3a–3j)
- role – physical (items 4a–4d)
- bodily pain (items 7 and 8)
- general health (items 1, 11a–11d)
- vitality (items 9a, 9e, 9g, 9i)
- social functioning (items 6 and 10)
- role – emotional (items 5a–5c)
- mental health (items 9b, 9c, 9d, 9f, 9h).

Also recorded was item 2, which gives a measure of the change in health over the previous year.

Missing items were treated as follows: if more than half the items in a score were missing, then the score was set to missing. If fewer than half were missing, then the missing items were set to the average of the rest of the scores for that participant's scale. Only once this procedure had been followed were values carried forward for missing scale values.

Scales (week 18 minus week 0) were summarised, and then analysed by ANCOVA.

Significant covariates were:

- physical functioning: baseline, Burke and Cunliffe baseline grade, height
- role – physical: baseline, height, family history of acne
- bodily pain: baseline, gender
- general health: baseline, previous prescription for acne
- vitality: baseline, gender

- social functioning: Burke and Cunliffe baseline grade, previous oral acne treatment
- role – emotional: baseline
- mental health: baseline.

DLQI and CDLQI

Questions were scored as per standard (*Table 49*), and the two parts of question 7 combined to form one answer. All ten items were added to form a total score (range 0–30). Only the total scores were formally analysed using ANCOVA. DLQI and CDLQI were analysed separately as it is not possible to combine them. Significant covariates were baseline and age for DLQI and baseline only for CDLQI.

Missing items were treated as follows: if more than two of the ten items were missing, then the total score was set to missing. If only one or two were missing, then the missing items were scored as zero and the total score was calculated. Only once this procedure had been followed were values carried forward for missing scale values.

Scores were combined into sections as shown in *Table 50*.

Fifty-five participants were given the incorrect version of the questionnaire to complete, for their age, at one or more visits (i.e. DLQI instead of CDLQI or vice versa). Although seven of the questions were similar enough to transfer between questionnaires, the rest were not, and hence total scores were set to missing by the above rules. These questionnaires were deleted from the analysis dataset and substituted by values carried forward.

DQOLS

The 41 items on this questionnaire were divided between three scales: psychosocial (17 questions), activities (12) and symptoms (12). Each item was rated on a five-point scale (*Table 51*).

Missing items were treated as follows: if more than half the items in a scale were missing, then the score was set to missing. If fewer than half were missing, then the missing items were scored as zero. Each scale was then calculated by summing the scores for that scale and calculating an adjusted score. The adjusted score is obtained from the sum by multiplying by 25 and dividing by the number of items comprising the score (17, 12 or 12), and thus has a possible range of 0–100. Only once this procedure had been followed were values carried forward for missing scale values.

Change in the scales (week 18 minus week 0) were summarised, and analysed by ANCOVA. Significant covariates were: scale baseline for psychosocial; baseline and age for activity; and baseline, age and previous acne treatment for symptoms.

TABLE 49 *Responses and scores for DLQI and CDLQI*

Response	Score
Very much	3
A lot/quite a lot	2
A little/only a little	1
Not at all	0
Not relevant	0
Unanswered	0
Question 7 prevented work/studying/school	3

TABLE 51 *DQOL responses and scores*

Response	Score
Not completed	0
Not relevant (activity only)	0
Very slightly or not at all	0
A little	1
Moderately	2
Quite a bit	3
Extremely	4

TABLE 50 *Categories for DLQI and CDLQI questionnaires*

DLQI		CDLQI	
Category	**Questions included**	**Category**	**Questions included**
Symptoms and feelings	1, 2	Symptoms and feelings	1, 2
Daily activities	3, 4	Leisure	4, 5, 6
Leisure	5, 6	School or holidays	7
Work and school	7	Personal relationships	3, 8
Personal relationships	8, 9	Sleep	9
Treatment	10	Treatment	10

Worst aspect

The worst aspect was analysed by logistic regression to take account of covariates. Duration of acne was the only significant covariate.

Dropout rates

The dropout rates included all reasons for not completing the study. They were summarised per treatment group: number and percentage by visit, plus mean number of weeks on treatment and in the study.

Re-referral rates

The numbers of participants who (1) needed, (2) requested and (3) received treatment at the end of the trial, and also the number offered specialist referral, were recorded. Re-referrals were defined as those who stopped treatment at the end of the trial, but started more (either prescribed or OTC) within 3 months of the end of the trial. A lot of these data are missing, and methods of recording were not adequately standardised, so data were summarised only. Participants were allowed to keep their remaining medications at the end of the trial, so many participants did not stop treatment at 18 weeks.

Adverse events

These were prompted by the following questions:

- Have you felt unwell since beginning your treatment?
- Have you experienced any symptoms which you previously didn't have?
- Have you experienced any worsening of any existing symptoms?

If necessary (e.g. the participant answered yes to any of the questions or needed further prompting) the assessors had a further list of questions. A short description of the event was recorded, along with the severity, outcome and dates.

The total number of participants with adverse events, and the number of adverse events by week and by body system were summarised. Body system was allocated by the study team. Meddra, the latest Food and Drug Administration (FDA)-approved system that the authors were hoping to use for body system allocation, turned out to be too expensive and too time-consuming to set up. Some adverse events carry over more than one visit, so checks using event text and dates were incorporated.

Antibiotic resistance

Some of the analysis methods for the microbiology data differed from the analysis plan, but these methods were changed before the treatment codes were broken; in particular, subsetting rather than including a factor in logistic regression, and presenting tables rather than plots. In addition, responder (improvement in patient global outcome) was replaced by success/failure (at least moderate improvement) as for other analyses.

Colonisation by resistant propionibacteria versus treatment failure

The patient global assessment at week 18 was tabulated against growth at week 0, first with all categories and then with categories combined to success/failure versus colonised/not colonised.

The primary end-points (patient global assessment and lesion counts) were analysed at week 18 and week 12 for the subgroups:

- participants colonised or not colonised by tetracycline-resistant organisms at baseline
- participants colonised or not colonised by erythromycin-resistant organisms at baseline
- participants colonised or not colonised by tetracycline-resistant organisms at week 18
- participants colonised or not colonised by erythromycin-resistant organisms at week 18.

For the discontinued treatment groups, primary end-points were also summarised by clindamycin-resistant organisms at baseline and week 18.

The additional analyses at week 12 were performed because topicals are usually prescribed by GPs for only 12-week courses.

Relevant resistances are given in the main body of the report (Chapter 2, 'Statistical methods; Antibiotic resistance', p. 14).

It was noted that:

- The degree of resistance (i.e. the MIC) rather than population density of resistant organisms may correlate with response. MIC data, however, are not available for this study.

TABLE 52 *Costs of treatment*

Treatment	Amount per pack	Cost per pack (£)	Amount per day	Cost per week (£)	Cost for 12 weeks (£)	Cost for 18 weeks (£)
Oxytetracycline (non-proprietary)	28 tablets	0.81	4 tablets	0.81	9.72	14.58
Minocin MR	56 capsules	35.23	1 capsule	4.40	70.46	105.69
Panoxyl Aquagel	40 g	1.92	0.8 g	0.27	3.84	5.76
Benzamycin	46.6 g	15.27	0.8 g	1.84	30.54	45.81 (30.54)
Stiemycin + Panoxyl Aquagel	50 ml + 40 g	8.60 + 1.92	0.7 ml + 0.8 g	0.42 + 0.14 = 0.56	10.52	12.44

Costs are from the BNF, September 2001, the most recent available version at the time of analysis. The amount needed for 18 weeks of treatment with Benzamycin is only just over two containers, so costs were calculated for both two and three containers.

- Any relationship between resistance status and response could be masked by other factors, for instance adherence to treatment. The adherence data (as for most studies) are probably not sufficiently complete and accurate to be included as a covariate in the analysis.

Prevalence and time-related resistance patterns

The percentage of participants with resistant organism status (both yes/no and categorised by number of strains) was summarised for each organism, by week and treatment group. These data estimate:

- the prevalence (any resistance versus none) of resistant organisms (tetracycline, erythromycin, clindamycin) from the baseline data
- the pattern of resistance over the time-course of the study, by treatment group. Presence/absence of resistant organisms was used as a cut-off point.

Cost-effectiveness

The costs of each treatment were calculated in terms of:

- drug costs (*Table 52*)
- cost of referral back to GP (£18: University of Kent figures, 2000)
- withdrawals counted as treatment failures and costed as referral to GP (£18)
- referral to dermatology specialist (£53: University of Kent, 2000).

For example, the cost of 18 weeks treatment with oxytetracycline for someone who was referred to a dermatology specialist was calculated as £14.58 + £53 = £67.58. Participants who withdrew from the study had the cost of referral to GP added to their total. Both mean and median costs were calculated. Although median costs are more appropriate for the data distribution, mean costs may be more useful for estimating costs to the health service.[48]

Any relationship between WTP and initial severity (Burke and Cunliffe grade), and WTP and patient global improvement at week 18 was investigated by frequency tables.

Adherence to treatment

About 40% of medication packs were returned, some of which were incomplete; 75–80% of patients returned at least one diary card. Additional textual information is available on the database.

The planned analyses (not carried out) are as follows. The percentage of tablets (out of what should have been taken, not of what the bottle contained, as there were extra tablets and visit intervals varied) will be calculated. The amount of topical used will also be calculated. These will be compared between treatments using ANOVA.

Where no treatment box or containers were returned the amount used will be regarded as missing. Where some of a kit was returned (e.g. cream, but no tablets, or an empty box), the unreturned portion will be assumed to be completely used (i.e. 100% compliance), since participants frequently commented that they had thrown away the bottle because it was empty. At week 18, where a participant asked to keep the remainder of the treatments it can only be

assumed that they were taken according to instructions, unless there are comments to the contrary.

Comments on the test medication forms will be listed by treatment group.

Information collected on diary cards will be scanned for obvious incidences of missed doses; while it cannot be assumed that a tick means the treatment was taken (the whole card was often completed in retrospect just before the visit), it seems likely that where it is indicated that the treatment was not taken, then it probably was not.

Analysis of these data was given low priority because of questions over their validity and reliability, and hence they were not included in this report.

Appendix 4

Protocol violations and deviations

Known protocol violations (inclusion/exclusion criteria not met at week 0)

Age 12–39 years

Participant 1095 was 42 years old, and 0870 was 11 years 10 months old at entry to the study.

At least 15 inflamed lesions

Participants 0073, 0092, 0165 and 0876 had 13, 13, 14 and 13 lesions at baseline, respectively. In the discontinued treatment groups participants 0027, 0029, 0164, 0191 and 0193 had 7, 11, 12, 13 and 13 lesions at week 0, respectively. Lesion counts fluctuate, and it is likely that the lesion count for these participants dropped between recruitment and week 0.

Known protocol deviations

Current therapy with interacting medication

Twenty-five out of 649 (4%) participants took or probably took (in three cases the participant was unsure of what the antibiotic was) β-lactam antibiotics (including penicillin) during the study; of these, seven were on the antibiotic at the start of treatment. Although as a potentially interacting medication this was a deviation from the protocol, it was not considered to be important for interpretation of the overall results, since evidence suggests that short courses of such therapy do not generally inhibit the growth of skin propionibacteria.

In the discontinued groups five out of 112 (4%) participants took or probably took (in three cases the participant was unsure of antibiotic) β-lactam antibiotics, all after starting in the study.

Significant systemic disease

Out of the five main treatment groups three participants reported significant systemic disease: participant 0320 reported rheumatoid arthritis at entry to the trial, and chose to withdraw before the 6-week visit; 1493 was withdrawn at week 6 owing to fever and convulsions which were thought to be due to a meningitis vaccine; 1186 was withdrawn at week 12 because of pneumonia.

Pregnancy

The following participants were withdrawn from the five main treatment groups because of pregnancy: patient 0672 at week 6, 0165 at week 18 and 1485 at week 6.

Visit timings

The visit window included up to 7 days before and up to 14 days after the nominal dates of 6, 12 and 18 weeks from week 0. One-hundred and sixty participants (21% of participants) had at least one visit outside the visit window (203 visits in total), excluding withdrawals occurring between visits. At least 37 questionnaires were not completed on the visit date: it was often not known when the questionnaire was completed, as the visit date rather than completion date was usually given; however, questionnaires were usually only received by the participant a few days before the visit. The utility questionnaire was improved (questions 2–4 replaced by one question) part way into the study (14 October 1998), and participants who received the old questionnaire were asked to answer the new question 2: 39 participants completed question 2 at week 6 and 16 at week 12. One-hundred and forty-one participants did not receive the revised questionnaire, and hence only provided data for question 1.

Early and late visits were usually a result of fitting visits into the assessors' busy schedule, rescheduling missed visits, avoiding holidays and difficulties contacting participants. In particular, several week 18 visits were late as it was thought more important to have a late final visit than no visit at all, given that this was the time-point for analysis. There also appeared to be confusion on the part of the assessors between the lapsed time from week 0 and time between visits, with visits occurring increasingly far from the nominal date.

Adherence to treatment

The data collected have not yet been analysed. Their reliability is considered to be low.

Incorrect version of DLQI

Fifty-five participants were given the incorrect version of the questionnaire to complete, for their age, at one or more visits (i.e. DLQI instead of CDLQI or vice versa).

Appendix 5

Recommendations for future research in order of priority

Recommendations for possible future research are given below in priority order. List A includes suggestions for clinical studies to inform the improved long-term management of acne. List B includes suggestions for the improvement of clinical trials of acne therapies. Ways in which the data collected in this trial could be explored more fully are given in list C.

A: Clinical studies

1. Antibiotics did not perform well in this community-based population. Because of this, and in the light of global pressure to curb practices that promote antibiotic resistance, studies which inform the replacement of antibiotics as the cornerstone of acne management should be a priority. To this end, trials that assess the efficacy, cost-effectiveness and risk–benefit of topical retinoids compared with the best of the antibiotic-based regimens are required. It may also be desirable to include a combined treatment group to test the hypothesis that treatments with different modes of action (in this case antibacterial versus comedolytic) may be additive in terms of either greater overall efficacy or speed of response.
2. Assuming that antibiotics will not be replaced overnight but will continue to play a part in acne management, how long should a course of antibiotic treatment be? Can antibiotics be stopped after 6 or 12 weeks and therapy continued with a non-antibiotic-based regimen (e.g. benzoyl peroxide or a topical retinoid?). If so, selective pressure (bacterial resistance) could be markedly reduced without compromising long-term outcomes.
3. In view of the temporary effects of topical and systemic antimicrobials for acne, studies that inform the choice between early intervention with oral isotretinoin and alternative treatments for moderate and possibly milder degrees of acne are needed. Oral isotretinoin can give rise to a permanent cure, albeit with a risk of teratogenicity and possible depression, so that widening indications for its use would require regulatory approval.
4. Although this study has helped to inform the management of mild to moderate inflammatory acne of the face, the findings may not be generalisable to truncal acne, for several reasons, including difficulty applying topical therapy to the back, occlusion of the skin by clothing and site-to-site differences in sebum excretion rate. Given that most patients have some degree of involvement of non-facial skin, trials of truncal acne are important. However, the assessment of truncal acne using severity scales and/or lesion counting is problematic. Few practitioners have the necessary expertise, suggesting that global assessment by patients may be the most reliable outcome measure in this context.
5. Do individuals with erythromycin/clindamycin resistant propionibacterial floras respond adequately when erythromycin or clindamycin are used without concomitant benzoyl peroxide and are these antibiotics more selective when used alone? To minimise selective pressure, would it be helpful to use benzoyl peroxide concomitantly whenever antibiotics are prescribed and, if so, would short washouts (say one week in four) suffice?
6. How might acne relapses be best treated? Can reliance on the use of long or sequential antibiotic courses be avoided?
7. This study, like most acne trials, recruited patients of both genders, from different ethnic groups and social backgrounds and with a wide variety of ages. It would be of interest to compare treatment responses of males and females, of individuals with different skin types and in different social classes, and of patients with persistent or late-onset acne compared with those with adolescent acne. See also recommendations in the systematic review by Lehmann and colleagues.[51]
8. Until licensing authorities insist that drug manufacturers should show that their 'me too' product produces substantial benefit over existing main acne treatments in terms of effectiveness, cost-effectiveness or side-effects, the NHS will continue to have difficulty in advising patients and their carers on which treatment is 'best'. The authors suggest that benzoyl peroxide be used as the gold standard

until another agent is proven to be statistically significantly superior for the routine management of mild to moderate inflammatory acne of the face.
9. Further studies on the effect of propionibacterial antibiotic resistance on treatment outcomes.

B: Improvements to clinical trials and clinical trial methodology

1. Patient-based outcome measures are probably the most relevant for informing prescribing decisions, but need refinement. Research is required to identify the best method of self-assessment and whether the use of baseline photographs is any more reliable than recall when estimating global improvement.
2. What degree of improvement (or level of residual disease) is regarded by acne patients as satisfactory? Could a point be identified at which most patients would be happy to leave the surgery with no further treatment or be transferred to a maintenance regimen? This information could be used to define a more meaningful end-point for future acne trials.
3. Further investigation is required to ascertain (1) whether any existing quality of life instrument satisfactorily captures the effects of acne on quality of life, particularly for patients managed exclusively in the community, and (2) whether the instrument is useful for assessing responses to treatment. If so, to what extent do changes in quality of life resulting from therapeutic intervention accord with changes in disease severity? If not, effort should be made to develop a new or revised instrument for quality of life that is specific for acne. In the meantime, the DQOLS could be used in parallel with any other quality of life instrument as a means of determining comparative performance.
4. A formal comparison of the new CASS with a well-established method of acne grading such as that of Burke and Cunliffe is warranted given the promising results in this study. This should be followed by a fuller evaluation of its usefulness in assessing acne.
5. The inclusion of the utility scales generated useful information on cost–benefit and the authors recommend the inclusion of utility analysis routinely in acne trials. However, utility analysis in acne trials is in its infancy. The questionnaires used here need modifying and retesting with well-defined patient populations. It should eventually be possible to rely on WTP or WTA, rather than both.
6. The quality of life scores we obtained at baseline were better (i.e. participants more healthy) than those previously reported for outpatients with acne of similar severity, and a possible explanation is that participation in a clinical trial affects well-being even before participants have begun therapy. One way to test this would be to use the most responsive of the three instruments (the DQOLS) in a large number of patients who are under the care of their family doctor for acne but who are not participating in a clinical trial, and to compare the data generated with those resulting from the present study.

C: Additional ways of exploring the data from this study

1. Analysis of the data on an individual participant basis to ascertain whether there is any correlation between clinical outcome and reduction in propionibacterial numbers or quality of life changes.
2. Plots of individual response curves and application of a smoothing function for time to maximum benefit. Identifying the shapes of response curves for different types of therapeutic agent would provide a rational basis for the selection of assessment points in clinical trials.
3. Expert checks: global evaluation of improvement by an expert panel using the photographs taken at baseline and during treatment.
4. In-depth analysis and reporting of the data from the monitoring sessions of intra-assessor and interassessor variability in lesion counting and acne grading.
5. Exploration of the available data on adherence to treatment (including individual microbiology data) and how this relates to efficacy.
6. Further evaluation of what study participants considered was the worst aspect of having acne with a view to pursuing the validation of this as a simple outcome measure and possibly to inform the development of a better quality of life instrument.
7. Further evaluation of what the study participants thought makes their acne worse.
8. A fuller exploration of the utility questions with a view to the development of an improved utility questionnaire.
9. Cost-effectiveness analysis of the age/gender differences in median bids, concerning WTA and WTP. Exploration of differences between subgroups, for example males and females (see point 7 in list A).

Appendix 6

Recruitment

A total of around 600 surgeries and colleges was approached (174 in Nottingham, of which 48 were recruited; and more than 400 in Leeds, of which 99 were recruited; from two of the recruited colleges no participants were recruited). Participants in 97 surgeries and seven colleges were randomised to treatment. Eighty-three participants (13%) were from colleges, all on the five main treatments. The remaining 41 surgeries and two colleges agreed to take part, but no participants were randomised at these centres. Included in the approached surgeries were 298 GPs, who were asked to recruit actively two patients each over a 4-week period. Twenty-one of the above surgeries were recruited with the help of Trent Focus, who approached 67 surgeries on their list; a further five of their surgeries were recruited independently.

Participant recruitment took place between July 1998 and April 2000. Participants who were currently on acne treatment at recruitment were required to stop treatment for 4 weeks before starting on study treatment. The first participant started study treatment on 7 September 1998; the last participant completed on 28 September 2000. See the flow diagram in Chapter 3 (*Figure 4*) for numbers of participants recruited and randomised.

Potential participants were identified by the surgeries as those patients in the age range 12–39 years who either had a diagnosis of acne or had been prescribed some of the most common treatments for acne (that were not very likely to have been prescribed for other diseases) within the past 2 years. At the time not all surgery computerised systems included diagnosis. Where possible, other exclusion factors were included in the search. Letters of invitation were sent from surgeries to identified patients, and those who were interested returned reply slips in prepaid envelopes to the authors. In cohort 1, 3049 letters were sent from surgeries, to which 847 people (28%) replied. It is estimated that over 10,000 letters were sent in cohorts 2 and 3, in addition to articles in newspapers (local and university), a radio broadcast, and recruiting by posters and e-mails from colleges.

Of the participants attending a recruitment visit, 990 were eligible for inclusion to the study: 128 did not sign the consent form (many were not available for appointments), 101 consented to the study, but then were not randomised, and 761 were randomised to study treatment (649 to the five main treatments); 897 were not eligible for inclusion in the study. Three-hundred and eighty-seven people booked (21%) did not attend the recruitment visit (some cancelled in advance); this number does not include participants who did not attend the first appointment, but did attend a subsequent one. A further 356 replies were received for whom no appointment was apparently made: reasons include the participant choosing not to take part after information was given by telephone, it not being possible to contact the participant, and no time to make appointments for all participants towards the end of cohort 1 and the end of the study.

The reasons for participants not meeting entry criteria are given in *Table 53*. Only one reason has been recorded per participant, as some participants were not eligible on more than one count, either the main one, or the first one on the exclusion list where other questions were not asked. Later in the study return slips for study inclusion asked participants to answer some of the inclusion criteria questions, so not all excluded participants attended a recruitment visit.

Twelve per cent of participants recruited were not randomised to treatment. The main reason was non-attendance at visit (43% in Nottingham; reasons were missing for many Leeds participants, so data were not included). Other reasons were no longer having enough inflamed lesions (20%), changed mind (14%), no longer available (8%), choosing not to stop current treatment (5%), and for the rest various other entry criteria were no longer satisfied. The percentage not randomised was higher in cohort 1 (21%), probably due to keeping participants waiting more than the 4 weeks between recruitment and starting study treatment, in an initial attempt to stick to a more rigid cohort design.

TABLE 53 *Recruitment: reasons why participants were not eligible*

Reason not eligible	No. of participants	% (of known reasons)
Fewer than 15 inflamed lesions on face	268	37
Not wishing to stop current treatment	73	10
On Dianette	71	10
Previously taken Roaccutane	63	9
Exclusively truncal acne	42	6
Late-onset acne (>26 years old)	40	6
Hypersensitivity to study treatments	35	5
Pregnant/intention/breast-feeding	20	3
Under care of dermatologist	18	3
Rosacea	17	2
Comedonal acne	16	2
Other dermatological facial disease	13	2
No facial acne	10	1
Significant systemic disease	8	1
Other with less than 1% incidence[a]	26	
Total	721	100%
Reason not known/recorded	176	

[a] Other: outside age range (7), family history of rheumatoid arthritis (5), cystic/nodular acne (4), potential interaction with current medication (4), fewer than 15 non-inflamed lesions (2), acne too severe (2), atypical acne (1), GP advised not to take part (1).

Appendix 7

Reasons for early withdrawal

TABLE 54 *Reasons for early withdrawal*

Treatment group	Patient	Week	Reason for withdrawal	Details
Oxytetracycline	0042	12	Exacerbation of acne	
	0165	18	Patient unable/unwilling to continue	Pregnancy
	0226	6	Patient unable/unwilling to continue	Long-awaited appt with skin specialist received
	0237	12	Patient unable/unwilling to continue	No reason given
	0245	6	Patient unable/unwilling to continue	
	0333	6	Patient unable/unwilling to continue	
	0375	12	Other	DNA T6 & T12
	0396	12	Patient unable/unwilling to continue	Job commitments
	0411	6	Adverse event	Migraine
	0447	18	Other	DNA, no response
	0459	18	Patient unable/unwilling to continue	Spots worse, & not motivated to continue
	0468	18	Other	DNA, no response
	0511	12	Adverse event	Candida infection
	0520	12	Patient unable/unwilling to continue	Can't commit & can't be bothered
	0541	12	Patient unable/unwilling to continue	Can't make appointments
	0557	6	Adverse event	Stomach aches & diarrhoea
	0610	6	Other	Potential hepatotoxicity
	0634	6	Patient unable/unwilling to continue	Cannot commit to appts & has forgotten treatments
	0718	6	Adverse event	V. sore red, dry skin + Rash & swelling to eyes
	0741	18	Patient unable/unwilling to continue	Can't commit
	0768	12	Patient unable/unwilling to continue	Can't commit or be bothered, plus contraception
	0839	18	Patient unable/unwilling to continue	No reason given
	0870	12	Patient unable/unwilling to continue	No reason given
	0894	6	Patient unable/unwilling to continue	
	0962	6	Patient unable/unwilling to continue	No reason given
	0982	6	Patient unable/unwilling to continue	No reason given
	1002	6	Patient unable/unwilling to continue	No reason given
	1034	18	Patient unable/unwilling to continue	No reason given
	1037	12	Patient unable/unwilling to continue	Pt going abroad & doesn't wish to take study meds
	1068	18	Patient unable/unwilling to continue	No reason given
	1088	6	Exacerbation of acne	
	1166	0	Patient unable/unwilling to continue	No reason given, letters not replied
	1175	18	Patient unable/unwilling to continue	
	1186	12	Adverse event	Pneumonia
	1325	12	Other	DNA, unable to contact
	1493	6	Adverse event	Fever & convulsions
	1509	12	Other	Acne has not improved w.r.t. white & blackheads
Minocycline	0023	6	Other	Not using treatments
	0038	12	Exacerbation of acne	
	0096	18	Patient unable/unwilling to continue	Pt not responding to attempts to contact
	0120	18	Other	DNA x2 T12 & T18, no response to letters/phone

continued

TABLE 54 *Reasons for early withdrawal (cont'd)*

Treatment group	Patient	Week	Reason for withdrawal	Details
Minocycline	0139	6	Adverse event	Diarrhoea + Stomach cramps
	0149	6	Other	Moved to London
	0170	6	Patient unable/unwilling to continue	No reason given
	0227	12	Patient unable/unwilling to continue	No reason given
	0275	18	Patient unable/unwilling to continue	
	0300	6	Patient unable/unwilling to continue	
	0317	18	Patient unable/unwilling to continue	Work commitments
	0320	6	Patient unable/unwilling to continue	
	0424	18	Other	DNA, no response
	0441	12	Other	DNA, no response
	0453	12	Patient unable/unwilling to continue	Consulted GP, spots no better, they decided
	0475	12	Adverse event	Severe headaches with dizziness
	0596	6	Other	Patient DNA × 2 & uncontactable
	0636	6	Patient unable/unwilling to continue	Couldn't swallow tablets & on penicillin
	0655	6	Adverse event	Breakthrough bleeding between periods
	0672	6	Adverse event	Pregnancy
	0813	18	Adverse event	Thrush
	0824	12	Exacerbation of acne	Needs a change of medication
	0873	6	Patient unable/unwilling to continue	
	0900	12	Patient unable/unwilling to continue	No reason given
	0917	6	Patient unable/unwilling to continue	No reason given
	0927	6	Patient unable/unwilling to continue	No reason given
	0963	6	Patient unable/unwilling to continue	No reason given
	0989	18	Patient unable/unwilling to continue	No reason given
	1045	12	Patient unable/unwilling to continue	No reason given
	1073	18	Patient unable/unwilling to continue	No reason given
	1081	0	Patient unable/unwilling to continue	
	1125	12	Patient unable/unwilling to continue	No reason given
	1160	12	Patient unable/unwilling to continue	Going abroad
	1265	6	Patient unable/unwilling to continue	Only used trt 1 week as made spots worse
	1266	12	Patient unable/unwilling to continue	Having problems with medication & not using it
	1289	12	Other	Unable to contact
	1313	6	Adverse event	Headache + nausea + rash
	1321	12	Other	DNA, unable to contact
	1336	18	Other	DNA
	1381	6	Other	Unknown
Benzoyl peroxide	0044	6	Exacerbation of acne	
	0086	6	Adverse event	Rash? Acne worsening to face only
	0100	6	Adverse event	Rash on legs, chest & arms
	0183	6	Patient unable/unwilling to continue	No reason given
	0261	6	Adverse event	Vomiting, headaches, dizziness
	0273	12	Patient unable/unwilling to continue	
	0309	6	Patient unable/unwilling to continue	
	0334	12	Patient unable/unwilling to continue	Persistent dry, flaking & sore skin
	0381	12	Other	DNA T6 & T12
	0421	12	Other	DNA, no response
	0435	12	Patient unable/unwilling to continue	Not using medication, & wished to withdraw
	0498	18	Patient unable/unwilling to continue	Pt not contactable
	0552	6	Adverse event	Eczematous rash to face
	0632	6	Adverse event	?Allergic reaction – rash & severe swelling to face

continued

TABLE 54 *Reasons for early withdrawal (cont'd)*

Treatment group	Patient	Week	Reason for withdrawal	Details
Benzoyl peroxide	0657	6	Adverse event	Severe dry skin + Rash + Swelling of eyes
	0692	18	Patient unable/unwilling to continue	Lack of progress & not using meds regularly
	0698	6	Other	Patient DNA twice & not contactable
	0750	12	Adverse event	Skin reaction (red & burning)
	0762	6	Other	Patient DNA × 2 & is not contactable
	0780	18	Exacerbation of acne	
	0850	6	Patient unable/unwilling to continue	
	0871	6	Patient unable/unwilling to continue	No reason given
	0952	6	Patient unable/unwilling to continue	No reason given
	0977	12	Patient unable/unwilling to continue	No reason given
	1011	6	Patient unable/unwilling to continue	Acne no longer a bother
	1022	12	Patient unable/unwilling to continue	No reason given
	1033	6	Patient unable/unwilling to continue	
	1039	12	Patient unable/unwilling to continue	No reason given
	1099	0	Patient unable/unwilling to continue	
	1107	6	Other	No reason given. DNA T6 or respond to letters
	1112	12	Patient unable/unwilling to continue	
	1158	18	Patient unable/unwilling to continue	Going on holidays
	1182	12	Exacerbation of acne	
	1271	12	Patient unable/unwilling to continue	Not using trt properly & thinks it make skin worse
	1297	18	Other	Not replied in time for visit
	1310	12	Patient unable/unwilling to continue	Will be out of the country & unable to attend T18
	1382	0	Patient unable/unwilling to continue	Parents could not make time to bring to T6 appt
	1523	6	Adverse event	Sore, dry, red skin
Ery. + BP bd	0007	6	Other	Not given
	0047	6	Patient unable/unwilling to continue	
	0125	6	Adverse event	Excessive dryness & burning sensation to skin
	0187	12	Patient unable/unwilling to continue	Sports commitment
	0192	6	Patient unable/unwilling to continue	No reason given
	0256	12	Patient unable/unwilling to continue	No reason given
	0315	18	Patient unable/unwilling to continue	No reason given
	0345	18	Other	DNA, unable to contact
	0384	18	Patient unable/unwilling to continue	
	0449	12	Patient unable/unwilling to continue	Death of father
	0497	18	Patient unable/unwilling to continue	Pt not contactable
	0682	12	Adverse event	Rash & swelling to face
	0691	12	Patient unable/unwilling to continue	Pt not contactable
	0828	6	Patient unable/unwilling to continue	
	0938	12	Patient unable/unwilling to continue	No reason given
	0948	12	Patient unable/unwilling to continue	No reason given
	0961	12	Patient unable/unwilling to continue	No reason given
	0978	6	Other	Unknown
	1043	6	Patient unable/unwilling to continue	No reason given
	1167	18	Patient unable/unwilling to continue	No reason given
	1221	18	Patient unable/unwilling to continue	Due to illness
	1327	12	Patient unable/unwilling to continue	Pt & GP: needed minocycline for spots on scalp
	1346	18	Other	DNA?
	1485	6	Other	Pregnancy
	1525	12	Patient unable/unwilling to continue	Due to work commitments

continued

TABLE 54 *Reasons for early withdrawal (cont'd)*

Treatment group	Patient	Week	Reason for withdrawal	Details
Ery. od + BP od	0019	6	Patient unable/unwilling to continue	Exacerbation of acne
	0036	18	Other	No T18 visit, reason unknown, T18 date used
	0050	18	Other	Pt only attended T0, no other info, T18 date used
	0090	6	Adverse event	Dry skin & discoloration
	0122	6	Adverse event	Skin tenderness
	0144	6	Adverse event	Rash to cheeks
	0162	6	Adverse event	(unknown)
	0212	18	Patient unable/unwilling to continue	No reason given
	0223	12	Patient unable/unwilling to continue	Family commitments
	0254	12	Patient unable/unwilling to continue	No reason given
	0284	6	Patient unable/unwilling to continue	
	0292	18	Patient unable/unwilling to continue	Change of address
	0307	6	Patient unable/unwilling to continue	
	0325	12	Other	DNA, unable to contact
	0386	12	Other	DNA, no response
	0419	6	Other	Possible topical reaction
	0432	18	Other	DNA, no response
	0456	12	Patient unable/unwilling to continue	Unexpectedly had to return to Spain
	0523	12	Adverse event	V. dry red 'blotchy' skin
	0540	12	Adverse event	Joint pain left knee + Increased appetite
	0635	6	Adverse event	Skin reaction/irritation
	0822	12	Patient unable/unwilling to continue	No longer interested
	0835	18	Patient unable/unwilling to continue	No reason given, DNA 3 visits
	0876	12	Patient unable/unwilling to continue	No reason given
	0918	6	Patient unable/unwilling to continue	
	0988	6	Patient unable/unwilling to continue	No reason given
	1041	12	Patient unable/unwilling to continue	No improvement in acne
	1106	18	Patient unable/unwilling to continue	No reason given
	1120	18	Patient unable/unwilling to continue	No reason given
	1164	12	Patient unable/unwilling to continue	
	1172	12	Patient unable/unwilling to continue	No reason given
	1188	18	Patient unable/unwilling to continue	No reason given
	1217	12	Patient unable/unwilling to continue	
	1262	6	Exacerbation of acne	
	1348	18	Other	DNA?
	1507	6	Adverse event	Thrush
	1512	12	Patient unable/unwilling to continue	Patient unwilling (back not responding)
	1524	12	Patient unable/unwilling to continue	Can't commit to study

Pt, patient; DNA, did not attend.

Appendix 8

Further treatment within 3 months of end of study

TABLE 55 *Further treatment within 3 months of end of study*

Treatment group	Patient	Sought further treatment?	Source	Medication received
Oxytetracycline	0020	Yes	Prescribed	Oxytetracycline
	0052	No	.	
	0062	No	.	
	0073	No	.	
	0079	Yes	Prescribed	Oxytetracycline tablets
	0092	Yes	Prescribed	Oxytetracycline – 6 month course
	0108	Yes	Prescribed	Oxytetracycline tablets
	0117	Yes	OTC	Face washes (don't know which) & witchdoctor gel
	0127	No	.	Continued med until ran out.
	0142	No	.	
	0153	Yes	Prescribed	Roaccutane
	0271	Yes	OTC	Clearasil
	0278	No	.	
	0293	Yes	Prescribed	Erythromycin
	0302	No	.	
	0311	Yes	Prescribed	Oxytetracycline tablets
	0327	Yes	Prescribed	Stiemycin- erythromycin
	0355	No	.	
	0491	Yes	Prescribed	Not quite sure
	0506	No	.	
	0565	No	.	
	0582	No	.	
	0589	No	.	
	0597	No	.	
	0622	Yes	OTC	Oxy10
	0646	No	.	
	0651	Yes	Prescribed	Oxytetracycline
	0665	No	.	
	0680	Yes	Prescribed	Continued oxytet. (study med) + Isotrexin gel
	0688	Yes	Prescribed	Oxytetracycline
	0697	No	.	
	0713	Yes	Prescribed	Zineryt solution
	0773	No	.	
	0792	No	.	
	0808	No	.	
	0818	Yes	Prescribed	Clindamycin topical lotion
	0851	Yes	Prescribed	Roaccutane
	0865	Yes	Prescribed	Oxytetracycline 250mg
	0882	Yes	Prescribed	Study medication
	1063	No	.	
	1110	No	.	
	1119	No	.	
	1130	Yes	Prescribed	Same tablets as in trial
	1155	No	.	
	1196	Yes	Prescribed	Extra med gone – will ask for oxytet. + OTC cream
	1409	No	.	
	1502	Yes	Prescribed	Panoxyl (benzoyl peroxide) 2.5% gel

continued

TABLE 55 *Further treatment within 3 months of end of study (cont'd)*

Treatment group	Patient	Sought further treatment?	Source	Medication received
Minocycline	0006	No	.	(None due to irritation
	0055	No	.	
	0065	Yes	Prescribed	Minocin MR
	0072	Yes	Prescribed	Same as study pills – don't know name
	0078	Yes	Prescribed	Minocycline
	0106	Yes	Prescribed	Minocin
	0124	No	.	
	0159	Yes	Prescribed	Minocycline
	0283	Yes	Prescribed	Minocin MR
	0337	Yes	Prescribed	Minocin MR
	0342	Yes	Prescribed	Differin gel, oxytetracycline 250 mg tablets
	0362	Yes	Prescribed	Minocin, Panoxyl Aquagel 5, Dianette, Benzamycin
	0369	Not known	.	Continued with previous medication
	0383	Yes	Prescribed	Retin-A gel 0.025%
	0485	No	.	Study med (Minocin) until ran out (no money)
	0502	No	.	Finished course of study med
	0509	Yes	Prescribed	Minocycline
	0518	Yes	Prescribed	Minocycline (micromyclin?) tablets + Panoxyl5 cream
	0543	Yes	Prescribed	Minocycline
	0554	Yes	Prescribed	Benzamycin gel
	0567	Yes	Prescribed	Study med (more prescribed by GP) – Minocin
	0583	No	.	
	0594	Yes	Prescribed	Minocin MR
	0615	No	.	
	0625	Not known	.	Going to seek further med
	0643	No	.	
	0693	No	.	
	0709	Yes	Prescribed	Minocycline
	0731	No	.	
	0738	No	.	
	0765	Yes	Prescribed	Minocin MR, Panoxyl aquagel
	0789	Yes	Prescribed	Minocin MR 100mg
	0842	Yes	Prescribed	Oxytetracycline & unknown cream
	0861	No	.	Spots got worse, but could not afford treatment
	1057	Yes	Prescribed	Minocin (half dosage)
	1091	Yes	Prescribed	Minocin + study cream
	1117	No	.	
	1177	Yes	Prescribed	Topicycline
	1183	Yes	Prescribed	Minocin MR & Zineryt
	1193	Yes	OTC	'Dermalux' light treatment unit from specialist co
	1419	No	.	
	1425	Yes	Prescribed	Minocin MR
	1494	No	.	
	1504	Yes	Prescribed	Dalacin T, Dianette
	1521	Yes	Prescribed	Minocycline
	1537	No	.	
Benzoyl peroxide	0017	Yes	Prescribed	Oxytetracycline 250mg
	0030	No	.	
	0049	Yes	Prescribed	Minocin MR (100mg)
	0061	No	.	
	0068	No	.	
	0095	Yes	Prescribed	Panoxyl Aquagel (study med) + Clean & Clear (OTC)

continued

TABLE 55 *Further treatment within 3 months of end of study (cont'd)*

Treatment group	Patient	Sought further treatment?	Source	Medication received
Benzoyl peroxide	0114	Yes	Prescribed	Tetracycline
	0130	Yes	Prescribed	Continued on study med
	0136	Yes	Prescribed	Panoxyl aquagel
	0146	Yes	OTC	Oxy10
	0157	Yes	Prescribed	Benzamycin gel (study med)
	0344	No	.	
	0374	Yes	Not recorded	Panoxyl – continued study med
	0486	No	.	
	0514	Yes	Prescribed	Quinoderm + vitamins + Hibiscus body wash
	0521	No	.	
	0535	Yes	Prescribed	Tetracycline
	0548	No	.	
	0564	Yes	Prescribed	Panoxyl aquagel
	0581	.	.	
	0590	Yes	Not recorded	Not had appt yet – hoping to get Panoxyl Aquagel 5
	0600	Yes	Prescribed	Dianette
	0611	Yes	Prescribed	Panoxyl Aquagel + ? (can't remember name)
	0617	Yes	Prescribed	Panoxyl
	0640	No	.	
	0666	No	.	
	0706	No	.	
	0720	No	.	(But only 1 month after end of study??)
	0727	Yes	Prescribed	Benzoyl peroxide (aquagel)
	0780	No	.	I felt disheartened
	0794	Yes	Prescribed	Panoxyl aquagel 5
	0809	Yes	Prescribed	Oxytetracycline
	0825	Yes	Prescribed	Minocin
	0867	No	.	
	0888	Yes	Prescribed	Oxytetracycline tablets (25mg)
	0901	Yes	Prescribed	Panoxyl Aquagel 5.
	0922	Yes	Prescribed	Panoxyl Aquagel 5
	1048	Yes	Prescribed	Minocin MR
	1067	No	.	But used study cream on chest.
	1075	No	.	
	1085	Yes	Prescribed	Oxytetracycline
	1126	Yes	Prescribed	Oxytetracycline tablets
	1171	No	.	
	1427	No	.	Still using cream used in study
	1484	Yes	OTC	Panoxyl (from Boots)
	1495	Yes	OTC	Benzoyl peroxide 5%
	1498	Yes	OTC	(Not given)
	1516	No	.	
	1538	No	.	
Ery. + BP bd	0022	No	.	
	0024	No	.	
	0040	No	.	
	0063	No	.	
	0080	Yes	Prescribed	Benzamyxin gel
	0107	No	.	
	0119	Yes	Prescribed	Benzamycin gel
	0138	No	.	Study med (Benzamycin) until ran out
	0152	Yes	Prescribed	Benzamycin gel
	0158	No	.	
	0244	No	.	
	0269	No	.	
	0288	No	.	

continued

TABLE 55 *Further treatment within 3 months of end of study (cont'd)*

Treatment group	Patient	Sought further treatment?	Source	Medication received
Ery. + BP bd	0392	Yes	Not recorded	Name not given
	0490	No	.	
	0508	Yes	Prescribed	Benzamycin gel
	0525	Yes	Prescribed	Minocin MR
	0550	Yes	Prescribed	Dianette tablets
	0559	No	.	
	0570	No	.	
	0578	Yes	Prescribed	Benzamycin gel
	0593	Yes	Prescribed	Benzamycin gel
	0599	Yes	Prescribed	Benzamycin, then oxytet+skinoren, then Minocycline
	0616	Yes	Prescribed	Benzamycin gel
	0620	Yes	Prescribed	Benzamycin gel
	0629	No	.	
	0642	No	.	
	0652	No	.	Will finish course of study medication
	0663	Yes	Prescribed	Benzamycin gel
	0702	No	.	Not yet
	0725	No	.	Still has study med left – will seek more later
	0744	Yes	Prescribed	Minocycline tablets & Benzoyl peroxide gel
	0757	Yes	Prescribed	Benzamycin gel
	0761	No	.	
	0800	Yes	Prescribed	Benzamycin gel
	0805	No	.	
	0820	Yes	Prescribed	Oxytetracycline tablets + Benzamycin gel
	0856	No	.	
	0868	Yes	Prescribed	Study medication (cream)
	0889	Yes	Prescribed	Roaccutane
	0897	Yes	Prescribed	Minocycline, Benzamycin gel, Skinoren gel
	0907	Yes	Prescribed	Benzoyl Peroxide
	0925	Yes	Prescribed	Adapalene & Minocycline
	1060	Yes	Prescribed	Benzamycin gel (as in study)
	1072	Yes	Prescribed	Benzamycin gel
	1089	Yes	OTC	Hepar Sulph (homeopathic remedy)
	1113	Yes	Prescribed	Same as study medication
	1500	Yes	Prescribed	Benzamycin gel (as per study med)
	1508	Yes	Prescribed	Minocycline
	1534	No	.	
Ery. od + BP od	0003	Yes	OTC	Clearasil
	0059	No	.	
	0075	Yes	Prescribed	Oxytetracycline
	0085	Yes	Prescribed	Minocin 100mg comprimidos
	0102	Yes	Prescribed	Stiemycin solution + panoxyl gel
	0115	Yes	Prescribed	Stiemycin + Panoxyl
	0134	Yes	Prescribed	Stiemycin lotion & Panoxyl aquagel (cont. study)
	0166	No	.	
	0310	Yes	Prescribed	Panoxyl Aquagel
	0340	Yes	Prescribed	Erythromycin
	0359	Yes	Prescribed	Panoxyl lotion
	0364	Yes	Prescribed	Oxytetracycline, Panoxyl gel
	0382	No	.	
	0489	No	.	Finished course of study med
	0505	Yes	Prescribed	Panoxyl aquagel & Stiemycin
	0512	No	.	
	0530	No	.	Continued study med
	0568	No	.	

continued

TABLE 55 *Further treatment within 3 months of end of study (cont'd)*

Treatment group	Patient	Sought further treatment?	Source	Medication received
	0579	.	.	
	0591	Yes	Prescribed	Same as during the study
	0605	Yes	Prescribed	Stiemycin solution + benzoyl peroxide cream
	0607	Yes	Prescribed	Zineryt
	0619	No	.	
	0647	No	.	
	0650	No	.	Continued study medication
	0667	No	.	
	0676	No	.	
	0684	No	.	
	0695	No	.	
	0715	Yes	Prescribed	Benzamycin gel
	0726	Yes	Prescribed	Roaccutane
	0728	Yes	OTC	Panoxyl Aquagel 5
	0748	No	.	
	0756	No	.	
	0774	Yes	Prescribed	Stiemycin solution, panoxyl aquagel
	0791	No	.	
	0795	No	.	
	0811	No	.	
	0887	Yes	Prescribed	Panoxyl
	1058	No	.	
	1071	Yes	Prescribed	Zineryt
	1083	Yes	Prescribed	Minocin MR & Differin (adapalene)
	1190	Yes	Prescribed	Minocin MR & witchhazel gel (OTC)
	1379	Yes	Prescribed	Stiemycin (to prevent reappearance)
	1417	No	.	
	1431	No	.	
	1481	No	.	
	1533	Yes	Prescribed	Panoxyl aqualgel 5

Medication received is printed from the database and is as reported by the participant.

Appendix 9

Baseline data: additional information

Weights and heights were generally those reported by the participants, and hence may be inaccurate; however, those with a BMI of more than 30 (definition of clinically obese) were confirmed to be very overweight by the assessors. Classification of skin complexion was not standardised between assessors: whereas the distribution of ethnicity is similar between assessors, that of skin complexion clearly is not. It was apparently not clear whether fair, medium and dark were to be used in relation to the participant's ethnic group or not. This is therefore not considered a useful variable for analysis, even though the distribution is similar between treatment groups. A similar problem exists with type of acne. Two assessors classified all participants (except one) as papularpustular, one assessor classified all as polymorphic, and the fourth a mixture (four papularpustular and 20 polymorphic).

The majority (97%) of participants answered 'yes' to the question 'are you fit and healthy?' Details are given for those who answered 'no'; missing details are due to unresolved data entry queries (assessor can no longer be contacted). Four participants reported liver problems, two participants kidney problems and six participants heart problems; however, none of these was thought to be a reason for exclusion from the study. Four participants reported other serious diseases not mentioned above: gallbladder scan imminent, cyst on leg, kidney infection (not on treatment) and arthritis to feet during winter.

Eighty-four participants (13%) reported sensitivities or allergies.

Half of the participants thought there was something that made their acne worse. These factors included stress, sweating, being run down, eating chocolate, not enough sleep, lack of sun, menstruation, certain skin products, eating badly, not washing, wearing make-up, alcohol and milk. When specifically asked, 68% of females reported premenstrual flare of acne.

Eighty-six per cent of participants reported some degree of facial oiliness, with 18% very oily. For those reporting oily faces, 61% were bothered by it, but only 7% were extremely bothered.

Details are given in *Tables 56–79*.

TABLE 56 *Age (years) and BMI (kg/m^2) at baseline*

	Treatment group	*n*	Mean	SD	Median	Min.	Max.
Age	Oxytetracycline	131	19.7	6.30	17.0	11	39
	Minocycline	130	19.2	5.95	17.0	12	36
	Benzoyl peroxide	130	20.2	6.45	18.0	13	37
	Ery. + BP bd	126	19.7	5.87	18.0	12	42
	Ery. od + BP od	131	19.7	5.77	18.0	12	36
	All	648	19.7	6.07	18.0	11	42
BMI	Oxytetracycline	131	23.0	2.58	21.8	13	47
	Minocycline	130	22.0	2.83	21.4	13	38
	Benzoyl peroxide	127	22.8	2.31	22.4	17	35
	Ery. + BP bd	124	22.6	2.36	21.8	16	37
	Ery. od + BP od	129	22.0	2.50	21.4	14	41
	All	641	22.5	2.52	21.6	13	47

TABLE 57 *Weight (kg) and height (cm) at baseline*

	Treatment group	*n*	Mean	SD	Median	Min.	Max.
Weight	Oxytetracycline	131	66.2	14.72	63.6	34	121
	Minocycline	130	63.9	13.16	62.0	35	124
	Benzoyl peroxide	127	65.5	11.54	63.6	45	116
	Ery. + BP bd	126	64.8	13.58	63.6	44	114
	Ery. od + BP od	130	64.2	13.12	63.0	32	112
	All	644	64.9	13.26	63.5	32	124
Height	Oxytetracycline	131	169.9	11.72	170.2	131	206
	Minocycline	130	170.0	9.67	170.0	137	191
	Benzoyl peroxide	129	169.8	10.23	167.6	150	203
	Ery. + BP bd	124	169.3	10.49	168.0	150	193
	Ery. od + BP od	130	170.7	10.25	169.5	145	196
	All	644	169.9	10.47	168.9	131	206

TABLE 58 *Burke and Cunliffe grade at baseline*

Treatment group	*n*	Mean	SD	Median	Min.	Max.
Oxytetracycline	131	1.09	0.703	1.00	0.10	3.00
Minocycline	130	1.11	0.714	1.00	0.05	3.00
Benzoyl peroxide	130	1.12	0.699	1.00	0.10	3.00
Ery. + BP bd	127	1.04	0.666	1.00	0.10	3.00
Ery. od + BP od	130	1.07	0.646	1.00	0.10	3.00
All	648	1.09	0.685	1.00	0.05	3.00

Missing grades are substituted by carrying backwards from other visits.

TABLE 59 *Summary of gender at baseline*

Treatment group	Male		Female		All
Oxytetracycline	53	(40.5)	78	(59.5)	131
Minocycline	62	(47.7)	68	(52.3)	130
Benzoyl peroxide	59	(45.4)	71	(54.6)	130
Ery. + BP bd	58	(45.7)	69	(54.3)	127
Ery. od + BP od	61	(46.6)	70	(53.4)	131
All	293	(45.1)	356	(54.9)	649

Data are shown as *n* (%).

TABLE 60 *Summary of skin complexion at baseline*

Treatment group	Fair		Medium		Dark		Not recorded		All
Oxytetracycline	88	(67.2)	42	(32.1)	1	(0.8)	0	(0)	131
Minocycline	86	(66.2)	43	(33.1)	1	(0.8)	0	(0)	130
Benzoyl peroxide	82	(63.1)	44	(33.8)	3	(2.3)	1	(0.8)	130
Ery. + BP bd	85	(66.9)	36	(28.3)	4	(3.1)	2	(1.6)	127
Ery. od + BP od	83	(63.4)	45	(34.4)	3	(2.3)	0	(0)	131
All	424	(65.3)	210	(32.4)	12	(1.8)	3	(0.5)	649

Data are shown as *n* (%).

TABLE 61 *Summary of ethnicity at baseline*

Treatment group	Caucasian		Afro-Caribbean		Hispanic		Asian		Other		Not recorded		All
Oxytetracycline	126	(96.2)	1	(0.8)	0	(0)	4	(3.1)	0	(0)	0	(0)	131
Minocycline	120	(92.3)	1	(0.8)	0	(0)	7	(5.4)	2	(1.5)	0	(0)	130
Benzoyl peroxide	119	(91.5)	2	(1.5)	0	(0)	4	(3.1)	4	(3.1)	1	(0.8)	130
Ery. + BP bd	113	(89.0)	4	(3.1)	0	(0)	7	(5.5)	2	(1.6)	1	(0.8)	127
Ery. od + BP od	121	(92.4)	4	(3.1)	1	(0.8)	3	(2.3)	2	(1.5)	0	(0)	131
All	599	(92.3)	12	(1.8)	1	(0.2)	25	(3.9)	10	(1.5)	2	(0.3)	649

Data are shown as *n* (%).

TABLE 62 *Fit and healthy at baseline*

Treatment group	Patient	Fit?	Details
Oxytetracycline	0245	Yes	Well but would like to be fitter
	0688	No	Raynaud's disease since 26 yrs (8 yrs)
	0803	No	Suffers from depression & cerebral palsy
	0982	No	Has asthma
	1175	No	
	1340	Yes	Asthma – mild, usually only on exertion. Hayfever during summer
Minocycline	0320	No	Rheumatoid arthritis
	0441	No	Recently seen GP re weight loss. No underlying pathology. Reason – not eating enough – advised to increase food intake
	0485	Yes	Tired out
	0723	Yes	Recent episode of manic depression stabilised through medication
	0999	No	A back problem, and post-natal depression
	1321	No	Suffers from epilepsy. Much improved on medication
Benzoyl peroxide	0901	No	
	1171	No	
Ery. + BP bd	0047	No	? Urine tract infection. Pain on micturition 1 week. No time off college, patient states now improving, no treatment from GP
	0361	No	Does have mild asthma & gets hayfever
	0550	No	
	0897	No	Suffers from depression
	1026	No	Has a heart murmur. EAE thinks it OK since GP aware & condition is under control
	1180	No	
Ery. od + BP od	0811	No	Diabetic, but stable
	1041	No	Got asthma
	1209	No	Myxoedema, iron deficiency, indigestion, nervous problem with arms (waiting to see specialist) – no diagnosis. Carpal tunnel syndrome. GP OK'd study
	1431	No	Presently has sinusitis

Details are printed from the database and are as reported by the participant.

TABLE 63 *Details of liver, kidney and heart problems at baseline*

Treatment group	Patient	Liver problems	Kidney problems	Heart problems
Oxytetracycline	0610	Hepatitis		
	1097	ITP (a pathology of liver) 5 yrs ago		
Minocycline	0258	Inflammation 12 months ago treated		
	0320			Blood clot 4 years ago
	0475		Some pain & kidney investigations, nothing found	
	0989			Heart murmur as a child
Ery. + BP bd	0158			Cardiac defibrillator fitted 1994
	0301		Size was small at birth, but it works OK	Mild systolic heart murmur at 6 wk gestation
	1026			Heart murmur, under control
Ery. od + BP od	0760	Previous LFT abnormal, but improving		
	1262			Leak in atrial valve – sees consultant every 2 yrs

Problems are printed from the database and are as reported by the participant.
ITP, idiopathic thrombocytopenic purpura; LFT, liver function tests.

TABLE 64 *Any other serious disease at baseline*

Treatment group	Patient	Any?	Details
Benzoyl peroxide	1171	Yes	Cyst at back of leg
	1523	Yes	Arthritis to feet during winter
Ery. od + BP od	0162	Yes	To go for a scan regarding gall bladder next Thurs
	1379	Yes	Kidney infections. No longer on treatment

Details are printed from the database and are as reported by the participant.

TABLE 65 *Details of sensitivities at baseline*

Treatment group	Patient	No.	Sensitivity	Treatment received for sensitivity?	Date treatment stopped
Oxytetracycline	0073	1	Penicillin	.	.
	0092	1	Penicillin	.	.
	0174	1	Phenobarbitone, makes mouth swell up	Yes	10/09/78
	0209	1	Penicillin – vomiting & unwell	Yes	21/09/96
	0311	1	Penicillin	.	.
	0327	1	Pollen+dust+feathers	Yes	.
	0352	1	Penicillin (Amoxycillin)	.	.
	0375	1	Hayfever	Yes	15/06/98
	0447	1	Pollen (hayfever)	Yes	.

continued

TABLE 65 *Details of sensitivities at baseline (cont'd)*

Treatment group	Patient	No.	Sensitivity	Treatment received for sensitivity?	Date treatment stopped
Oxytetracycline	0477	1	Was sick using oral erythromycin	.	.
	0831	1	Septrin	Yes	24/05/93
	0865	1	Hayfever	Yes	15/07/98
	0929	1	Penicillin	.	.
	0982	1	Tylex analgesic	.	.
	1002	1	Penicillin	.	.
	1155	1	Penicillin	Yes	.
	1202	1	Hayfever	Yes	.
	1241	1	Penicillin	.	.
	1287	1	Crab meat	.	.
	1311	1	Pumpkin	.	.
	1340	1	Asthma	Yes	.
		2	Hayfever	Yes	.
Minocycline	0023	1	Amoxycillin	.	.
	0170	1	Asthma	Yes	.
	0189	1	Distaclor (vomiting, rash)	.	15/09/86
	0227	1	Cephalex: came out in rashes	Yes	29/09/92
	0258	1	Aspirin (due to ulcers)	.	.
	0369	1	Penicillin	.	.
	0383	1	Penicillin	.	.
	0390	1	Honey	.	.
	0475	1	Reaction to drug given during renogram	Yes	.
	0485	1	Aspirin – bleeds post taking	.	.
	0738	1	Penicillin	.	.
	0772	1	Penicillin	.	.
	1057	1	Penicillin	Yes	01/01/93
	1253	1	Dust – dust mites	.	.
		2	Cats	No	.
Benzoyl peroxide	0017	1	Penicillin	No	.
	0130	1	Prochlorperazine	.	.
	0136	1	Penicillin	.	.
	0176	1	Penicillin – brings out in rashes	.	.
	0190	1	Aspirin – warned not to use – has asthma	.	.
	0287	1	Asthma (ventolin inhaler)	Yes	.
	0328	1	Penicillin	.	.
	0406	1	Hayfever	.	.
	0455	1	Pollen	Yes	.
		2	House dust	Yes	.
	0481	1	Animal fur	.	.
	0809	1	Penicillin	.	.
	1112	1	Moisturising creams	.	.
	1171	1	Dihydrocodeine	Yes	.
	1208	1	Caffeine	.	.
	1329	1	Ibuprofen	.	.
Ery. + BP bd	0024	1	Hayfever for approx 1 month per year	Yes	.
	0047	1	Penicillin	.	.
	0107	1	Lanolin	.	.
	0138	1	Penicillin – rash	.	.
	0345	1	Washing powder	.	.
	0361	1	Pollen, i.e. hayfever	Yes	.
	0384	1	Sensitive skin, (e.g. some soap & washing powder)	.	.
	0405	1	Pollen	Yes	.
	0426	1	Penicillin	.	.

continued

TABLE 65 *Details of sensitivities at baseline (cont'd)*

Treatment group	Patient	No.	Sensitivity	Treatment received for sensitivity?	Date treatment stopped
Ery. + BP bd	0473	1	Lanolin	.	.
		2	Powder in latex gloves	.	.
	0474	1	Septrin	No	.
	0629	1	Penicillin: rash	.	.
	0682	1	Penicillin	.	.
	0907	1	Dust mite	.	.
	1180	1	Potassium dichromate	.	.
		2	Thiomersal cosmetics	.	.
		3	Colbat chloride	.	.
		4	Balsam of Peru	.	.
	1224	1	Shellfish	.	.
	1316	1	Penicillin	.	.
		2	Suprafloxacin	.	.
	1342	1	Penicillin	.	.
	1346	1	Penicillin	.	.
Ery. od + BP od	0003	1	Penicillin	No	.
	0028	1	Trimethoprim	.	.
	0223	1	Erythromycin for spots 1 yr ago, tired, sick, drowsy	.	.
	0307	1	Hayfever	.	.
	0419	1	Pollen	Yes	.
	0432	1	Trimethoprim	.	.
		2	Pollen	Yes	.
	0443	1	Pollen – hayfever	.	.
	0483	1	Oral erythromycin – vomiting	.	.
	0676	1	Penicillin – rash	.	.
	0845	1	Hayfever	.	.
	0988	1	Measles injection	.	.
	1052	1	Oral erythromycin	Yes	.
	1058	1	Penicillin	Yes	03/02/99
	1209	1	Lemons	.	.
	1348	1	Nickel	.	.

Sensitivities are printed from the database and are as reported by the participant.

TABLE 66 *Baseline data: reported age of onset of acne (years)*

Treatment group	*n*	Mean	SD	Median	Min.	Max.
Oxytetracycline	131	13.3	2.58	13.0	8	25
Minocycline	129	13.6	2.83	13.0	5	24
Benzoyl peroxide	129	13.7	2.31	13.0	8	25
Ery. + BP bd	126	13.3	2.36	13.0	9	24
Ery. od + BP od	131	13.6	2.50	13.0	8	25
All	646	13.5	2.52	13.0	5	25

TABLE 67 *Baseline data: calculated duration of acne (years)*

Treatment group	*n*	Mean	SD	Median	Min.	Max.
Oxytetracycline	131	6.4	5.86	4.0	0	29
Minocycline	129	5.7	4.92	4.0	0	21
Benzoyl peroxide	129	6.5	6.11	4.0	0	26
Ery. + BP bd	126	6.4	5.08	5.0	0	21
Ery. od + BP od	131	6.2	5.25	4.0	0	24
All	646	6.2	5.46	4.0	0	29

TABLE 68 *Summary of acne sites at baseline*

Treatment group	Face				Neck				Back				Chest				Other site				All
	No		Yes		No		Yes		No		Yes		No		Yes		No		Yes		
Oxytetracycline	0	(0)	131	(100)	81	(61.8)	50	(38.2)	51	(38.9)	80	(61.1)	81	(61.8)	50	(38.2)	119	(90.8)	12	(9.2)	131
Minocycline	0	(0)	130	(100)	83	(63.8)	47	(36.2)	53	(40.8)	77	(59.2)	86	(66.2)	44	(33.8)	123	(94.6)	7	(5.4)	130
Benzoyl peroxide	0	(0)	130	(100)	83	(63.8)	47	(36.2)	58	(44.6)	72	(55.4)	79	(60.8)	51	(39.2)	123	(94.6)	7	(5.4)	130
Ery. + BP bd	1	(0.8)	126	(99.2)	91	(71.7)	36	(28.3)	56	(44.1)	71	(55.9)	81	(63.8)	46	(36.2)	116	(91.3)	11	(8.7)	127
Ery. od + BP od	0	(0)	131	(100)	95	(72.5)	36	(27.5)	58	(44.3)	73	(55.7)	86	(65.6)	45	(34.4)	127	(96.9)	4	(3.1)	131
All	1	(0.2)	648	(99.8)	433	(66.7)	216	(33.3)	276	(42.5)	373	(57.5)	413	(63.6)	236	(36.4)	608	(93.7)	41	(6.3)	649

Data are shown as *n* (%).
The only participant with a 'no' for facial acne actually had missing data, but they would not have been included in the study without facial acne.

TABLE 69 *Other sites of acne present at baseline*

Treatment group	Patient	Description of site
Oxytetracycline	0026	Shoulder
	0165	Top of arm
	0396	Scalp
	0894	Shoulders
	0929	Legs
	0979	Arms
	1037	Arm
	1097	Shoulders
	1119	Arms
	1196	Shoulders, arms & legs
	0352	Shoulders
	0411	Few on shoulders
Minocycline	0234	Arm
	0317	Arms
	0833	Shoulders
	1053	Shoulders
	1073	Arms
	1105	Arms
	0475	Shoulders
Benzoyl peroxide	0514	Shoulder
	0287	Upper arm
	0867	Shoulders, back of legs
	0977	Arms, legs
	1022	Legs
	1107	Ear
	0344	Arms
Ery. + BP bd	0080	Buttocks
	0228	Arm
	0244	Shoulders
	0288	Arms
	0392	Legs/arms
	0828	Arm
	0838	Shoulders
	0868	Shoulders
	0872	Arm
	0897	Shoulder
	0938	Arms
Ery. od + BP od	0199	Scalp occasionally
	0223	Arms
	0887	Shoulders
	1058	Shoulders

TABLE 70 *Time since first sought help for acne (years)*

Treatment group	*n*	Mean	SD	Median	Min.	Max.
Oxytetracycline	121	3.5	4.06	2.0	0.0	21.0
Minocycline	125	3.8	4.72	2.0	0.0	26.0
Benzoyl peroxide	123	3.8	4.53	2.0	0.0	21.0
Ery. + BP bd	118	4.3	4.44	2.7	0.0	18.0
Ery. od + BP od	121	4.0	4.36	2.0	0.0	20.0
All	608	3.9	4.42	2.0	0.0	26.0

TABLE 71 *Summary of previous treatments for acne (OTC versus prescription)*

Treatment group	OTC						Prescription						All
	No		Yes		Not known		No		Yes		Not known		
Oxytetracycline	14	(10.7)	117	(89.3)	0	(0)	13	(9.9)	117	(89.3)	1	(0.8)	131
Minocycline	20	(15.4)	110	(84.6)	0	(0)	12	(9.2)	117	(90.0)	1	(0.8)	130
Benzoyl peroxide	11	(8.5)	117	(90.0)	2	(1.5)	12	(9.2)	116	(89.2)	2	(1.5)	130
Ery. + BP bd	15	(11.8)	111	(87.4)	1	(0.8)	10	(7.9)	116	(91.3)	1	(0.8)	127
Ery. od + BP od	19	(14.5)	111	(84.7)	1	(0.8)	14	(10.7)	116	(88.5)	1	(0.8)	131
All	79	(12.2)	566	(87.2)	4	(0.6)	61	(9.4)	582	(89.7)	6	(0.9)	649

Data are shown as *n* (%).

TABLE 72 *Summary of previous treatments for acne (oral versus topical)*

Treatment group	Oral						Topical						All
	No		Yes		Not recorded		No		Yes		Not recorded		
Oxytetracycline	49	(37.4)	82	(62.6)	0	(0)	20	(15.3)	110	(84.0)	1	(0.8)	131
Minocycline	60	(46.2)	70	(53.8)	0	(0)	18	(13.8)	111	(85.4)	1	(0.8)	130
Benzoyl peroxide	49	(37.7)	79	(60.8)	2	(1.5)	15	(11.5)	111	(85.4)	4	(3.1)	130
Ery. + BP bd	49	(38.6)	74	(58.3)	4	(3.1)	17	(13.4)	105	(82.7)	5	(3.9)	127
Ery. od + BP od	48	(36.6)	79	(60.3)	4	(3.1)	29	(22.1)	98	(74.8)	4	(3.1)	131
All	255	(39.3)	384	(59.2)	10	(1.5)	99	(15.3)	535	(82.4)	15	(2.3)	649

Data are shown as *n* (%).

TABLE 73 *Summary of 'Does anything make acne worse'?*

Treatment group	No		Yes		Not known		All
Oxytetracycline	68	(51.9)	61	(46.6)	2	(1.5)	131
Minocycline	64	(49.2)	65	(50.0)	1	(0.8)	130
Benzoyl peroxide	70	(53.8)	59	(45.4)	1	(0.8)	130
Ery. + BP bd	54	(42.5)	70	(55.1)	3	(2.4)	127
Ery. od + BP od	73	(55.7)	57	(43.5)	1	(0.8)	131
All	329	(50.7)	312	(48.1)	8	(1.2)	649

Data are shown as *n* (%).

TABLE 74 *Details of what makes acne worse*

Treatment group	Patient	Anything?	Details of what makes it worse
Oxytetracycline	0008	Yes	(No details given)
	0020	Yes	Chocolate
	0026	Yes	Working in factory with dirty boxes
	0042	Yes	
	0073	Yes	Fizzy drinks aggravate it
	0127	Yes	Beauty products irritate my skin
	0153	Yes	Sports – sweating increases acne
	0165	Yes	When stressed
	0184	Yes	If I leave it
	0209	Yes	Stress
	0210	Yes	Work – oily work tends to make it worse
	0226	Yes	Maybe the food I eat is greasy
	0245	Yes	Long hair at front of head
	0257	Yes	Hot weather, stress
	0271	Yes	Chocolate, red meats
	0293	Yes	Better in summer
	0302	Yes	Make-up
	0311	Yes	Stress
	0371	Yes	Stress, bad diet & alcohol
	0396	Yes	Stress, spots better in summer
	0400	Yes	Before periods
	0411	Yes	Stress + before & during periods
	0437	Yes	Wearing cheap make-up
	0459	Yes	Dirt in place of work
	0477	Yes	Alcohol – overindulgence
	0557	Yes	Smoke in pubs
	0565	Yes	Sweating
	0582	Yes	Wet shaving
	0589	No	Haven't noticed
	0610	Yes	Tiredness
	0646	Yes	Feels soap aggravates it
	0651	Yes	Winter – feels sunshine (helps?)
	0665	Yes	Shaving
	0718	Yes	Stress
	0741	Yes	Tired & run-down, or ill-health
	0759	Yes	OTC meds & exercise
	0768	Yes	Soap
	0773	Yes	Chocolate and milk
	0803	Yes	Some creams irritate it
	0808	Yes	Stress
	0831	Yes	Hot weather
	0851	Yes	A bit worse in winter. Cream given by doctor made it worse
	0894	Yes	They dry up in summer
	0919	Yes	Menses
	0962	Yes	Menses
	0979	Yes	Sweat from sport
	0997	Yes	Sweating
	1017	Yes	
	1037	Yes	If I don't wash my hair
	1047	Yes	Before my periods
	1063	Yes	Stress, during ovulating and calms down during period
	1068	Yes	Hair sprays
	1186	Yes	Not eating fruits
	1202	Yes	Stress & post-menstrual
	1241	Yes	Excessive drinking & smoking
	1267	Yes	Stress, lack of sleep, alcohol, being generally unhealthy
	1287	Yes	Eating chocolate & lack of sleep
	1288	Yes	Lack of sleep

continued

TABLE 74 *Details of what makes acne worse (cont'd)*

Treatment group	Patient	Anything?	Details of what makes it worse
Oxytetracycline	1311	Yes	Not washing, eating greasy food
	1325	Yes	Using certain products, i.e. tea-tree oil
	1340	Yes	Working in kitchen – hot environment
	1479	No	If I don't look after it
	1520	Yes	Some treatments
Minocycline	0015	Yes	Chocolate
	0023	Yes	Soap
	0038	Yes	Sweating during sport
	0096	Yes	Heat
	0120	Yes	Chocolate
	0124	Yes	Shaving – especially wet shaving causes it to flare up
	0139	Yes	Excessive sweating, e.g. running exacerbates acne
	0149	Yes	Squeezing spots makes them worse
	0170	Yes	Soaps, especially provokes blackheads & makes skin tight
	0189	Yes	When I wash my face
	0208	Yes	Soaps
	0215	Yes	Picking them
	0227	Yes	Washing with perfumed soap, tiredness, when using hair fringe
	0246	Yes	I thought it was food
	0283	Yes	They are fewer in summer
	0295	Yes	Fatty foods, seafoods, stress
	0300	Yes	It is worse in winter
	0383	Yes	If doing physical exercise and washing immediately afterwards
	0390	Yes	Stress. Before, during & after menstruation
	0417	Yes	Make-up, getting dirty at work
	0424	Yes	Stress or being run down
	0433	Yes	A previously used treatment made it worse, but don't know what
	0441	Yes	Spots get worse just after periods
	0470	Yes	Illness/indigestion, stress, sunlight
	0485	Yes	Some products used on face aggravate acne
	0502	Yes	When I don't use treatment for a while
	0554	Yes	Anything I use on my face
	0583	Yes	Lack of sleep
	0594	Yes	Summer & sweating
	0643	Yes	Antibacterial scrubs
	0655	Yes	Stress
	0694	Yes	Washing with soap
	0709	Yes	Stress, post-menstrual flare
	0723	Yes	Stress
	0731	Yes	Stress
	0738	Yes	Picking it
	0752	Yes	Sport – sweating
	0772	Yes	Stopping medication. Stress & late nights
	0789	Yes	Not washing
	0813	Yes	Wool – tickles it
	0833	Yes	Profession – plumbing
	0848	Yes	Stress, worse in winter
	0861	Yes	Periods
	0873	Yes	Stress – exams?
	0881	Yes	They are worse in winter
	0904	Yes	Sun tends to clear it up a bit
	0927	Yes	Greasy hair
	0955	Yes	Heat
	0999	Yes	Before periods, better in summer
	1006	Yes	Milk in diets
	1053	Yes	The sun can make my shoulders worse
	1057	Yes	Stress & sweets make my face more greasy
	1200	Yes	Using 10% benzoyl peroxide

continued

TABLE 74 *Details of what makes acne worse (cont'd)*

Treatment group	Patient	Anything?	Details of what makes it worse
Minocycline	1230	Yes	Wearing make-up
	1233	Yes	Use of medicated cleanser!
	1253	Yes	Eating chocolate
	1266	Yes	Drinking alcohol
	1282	Yes	Eating hot, spicy food & chocolate
	1309	Yes	Pre-menstrual, lack of sleep
	1313	Yes	Fluctuates with monthly cycle
	1336	Yes	Stress & possibly excessive alcohol consumption
	1351	Yes	Eating unhealthy food
	1480	Yes	Sweat
	1494	Yes	Stress
	1515	Yes	Moisturisers
Benzoyl peroxide	0030	Yes	Chocolate
	0049	Yes	Not washing face
	0061	Yes	Greasy skin
	0068	Yes	Sweating
	0095	Yes	Pre-menstrual flare
	0100	Yes	Oily things on face – makeup + stress
	0136	Yes	Foods containing animal fats
	0146	Yes	Stopping treatment & stress makes it worse
	0157	Yes	Heat & sweating makes acne worse
	0176	Yes	Contraception – depot injection. Cold, nippy wind makes spots itchy
	0190	Yes	Oily moisturisers
	0225	Yes	Stressed
	0253	Yes	Stress
	0261	Yes	Smoke in enclosed spaces
	0303	Yes	Better in summer, stresses
	0309	Yes	Worse in winter
	0412	Yes	Hair in contact with face
	0421	Yes	Certain types of soap
	0444	Yes	Stress
	0455	Yes	Greasy moisturisers, bad diet, stress
	0498	Yes	Products with oil in them
	0514	Yes	Sweating makes acne worse
	0521	Yes	Sweating
	0552	Yes	Stress
	0581	Yes	Diet
	0611	Yes	Picking at it
	0617	Yes	Picking them
	0632	Yes	Alcohol
	0640	Yes	Change in water – moving
	0657	Yes	
	0666	Yes	Sun beds
	0675	Yes	Stress
	0698	Yes	Cleansers and soaps
	0727	Yes	Diet – fatty foods
	0750	Yes	Pre-menstrual
	0850	Yes	Stress
	0867	Yes	Stress
	0888	Yes	Worse in summer
	0910	Yes	Stress
	0922	Yes	Only if I pick them
	0936	Yes	Better in summer
	0952	Yes	A yellow cream prescribed by GP
	0964	Yes	Worse in winter
	0980	Yes	Sweaty, hot atmosphere
	1022	Yes	Sweat

continued

TABLE 74 *Details of what makes acne worse (cont'd)*

Treatment group	Patient	Anything?	Details of what makes it worse
Benzoyl peroxide	1048	Yes	When I'm stressed
	1099	Yes	Chocolate
	1107	Yes	Using antibacterial wash, post-menstrual flare
	1112	Yes	Clearasil made it worse
	1171	Yes	Since I stopped playing the guitar 7 yrs ago, health has deteriorated, & taking glucose
	1194	Yes	Some soaps
	1208	Yes	Eating chocolate
	1213	Yes	Using Clearasil & some facial washes
	1228	Yes	Cold weather & sweating
	1236	Yes	Eating chocolate, but this tends to occur at end of menstrual cycle so not sure!
	1263	Yes	Stress
	1271	Yes	Eating chocolate, not using Dove soap
	1286	Yes	Hot, humid environment
	1297	Yes	Stress
	1411	No	Summer – sweating
Ery. + BP bd	0024	Yes	Sweating
	0047	Yes	Soap
	0063	Yes	Sunshine
	0076	Yes	Period
	0107	Yes	Hot weather – but sunshine helps
	0119	Yes	Pre-menstrual flare
	0138	Yes	Menstrual cycle
	0158	Yes	Sometimes sweating can aggravate it
	0187	Yes	Sweating, getting hot
	0220	Yes	Stress
	0228	Yes	The sweating
	0240	Yes	Probably greasy food
	0244	Yes	Stress
	0269	Yes	Perfumed soaps
	0277	Yes	Alcohol, sweat
	0288	Yes	Sex
	0321	Yes	Make-up, worse in winter
	0361	Yes	Chemicals used in steel turning on a lathe. Doesn't know what it was. Stopped this work now
	0426	Yes	Used benzoyl peroxide previously which made spots worse at first
	0431	Yes	Use of perfumed soap
	0449	Yes	Using skin cleansing lotion
	0461	Yes	Perfumed health or cleaning products, i.e. washing powder & fabric softener
	0473	Yes	Working in hot, dry environment
	0474	Yes	Wearing lots of make-up
	0497	Yes	Some lotions make acne worse, e.g. Clearasil
	0508	Yes	Harsh products aggravate skin
	0525	Yes	Sweating makes skin flare up
	0534	Yes	Swimming – chlorine stings skin
	0570	Yes	No washing
	0578	Yes	Oxy10 made them red and sore
	0593	Yes	Diet
	0599	Yes	Stress
	0616	Yes	Hair gel
	0629	Yes	Heat, alcohol, spicy food
	0642	Yes	Working with oil doesn't help it
	0712	Yes	Not washing my face
	0725	Yes	Stress
	0735	Yes	Drinking alcohol & tiredness & stress
	0771	Yes	Rich food & stress. Pollution

continued

TABLE 74 *Details of what makes acne worse (cont'd)*

Treatment group	Patient	Anything?	Details of what makes it worse
Ery. + BP bd	0820	Yes	Wearing make-up
	0828	Yes	Greasy environment
	0838	Yes	Worse in summer
	0868	Yes	Slightly worse in winter
	0872	Yes	Sweating
	0889	Yes	Heat & sweat
	0897	Yes	Time of month
	0925	Yes	Heat, hot environment
	0961	Yes	Eating junk food
	0978	Yes	Sun used to make them worse
	0995	Yes	Worse in summer
	1004	Yes	Vibramycin made them worse
	1018	Yes	Stress
	1026	Yes	Stress
	1043	Yes	If I do not get fresh air & when I play sports
	1072	Yes	Dairy products make my skin greasy
	1089	Yes	Stress
	1095	Yes	Heat, other people's hair, contact with grasses
	1180	Yes	Stress, pre-menstrual – sometimes
	1203	Yes	Hot weather
	1221	Yes	Stress & using make-up
	1224	Yes	Stress & lack of sleep, eating greasy food
	1245	Yes	Being run down or eating unhealthily
	1273	Yes	Stress
	1327	Yes	Stress
	1346	Yes	Eating greasy food
	1410	Yes	Sweating & hot weather
	1430	Yes	Wearing jewellery
	1485	Yes	Stress
	1500	Yes	Hot & sweaty
	1508	Yes	Stress +
Ery. od + BP od	0028	Yes	
	0036	Yes	Cats
	0075	Yes	Stopping medication
	0085	Yes	Oxy 5 cream made it worse
	0122	Yes	Smoky, sweaty environment
	0162	Yes	More spots appear when stressed – she calls her acne 'stress spots'
	0177	Yes	Gets redder in the sun and soap
	0199	Yes	Soaps
	0212	Yes	Sweating
	0265	Yes	Some make-up
	0292	Yes	Squeezing them
	0307	Yes	Stress
	0310	Yes	Chocolate, flare is during period
	0325	Yes	Fatty food
	0359	Yes	Eating very rich, sugary, fatty foods
	0386	Yes	Not washing off make-up properly. Before & during menstruation
	0404	Yes	Exercise with make-up on
	0419	Yes	Minocycline made acne worse, excessive drinking, working in dirty/greasy environment
	0432	Yes	Being pregnant triggered off a bad outbreak with greasier skin that has persisted
	0456	Yes	Stress
	0469	Yes	Stress
	0579	Yes	Spicy food
	0591	Yes	Stress. Using moisturisers
	0605	Yes	Varies with seasons

continued

TABLE 74 *Details of what makes acne worse (cont'd)*

Treatment group	Patient	Anything?	Details of what makes it worse
Ery. od & BP od	0619	Yes	Using moisturisers not suitable for my skin
	0667	Yes	Stress
	0695	Yes	Drinking alcohol
	0715	Yes	Diet
	0726	Yes	Seasons – winter worse. Stress
	0756	Yes	Rubbing it & irritating
	0760	Yes	Use of soap, smoky environment
	0774	Yes	Soap – shampoo
	0822	Yes	Better in summer (Minocin made them worse)
	0835	Yes	Stress
	0845	Yes	Menses, stressed
	0853	Yes	Profession – not sure
	0876	Yes	Drier & flaky in winter, oily in summer
	0887	Yes	Stress
	0909	Yes	Worse in summer
	0944	Yes	Stress, depression
	0968	Yes	Stopping use of Topicycline
	1041	Yes	A cream prescribed by GP made them worse
	1052	Yes	Stress, and sensitivity to certain products, tiredness
	1071	Yes	Stress
	1094	Yes	Stress
	1131	Yes	Stress
	1209	Yes	Excessive sweating, eating sweet food especially chocolate, perfumed beauty products, soap
	1217	Yes	Eating chocolate, lack of sleep and stress
	1225	Yes	Working in restaurant/nightclub – hot, sweaty, smoky environment. Eating badly
	1239	Yes	Eating unhealthily & not washing
	1246	Yes	Cold weather
	1262	Yes	Stress
	1348	Yes	Stress
	1379	Yes	Stress, hormonal changes, depression
	1422	Yes	Soap
	1481	Yes	Working outdoors with horses
	1533	Yes	The washes (medicated)

Only participants who answered 'yes' or gave details are included in this listing. Details are printed from the database and are as reported by the participant.

TABLE 75 *Summary of premenstrual flare (females only)*

Treatment group	No		Yes		Not known		All
Oxytetracycline	23	(29.5)	53	(67.9)	2	(2.6)	78
Minocycline	23	(33.8)	40	(58.8)	5	(7.4)	68
Benzoyl peroxide	17	(23.9)	50	(70.4)	4	(5.6)	71
Ery. + BP bd	16	(23.2)	51	(73.9)	2	(2.9)	69
Ery. od + BP od	17	(24.3)	49	(70.0)	4	(5.7)	70
All	96	(27.0)	243	(68.3)	17	(4.8)	356

Data are shown as *n* (%).

TABLE 76 *Oiliness of face*

Treatment group	How oily?										All
	Not oily at all		A little oily		Moderately oily		Very oily		Not recorded		
Oxytetracycline	18	(13.7)	40	(30.5)	50	(38.2)	21	(16.0)	2	(1.5)	131
Minocycline	18	(13.8)	40	(30.8)	52	(40.0)	20	(15.4)	0	(0)	130
Benzoyl peroxide	19	(14.6)	38	(29.2)	48	(36.9)	22	(16.9)	3	(2.3)	130
Ery. + BP bd	17	(13.4)	45	(35.4)	39	(30.7)	25	(19.7)	1	(0.8)	127
Ery. od + BP od	14	(10.7)	44	(33.6)	46	(35.1)	27	(20.6)	0	(0)	131
All	86	(13.3)	207	(31.9)	235	(36.2)	115	(17.7)	6	(0.9)	649

Data are shown as *n* (%).

TABLE 77 *How bothered by oily face*

Treatment group	How bothered?										All
	Extremely		Moderately		Slightly		Not at all		Not relevant		Not recorded		
Oxytetracycline	8	(6.1)	24	(18.3)	41	(31.3)	44	(33.6)	14	(10.7)	0	(0)	131
Minocycline	6	(4.6)	24	(18.5)	42	(32.3)	49	(37.7)	9	(6.9)	0	(0)	130
Benzoyl peroxide	7	(5.4)	19	(14.6)	37	(28.5)	50	(38.5)	14	(10.8)	3	(2.3)	130
Ery. + BP bd	9	(7.1)	26	(20.5)	37	(29.1)	40	(31.5)	15	(11.8)	0	(0)	127
Ery. od + BP od	10	(7.6)	23	(17.6)	42	(32.1)	45	(34.4)	11	(8.4)	0	(0)	131
All	40	(6.2)	116	(17.9)	199	(30.7)	228	(35.1)	63	(9.7)	3	(0.5)	649

Data are shown as *n* (%).

TABLE 78 *Summary of any family history of acne*

Treatment group	No		Yes		All
Oxytetracycline	43	(32.8)	88	(67.2)	131
Minocycline	32	(24.6)	98	(75.4)	130
Benzoyl peroxide	31	(23.8)	99	(76.2)	130
Ery. + BP bd	42	(33.1)	85	(66.9)	127
Ery. od + BP od	41	(31.3)	90	(68.7)	131
All	189	(29.1)	460	(70.9)	649

Data are shown as *n* (%).

TABLE 79 *Summary of truncal acne*

Treatment group	No		Yes		All
Oxytetracycline	37	(28.2)	94	(71.8)	131
Minocycline	43	(33.1)	87	(66.9)	130
Benzoyl peroxide	49	(37.7)	81	(62.3)	130
Ery. + BP bd	44	(34.6)	83	(65.4)	127
Ery. od + BP od	54	(41.2)	77	(58.8)	131
All	227	(35.0)	422	(65.0)	649

Data are shown as *n* (%).

Appendix 10

Missing efficacy data

Original data

The frequency of original available data is given in *Table 80*. Efficacy data for these outcome measures were deleted for two participants at week 6 (0086 in the benzoyl peroxide group and 0122 in the ery. od + BP od group) as both participants had eruptions that were not acne and should not have been assessed using these outcome measures. *Table 80* reflects this.

TABLE 80 *Non-missing efficacy data* (n)

Outcome	Treatment group	Week			
		0	6	12	18
Patient global	Oxytetracycline	–	118	107	95
	Minocycline	–	111	100	91
	Benzoyl peroxide	–	113	97	94
	Ery. + BP bd	–	118	106	102
	Ery. od + BP od	–	116	104	93
Assessor global	Oxytetracycline	–	114	107	95
	Minocycline	–	108	100	91
	Benzoyl peroxide	–	107	97	94
	Ery. + BP bd	–	114	106	102
	Ery. od + BP od	–	114	104	93
Inflamed lesion counts	Oxytetracycline	131	108	101	93
	Minocycline	130	106	97	89
	Benzoyl peroxide	129	100	92	91
	Ery. + BP bd	126	110	98	100
	Ery. od + BP od	131	110	97	92
Burke and Cunliffe grade	Oxytetracycline	130	107	100	93
	Minocycline	129	106	97	89
	Benzoyl peroxide	128	101	92	93
	Ery. + BP bd	126	111	97	99
	Ery. od + BP od	129	110	98	93
CASS	Oxytetracycline	126	107	101	93
	Minocycline	125	103	95	88
	Benzoyl peroxide	127	100	93	93
	Ery. + BP bd	124	110	97	98
	Ery. od + BP od	127	110	96	93

Intention-to-treat analysis

Missing data were substituted by values carried forward (and backwards if necessary). From the point at which a participant dropped out of the study, global outcome measures (patient, assessor and worst case) were substituted by failure (i.e. less than moderate improvement), whatever the reason for dropping out and regardless of whether there was an available response at that visit. Numbers for the ITT analysis are as in the main report (131, 130, 130, 127 and 131 per group, respectively), except for the benzoyl peroxide group, where numbers analysed for the CASS were 129 (not 130), and the ery. od + BP od group, where numbers analysed were 130 (not 131) for both the Burke and Cunliffe grade and the CASS.

Appendix 11

Additional efficacy results

TABLE 81 *Inflamed lesion counts for baseline Burke and Cunliffe grade less than 1.0: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	0.3	–6.6	7.1
Ery. + BP bd – oxytetracycline	–0.3	–7.0	6.4
Ery. + BP bd – minocycline	–0.5	–7.1	6.1
Ery. od + BP od – ery. + BP bd	–3.6	–10.2	3.0
Benzoyl peroxide – oxytetracycline	–3.8	–10.6	3.1
Benzoyl peroxide – minocycline	–4.1	–10.9	2.8
Benzoyl peroxide – ery. + BP bd	–3.5	–10.1	3.1
Ery. od + BP od – oxytetracycline	–3.9	–10.7	2.9
Ery. od + BP od – minocycline	–4.1	–10.9	2.6
Ery. od + BP od – benzoyl peroxide	–0.1	–6.8	6.6

TABLE 82 *Inflamed lesion counts for baseline Burke and Cunliffe grade at least 1.0: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	–4.3	–11.5	2.8
Ery. + BP bd – oxytetracycline	–11.8	–19.2	–4.5
Ery. + BP bd – minocycline	–7.5	–14.9	–0.1
Ery. od + BP od – ery. + BP bd	–0.0	–7.5	7.4
Benzoyl peroxide – oxytetracycline	–4.3	–11.5	2.8
Benzoyl peroxide – minocycline	0.0	–7.2	7.2
Benzoyl peroxide – ery. + BP bd	7.5	0.1	14.9
Ery. od + BP od – oxytetracycline	–11.9	–19.1	–4.6
Ery. od + BP od – minocycline	–7.5	–14.8	–0.3
Ery. od + BP od – benzoyl peroxide	–7.5	–14.8	–0.3

Inflamed lesion counts

Ranks for baseline Burke and Cunliffe grade

<1:

minocycline < oxytetracycline < ery. + BP bd < benzoyl peroxide < ery. od + BP od

≥1:

oxytetracycline < benzoyl peroxide = minocycline < ery. + BP bd = ery. od + BP od

To investigate the interaction further, analyses were carried out for the several smaller ranges of grade, attempting to keep sample sizes similar for each range; certain grades were used more than others.

Ranks for baseline Burke and Cunliffe grade

<0.5 (n = 100):
ery. + BP bd < oxytetracycline < ery. od + BP od < benzoyl peroxide < minocycline

[0.5–1) (n = 155):
minocycline < oxytetracycline < ery. + BP bd < benzoyl peroxide < ery. od + BP od

[1–1.25) (n = 141):
oxytetracycline < minocycline < benzoyl peroxide < ery. + BP bd < ery. od + BP od

[1.25–1.75) (n = 123):
benzoyl peroxide < oxytetracycline < ery. od + BP od < minocycline < ery. + BP bd

[>1.75) (n = 127):
oxytetracycline < minocycline < benzoyl peroxide < ery. + BP bd < ery. od + BP od

Numbers of participants with residual acne at 12 and 18 weeks

TABLE 83 *Participants with residual acne by Burke and Cunliffe grade, ITT data*

Treatment	Week 12			Week 18		
Grade:	**=0**	**≤ 0.1**	**>0.1**	**=0**	**≤ 0.1**	**>0.1**
Oxytetracycline	0	16	115	0	21	110
Minocycline	0	23	107	0	32	98
Benzoyl peroxide	2	23	107	1	32	98
Ery. + BP bd	0	23	104	1	40	87
Ery. od + BP od	0	28	102	0	52	78

TABLE 84 *Participants with residual acne by total inflamed lesion count, ITT data*

Treatment	Week 12				Week 18			
Lesion count:	**=0**	**<5**	**≥ 5**	**>66% decr.**	**=0**	**<5**	**≥ 5**	**>66% decr.**
Oxytetracycline	0	1	130	20	0	1	130	28
Minocycline	0	4	126	31	0	5	125	36
Benzoyl peroxide	2	4	126	26	0	8	122	36
Ery. + BP bd	0	4	123	32	1	12	115	48
Ery. od + BP od	0	2	129	41	0	9	122	52

Counts do not include nodules.
Decr., decrease.

TABLE 85 *Participants with residual acne by Burke and Cunliffe grade, non-ITT data*

Treatment	Week 12			Week 18		
Grade:	**=0**	**≤ 0.1**	**>0.1**	**=0**	**≤ 0.1**	**>0.1**
Oxytetracycline	0	14	86	0	17	76
Minocycline	0	20	77	0	26	63
Benzoyl peroxide	2	20	72	1	29	64
Ery. + BP bd	0	19	78	1	37	62
Ery. od + BP od	0	26	72	0	49	44

TABLE 86 *Participants with residual acne by total inflamed lesion count, non-ITT data*

Treatment	Week 12				Week 18			
Lesion count:	**=0**	**<5**	**≥ 5**	**>66% decr.**	**=0**	**<5**	**≥ 5**	**>66% decr.**
Oxytetracycline	0	0	101	18	0	1	92	25
Minocycline	0	4	93	30	0	5	84	33
Benzoyl peroxide	2	4	89	24	0	8	85	34
Ery. + BP bd	0	3	95	27	1	11	89	44
Ery. od + BP od	0	2	96	38	0	9	84	48

Counts do not include nodules.
Decr., decrease.

Burke and Cunliffe grade

TABLE 87 *Burke and Cunliffe grade for baseline grade less than 1.0: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	–0.068	–0.161	0.025
Ery. + BP bd – oxytetracycline	–0.057	–0.148	0.034
Ery. + BP bd – minocycline	0.011	–0.079	0.100
Ery. od + BP od – ery. + BP bd	–0.011	–0.101	0.079
Benzoyl peroxide – oxytetracycline	–0.061	–0.154	0.031
Benzoyl peroxide – minocycline	0.007	–0.085	0.099
Benzoyl peroxide – ery. + BP bd	–0.004	–0.094	0.086
Ery. od + BP od – oxytetracycline	–0.068	–0.161	0.024
Ery. od + BP od – minocycline	–0.000	–0.092	0.091
Ery. od + BP od – benzoyl peroxide	–0.007	–0.098	0.084

TABLE 88 *Burke and Cunliffe grade for baseline grade at least 1.0: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	–0.131	–0.310	0.048
Ery. + BP bd – oxytetracycline	–0.235	–0.419	–0.050
Ery. + BP bd – minocycline	–0.104	–0.290	0.082
Ery. od + BP od – ery. + BP bd	–0.073	–0.259	0.114
Benzoyl peroxide – oxytetracycline	–0.037	–0.216	0.141
Benzoyl peroxide – minocycline	0.094	–0.087	0.274
Benzoyl peroxide – ery. + BP bd	0.197	0.012	0.382
Ery. od + BP od – oxytetracycline	–0.307	–0.488	–0.127
Ery. od + BP od – minocycline	–0.176	–0.358	0.005
Ery. od + BP od – benzoyl peroxide	–0.270	–0.451	–0.088

Appendix 12

Participants' worst aspect of having acne (recorded at week 0)

TABLE 89 *Participants' worst aspect of having acne*

Patient	Worst aspect
0003	People notice them
0004	Teased at school
0006	Embarrassing
0007	They itch
0008	Social stigma
0015	Look of it, especially under lights
0017	Makes me look ugly
0019	I feel self-conscious
0020	People look at them, noticeable
0022	They make me look ugly
0023	Annoying, painful
0024	How it looks
0026	Having people see spots
0028	Appearance, feel of them
0030	The look of them (can't stand the sight of them)
0036	Appearance
0038	The way it looks, makes me feel horrible
0040	Having to cover forehead with fringe
0042	People call me names
0044	The way they look
0047	The way they look
0049	The look of them
0050	People at school – get on my nerves
0052	The way they look
0055	The way they look
0059	The way they look
0061	They're ugly
0062	Not bothered by them
0063	The way it looks
0065	Embarrassing
0068	Makes me feel uncomfortable around people
0072	Going out – feels self-conscious + stupid
0073	Lack of confidence – doesn't go out without make-up on. Hassle of worrying about it
0075	Other people's responses
0076	Lads take the micky out of me
0078	It's there
0079	Doesn't look very nice
0080	Appearances – doesn't feel like I fit in
0085	Makes me feel afraid and when it is hot I scratch
0086	Don't like it. I think it is unattractive
0089	Sight of them – sometimes are quite painful
0090	The scars it leaves on the skin
0092	Damn ugly
0095	It is visible – people seeing them
0096	Don't like it – they are really irritating
0100	Doesn't look very attractive – makes you look scruffy
0102	Self-conscious of it
0106	The sight of it for other people – got to try to cover everything up

continued

TABLE 89 *Participants' worst aspect of having acne (cont'd)*

Patient	Worst aspect
0107	If they are big I think people are staring at them
0108	Socially – tend not to mix much
0114	Don't feel right when you've got lots of things on your face
0115	Irritates every now and then – itches + can feel them
0117	It's just annoying
0119	Feeling self-conscious – doesn't like to go out without make-up on
0120	Lack of confidence
0122	Feeling embarrassed sometimes
0124	Little painful spots + shaving is a nuisance
0125	The scars
0127	Embarrassing
0130	Don't feel confident
0134	I just don't like it and it doesn't give me a lot of confidence
0136	Not very nice is it
0138	Comments that people make
0139	Depends if go out at night – sometimes when look in the mirror – otherwise doesn't bother me
0142	Feels depressed a lot – feels other people look nicer
0144	Sometimes the spots hurt
0146	When you get a great big spot you feel everyone is staring at it
0149	Embarrassing – puts off the opposite sex. Makes you feel self-conscious
0152	Self-consciousness
0153	You don't feel confident in front of people
0157	Doesn't really affect me
0158	It itches sometimes & it's the way it looks
0159	Just doesn't feel nice
0162	Embarrassment, cannot wear clothes as she likes
0165	Makes you feel scruffy
0166	Not bothered
0167	Embarrassment
0170	Pain in the face when spots are picked, and nodules
0174	The spots & having to cover with make-up
0176	The itching, its being there
0177	Redness
0179	Visual appearance of it
0183	I don't know, really
0184	The appearance
0187	Annoying, when rubs against my clothes they start to bleed
0188	I'm not bothered
0189	The redness – the way it looks
0190	You can see them – embarrassment
0192	Makes you feel uncomfortable
0198	Appearance
0199	Not wanting to go out in public
0202	Talking to people knowing I've got it
0205	They are annoying
0208	The oiliness
0209	How they look
0210	My parents are worried
0212	Brothers have a go at me
0215	Not sure
0217	The way it looks
0220	The way I look
0223	The way people look at you
0225	Embarrassment
0226	Embarrassing
0227	Getting picked on
0228	When out with friends
0232	The itchiness

continued

TABLE 89 *Participants' worst aspect of having acne (cont'd)*

Patient	Worst aspect
0234	Not bothered
0237	They are all over my face
0238	Makes you feel a bit dirty
0240	People notice
0244	The embarrassment
0245	The big ones leave a red mark
0246	You don't look as clean
0250	Don't look very attractive
0253	The embarrassment
0254	Embarrassment
0257	Embarrassment, I do not want to go out
0258	A nuisance
0261	Name calling
0265	Name calling
0269	No one else has got them as much
0271	Affect job prospects
0273	Irritating
0275	They itch quite a bit
0277	The sight of it
0278	What people say
0279	Have got used to it
0283	'The look' – embarrassment
0284	Some of them are a bit sore
0287	Self-esteem low
0288	The appearance
0292	People's comments
0293	Gets on your nerves
0295	The appearance
0300	Embarrassment
0301	Self-consciousness
0302	Embarrassment, self-consciousness
0303	Embarrassment
0307	Not bothered
0309	Not bothered
0310	I'm conscious of them
0311	No confidence
0315	The looks
0317	The embarrassment
0320	The look of it
0321	Self-conscious about them
0325	Bothered about appearance
0327	Treatment is a hassle
0328	Treatments are a pain to use
0333	Appearance of spots
0334	Appearance of skin
0336	Appearance of skin
0337	Compulsion to pick at lesions
0340	Appearance of skin makes me self-conscious
0342	Appearance of skin
0344	Appearance of skin
0345	Appearance of skin
0346	Big red itchy spots
0352	Appearance of skin
0355	Spots hurt
0359	Appearance of skin
0361	Appearance of skin
0362	Other people looking at skin
0363	Appearance of skin

continued

TABLE 89 *Participants' worst aspect of having acne (cont'd)*

Patient	Worst aspect
0364	Appearance of skin
0366	Appearance of skin
0369	Appearance of skin
0371	Lack of self-confidence
0374	Appearance of skin
0375	Appearance of skin
0381	Appearance of skin
0382	Comments from other people
0383	Appearance of skin
0384	Lack of self-confidence
0386	Appearance
0390	Self-conscious. Aware of people looking at spots
0392	Name-calling
0395	I'm not bothered
0396	The scarring
0398	Parental pressure to do something about spots
0400	Self-consciousness in social occasions
0404	Having to wear make-up or feeling that she has to wear make-up
0405	Self-consciousness due to spots
0406	Appearance of skin
0411	Lack of self-confidence
0412	Parental pressure to get treatment for spots
0413	Scarring
0417	Self-consciousness
0418	Appearance
0419	Lack of self-confidence in social situations
0421	Appearance
0423	Appearance of red spots
0424	Spots never clear – always have some
0426	Scarring left by spots
0431	Appearance of skin
0432	Self-conscious of people looking at spots, paranoid
0433	Self-consciousness in social situations
0435	Appearance
0437	Blackheads, red sore painful spots + duration
0441	Appearance of skin
0443	Appearance
0444	Self-conscious of spots
0447	Appearance
0449	Self-conscious
0453	Lack of self-confidence
0455	Persistence of acne – feels unkempt & dirty when spots present
0456	Appearance
0459	Appearance
0461	Self-consciousness
0463	People making comments about bad skin
0468	Appearance
0469	Appearance
0470	Appearance and painful skin
0473	Dislikes having to wear make-up to cover up spots
0474	Appearance
0475	Painful & messy, big red spots
0477	Self-confidence lower
0481	Self-consciousness
0483	Make-up can make spots worse, so has to avoid
0485	Just looks horrible
0486	People can see it
0489	Self-consciousness

continued

TABLE 89 *Participants' worst aspect of having acne (cont'd)*

Patient	Worst aspect
0490	Just annoy you
0491	People stare at you all the time. Feels self-conscious
0497	Skin feels mucky
0498	Having to wear make-up
0502	Can be embarrassing sometimes
0505	Embarrassing & uncomfortable. Gets sore at times
0506	Not bothered, but would like to get rid of them
0508	Not being able to go out without wearing make-up
0509	Social aspect – makes you feel like a teenager in a suit. People view you different
0511	Feeling embarrassed that nobody else my age has it and it just doesn't look healthy
0512	Annoying
0514	Self-consciousness – not being able to wear short tops and soreness from skin
0518	Appearance – semi-self-conscious
0520	Doesn't like it sometimes, but usually doesn't bother them
0521	Not being able to sunbathe because of spots on back
0523	It is time-consuming to have to get ready for day to conceal skin & it costs a lot to manage
0525	Dents my confidence – don't like looking in mirrors
0530	Not very nice to look at
0533	
0534	People tormenting me
0535	The way they look
0536	Affects my confidence
0540	Having to cover it up all the time with make-up
0541	Makes me feel self-conscious when I have a really big one on my face
0543	Makes me self-conscious + hurts when I shave
0548	Just having it – its appearance
0550	Affects my confidence
0552	Feel so unattractive
0554	Just don't like it at all
0557	The actual spots – the way they look
0559	The appearance of my cheeks being red
0561	Affects appearance & bothered by what people think
0564	Appearance – feels difficult to socialise
0565	Not being able to wear vest tops and not being able to swim
0567	It itches
0568	Doesn't bother me
0570	Wishing I was more handsome without it. I get really tired of it
0578	Scabs
0579	Affects my confidence
0581	Nothing
0582	Not conscious of it, but when I look at it it doesn't look very good
0583	Generally a bit of a pain
0589	Affects my confidence
0590	Appearance
0591	The itchiness makes you want to scratch it
0593	When I was younger it affected me a lot, but now it does not really affect me
0594	Affects relationships – self-conscious & self-confidence
0596	Appearance – try to cover up with hair style
0597	Doesn't look very smart
0599	Self-esteem related – not knowing how I'm going to look in the morning, hyper-aware of my appearance
0600	Looks awful and is painful
0605	Affects confidence to an extent
0607	Just a bit annoying
0610	Feeling dowdy conspicuous – feels like other people notice them
0611	Can't wear make-up – feels skin complexion is 'mucky'
0615	Lack of self-confidence when meeting people
0616	Doesn't [word missing] acne
0617	The look of it

continued

TABLE 89 *Participants' worst aspect of having acne (cont'd)*

Patient	Worst aspect
0619	Feel embarrassed and lack confidence
0620	Embarrassing – don't want to talk to people when I've got it
0622	Doesn't make one feel very confident when going out
0625	Doesn't look nice and is painful and itchy
0629	Gets you down. I wish I had nice skin
0632	Makes me self-conscious and that people are going to look at me
0634	Hurts my face – you can tell they are there and people look at them
0635	Doesn't bother me too much
0636	When I go out feel embarrassed
0640	Affects my confidence
0642	It's just there, that's all – it doesn't really affect me
0643	Just don't want them as such
0646	Doesn't really
0647	Don't like to see it myself – makes me feel self-conscious
0650	Embarrassing at my age
0651	Tends not to wear clothes that reveal back and can't go out without make-up on
0652	Don't really bother me – I've got so used to it
0655	Feel embarrassed
0657	Self-confidence – upset me after a while and can't model
0663	The looks of it, the time it takes me to get ready
0665	Don't like it
0666	Bright lights really show the spots up
0667	Always conscious of it
0668	People notice you when you are out
0672	It's what other people think of you
0675	Don't like people coming too close
0676	Don't like the way it looks
0680	Don't feel very nice
0682	Quite annoying – feel self-conscious
0684	Just annoying – have to wear make-up to cover it
0688	Being conscious of it – it has an itching soreness
0691	Get called spotty
0692	Looks different than other kids
0693	Embarrassing when you want to go out
0694	Appearance
0695	On a bad day I do not like to go out socialising
0697	Affects self-confidence – can't take children swimming. Covers face as don't like it to be seen
0698	Affects my confidence – feel that people are looking
0702	Affects the clothes that I wear
0706	Just having spots isn't very nice and I have to cover them up
0709	Embarrassing
0712	Just want to get rid of it. Feel a little self-conscious
0713	Don't like it – think it looks a mess & horrible
0715	Doesn't affect me
0718	The appearance of my skin affects how I feel in myself, & spots are pain. I feel my skin is dirty
0720	Just embarrassing
0723	Not so conscious of it now – but I feel my skin should have improved by now
0725	Not very nice having lots of spots all over your face
0726	The routine of having to wash my face etc gets me down. Affects my self-confidence in relationships
0727	Going out – affects my confidence
0728	Having spots on face – visual – don't look nice
0731	Doesn't affect me
0735	Redness doesn't look very nice
0737	Affects my confidence 'cowering away from people'
0738	Cross between the appearance and the pain
0741	Embarrassing
0742	Affects my confidence – not a nice thing
0744	Affects my confidence

continued

TABLE 89 *Participants' worst aspect of having acne (cont'd)*

Patient	Worst aspect
0748	Annoys me
0750	Unsightly
0752	It hurts on my back & is embarrassing
0756	When I get the big ones – self-conscious of folks looking at them
0757	Difficulty shaving – affects confidence
0759	Getting teased
0760	Doesn't affect me – live with it
0761	Affects my appearance
0762	Worst thing is having one great big spot
0765	They get itchy
0768	Don't like going out without make-up – people look at them
0771	Used to be picked on & felt I had to hide it
0772	The pain & the way I look
0773	Affects me socially – don't go out often as concerned about appearance
0774	Doesn't really affect me
0780	Feels untidy – don't know how other people react to them
0783	Embarrassing, especially meeting people for the 1st time. I feel dirty & can never look at my back
0789	The redness and it knocks my confidence
0790	Wearing vest tops reveals the spots on my back – self-conscious
0791	The stigma surrounding them – they are there, but doesn't really bother me
0792	The appearance of them – get teased at school
0793	Doesn't affect me, but I'd rather they weren't there – they are a bind
0794	The redness – you can see them – affects confidence
0795	Can't wear the clothes I like
0800	'Annoys me' – know they are there – they get painful
0803	Don't want people thinking I'm not looking after my skin
0805	Makes me feel self-conscious – even when look in a mirror – makes me think people are staring at my skin
0808	Affects my self-esteem. Spend huge amounts of money on make-up
0809	Just don't like it – doesn't make me very confident
0811	People noticing – not very nice
0813	Doesn't look very good – self-consciousness
0818	Old enough not to have them – feel ashamed people think you are younger
0820	What people think – people stereotype me
0822	My appearance
0824	Not bothered
0825	They make you look strange
0828	Looks ugly
0831	Not really bothered
0833	The way they look
0835	The soreness
0836	Appearance
0837	The embarrassment
0838	I hate going out
0839	Making friends (girls)
0842	Have to wear make-up all the time
0845	Still having spots at my age
0848	Feel self-conscious
0850	Self-conscious
0851	The appearance
0853	The general appearance – what people think
0856	Self-consciousness
0859	Don't look very nice
0861	It is embarrassing at my age
0865	Embarrassment
0867	Embarrassment, having to wear make-up all the time
0868	The redness & soreness
0870	They stick out
0871	I'm not bothered

continued

TABLE 89 *Participants' worst aspect of having acne (cont'd)*

Patient	Worst aspect
0872	People say you do not wash your face
0873	Embarrassment
0876	Not sure
0881	Not bothered much
0882	Trying to cover them up
0887	Self-confidence
0888	The appearance
0889	Embarrassment
0894	People looking at me
0897	Affects confidence & makes me depressed
0900	Embarrassment
0901	Children often pick on me
0902	The look of it
0904	Finding clothes I can wear
0907	The look of it
0909	Always looking like a teenager
0910	The appearance
0912	Not sure
0916	Going out – embarrassment
0917	The look, & they can hurt
0918	I'm not bothered
0919	Embarrassment
0922	My appearance
0925	Its visibility
0926	The spots can be hurting
0927	Embarrassment
0929	The embarrassment
0935	Embarrassment
0936	Embarrassing
0937	You feel that people are looking at you
0938	The embarrassment
0943	My appearance
0944	Makes you feel less attractive & generally under the weather & less confident
0948	I'm not really bothered
0952	The embarrassment
0953	Not bothered
0954	The look of them
0955	Taking the micky out of me
0961	It's annoying – I'm not used to it
0962	Going out
0963	The looks of it
0964	It catches on shaving
0968	People's comments
0969	The soreness
0975	Makes me more self-conscious
0977	They make me feel ugly
0978	The appearance
0979	Worry about appearance
0980	Going out
0982	Embarrassment
0988	Some of them are painful – the looks of it
0989	The way it looks
0990	They don't look nice
0993	Always got to wear make-up – embarrassing
0995	I'm not bothered
0997	Not being able to go swimming
0998	The yellow spots and the peeling
0999	Having to wear make-up all the time

continued

TABLE 89 *Participants' worst aspect of having acne (cont'd)*

Patient	Worst aspect
1002	It's the big ones that bother me
1003	Just annoying
1004	It's a social thing, you lose your self-confidence
1006	The embarrassment
1011	They get sore
1014	The appearance of them
1015	The soreness & embarrassment
1017	When people see you
1018	Affects my self-confidence
1022	More self-conscious
1024	The look of it
1026	The embarrassment
1029	The teasing & having to wear make-up
1033	When my skin goes really red
1034	My little sister picks on me
1037	The way it looks
1039	The looks of it
1041	They're horrible
1043	The way they look in the morning
1045	Sometimes it itches
1047	The look of them & they hurt, I don't like them
1048	Hard to cover with make-up
1050	The look of it, having to cover it up all the time
1052	Having spots like a teenager
1053	The image
1057	Socialising, meeting people
1058	The appearance and it gets sore
1060	Name calling. It don't look nice
1063	Embarrassing
1067	Unsightly
1068	Looks awful
1071	Going out – being noticed affects my self-confidence
1072	I didn't get them till I was 21 & have to explain to people
1073	The embarrassment
1075	How it looks
1081	I'm not bothered
1083	Embarrassment, low self-esteem
1085	When they are red – the look of them
1088	Embarrassing
1089	Embarrassment
1091	Not being able to go out & they can be quite painful
1094	Having to cover them up – going out
1095	The embarrassment
1097	They bother me sometimes
1099	They don't bother me
1105	It doesn't bother me
1106	Not being able to look at people
1107	The embarrassment
1108	The way they look
1110	The itch
1112	The pain, more self-conscious
1113	I can't wear the clothes I want – embarrassing
1117	I'm not bothered
1119	I'm used to them now
1120	The look of it
1125	My appearance
1126	Makes you very self-conscious
1130	They look so awful

continued

TABLE 89 *Participants' worst aspect of having acne (cont'd)*

Patient	Worst aspect
1131	My appearance
1155	Having to wear make-up
1158	It's annoying to look at
1160	Not much of a problem
1162	Gets your confidence down
1164	They look awful – affects confidence
1166	Sometimes you pick them
1167	Self-confidence
1171	When they burst and blood stains my clothes
1172	They are horrible – I don't like them on my face
1175	The look of it
1177	I hate them the way they look
1180	I feel conscious of them
1182	Everyone taking a micky
1183	The look of them
1186	None of my other friends have them
1188	Makes you self-conscious
1190	How they look
1193	Embarrassment when red, and as a dance student I can't wear low back clothes
1194	Sometimes they bother me
1196	They can be uncomfortable & painful, self-conscious about them
1200	Still having spots at 32 & very cyclical nature. Sometimes good, but then get worse
1202	Appearance
1203	Painful spots
1208	Lack of self-confidence
1209	Itchiness & soreness + treatment for spots
1213	Feeling that I have to wear make-up to cover up the spots
1215	Appearance
1217	Self-consciousness in social situations – particularly when pustules present
1220	Appearance of skin
1221	Appearance of skin
1224	Appearance
1225	Very self-conscious – loss of self-confidence
1228	Appearance & feel of skin
1229	Appearance
1230	Appearance of skin – lack of confidence without make-up
1233	Appearance of yellow pustules
1236	Grease & spots feel dirty & looking bad in professional capacity
1239	Appearance
1241	Appearance of skin
1243	Post-inflammatory pigmentation + scarring
1245	Appearance
1246	Feels less attractive with spots
1247	Other people's reactions
1253	Lack of self-confidence in social situations
1254	Leaving black marks in the skin
1256	Appearance of skin
1257	Appearance of skin
1262	Low self-esteem
1263	Scarring – long lasting effects
1265	Appearance
1266	Self-conscious – feel people are looking at spots
1267	Lack of self-confidence, if skin is bad
1268	Aesthetics – appearance of skin
1271	Low self-esteem
1273	Self-conscious in social situations
1278	Embarrassed at spots
1282	Upset at appearance of big red spots – skin looks uneven & discoloured

continued

TABLE 89 *Participants' worst aspect of having acne (cont'd)*

Patient	Worst aspect
1283	Appearance of skin
1286	Appearance
1287	Appearance of skin
1288	Feel spots look ugly, particularly to other people
1289	Appearance
1293	Self-conscious of appearance of skin
1296	Self-conscious of big facial spots
1297	Appearance of skin – hard to cover up
1301	Itching spots which leave scars
1303	Appearance of skin on face – spots shouldn't be there!
1306	Pain from large spots
1308	Appearance of skin
1309	Worries about other people's ignorance, i.e. thinking it's dirty
1310	Appearance of skin
1311	Appearance
1313	Self-conscious – thinks people are looking & painful spots
1316	Feeling that I have to wear make-up when going out at all
1317	Going out & feeling they are not covered up very well
1321	Self-conscious of appearance
1325	Appearance of skin
1327	Spots look unsightly
1329	Having to wear make-up – difficult to cover up spots
1331	Appearance of skin
1333	Other people commenting on skin – at school
1336	Frustration at appearance of skin. Self-conscious when meeting people especially with regard to work
1339	Self-conscious – always conscious spots are there
1340	Appearance of skin
1342	Feeling self-conscious & always having to wear make-up
1343	Skin is painful – on moving face particularly
1346	Can be embarrassing
1348	Hates appearance of spots & pain
1351	Having to wear make-up – feeling that I have to wear make-up
1379	It's quite stressful
1381	Not much bothered
1382	Self-confidence, people looking at them
1409	Not really fussed about having them
1410	Irritation of spots – self-conscious embarrassed about it
1411	Downside is having spots – bumpiness
1417	I don't like it – feel a bit embarrassed
1419	Don't like going out as much
1421	When the children ask me if I've had chicken pox. Self-conscious – some are painful
1422	I can't get rid of them
1425	Just having them – the way they look
1427	Don't know – it doesn't bother me
1430	When going out – people look at you
1431	They get sore & itchy sometimes
1432	Affects my confidence – can't wear some types of clothes because of my back, & makeup
1474	Other people can see them
1479	Not much confidence – never go out without make-up & cover back up if spots there
1480	Feel self-conscious
1481	Doesn't affect me
1484	Having to cover them up & can't go swimming
1485	The appearance
1490	Just annoying really
1491	Don't look very nice
1493	Get called a lot for them
1494	The pain when they are bad, & self-conscious
1495	When red & inflamed they get to me sometimes

continued

TABLE 89 *Participants' worst aspect of having acne (cont'd)*

Patient	Worst aspect
1498	Conscious of them on my appearance
1500	Feeling conscious of it
1502	Having to wear make-up to cover them up
1504	They hurt sometimes – don't let them bother me
1507	Hate it when they are noticeable
1508	Feel like everybody is looking at them – my confidence really – especially with my work (beautician)
1509	Doesn't really affect me that much
1512	Taking my top off in the summer
1515	They get sore
1516	It's just there – find it embarrassing
1520	Come at wrong time
1521	Nothing really
1523	Feel I can't go out because of people calling me
1524	Annoys me
1525	When people call each other – they pick up on the spots
1531	Just want to get rid of them – nothing really bothers
1533	Doesn't affect me
1534	They are there – don't like looking at them
1537	Get called names
1538	Going out – appearance

Details are printed from the database and are as reported by the participant.

Appendix 13

Quality of life analyses

SF-36 scales by gender and age at baseline

TABLE 90 *Summary of SF-36 scales by gender and age at baseline*

		Physical functioning			Role – physical			Bodily pain			General health		
Gender	**Age (years)**	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***
Male	<16	91.3	22.3	73	96.6	13.4	73	85.3	16.1	73	82.2	15.2	73
	16–24	89.6	23.6	191	95.2	16.9	190	86.1	18.9	191	78.4	15.5	191
	25–34	99.4	1.6	18	100.0	0.0	18	95.6	8.9	18	78.4	15.8	18
	35–44	86.3	24.3	4	100.0	0.0	4	85.3	29.5	4	64.8	23.4	4
Female	<16	87.7	24.6	101	96.8	13.1	101	81.5	18.6	101	77.0	17.6	101
	16–24	92.0	17.8	139	91.1	23.9	139	82.0	21.0	141	72.3	18.5	139
	25–34	95.1	11.1	91	90.1	26.6	91	83.8	22.1	91	76.2	19.1	91
	35–44	90.6	13.2	17	91.2	19.6	17	71.1	17.0	17	69.3	20.8	17
		Vitality			**Social functioning**			**Role – emotional**			**Mental health**		
Gender	**Age (years)**	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***
Male	<16	74.6	18.8	73	89.6	17.1	73	93.2	20.8	73	79.6	16.6	72
	16–24	67.9	18.2	191	88.0	19.0	191	88.7	25.7	191	75.2	17.3	191
	25–34	67.2	14.9	18	92.4	14.3	18	98.1	7.9	18	76.0	15.3	18
	35–44	47.5	35.9	4	84.4	23.7	4	75.0	50.0	4	59.0	31.7	4
Female	<16	72.0	16.5	101	91.2	15.4	101	90.8	24.1	101	75.9	14.0	101
	16–24	63.5	19.2	139	81.5	21.8	141	76.0	35.2	139	69.8	18.6	139
	25–34	59.2	19.0	91	80.6	23.7	91	76.6	35.7	91	66.1	19.3	91
	35–44	57.9	20.7	17	92.6	9.9	17	90.2	22.9	17	67.1	18.1	17

Scores are generally expected to decrease with age, although some more quickly than others.[71]

SF-36 analysis

Physical functioning

This scale measures limitations in behavioural performance of everyday activities. Physical functioning scores were high (i.e. good) to start (a mean of around 90/100, and median of 100 in all groups), but scores still increased slightly in all groups by the end of the study (*Table 91*).

TABLE 91 *Mean SF-36 physical functioning*

Treatment group	***n***	**Week**			**LSmean**	**95% CI**
		0	**18**	**18–0**		
Oxytetracycline	126	92.1	95.2	3.1	3.9	(1.6 to 6.1)
Minocycline	129	90.4	92.5	2.1	1.7	(–0.5 to 4.0)
Benzoyl peroxide	127	88.3	92.1	3.8	2.1	(–0.2 to 4.4)
Ery. + BP bd	124	93.2	94.2	1.0	1.6	(–0.7 to 3.9)
Ery. od + BP od	128	91.5	93.2	1.6	1.7	(–0.5 to 4.0)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 92*.

Ranking of treatments for physical functioning:

ery. + BP bd < ery. od + BP od = minocycline < benzoyl peroxide < oxytetracycline

TABLE 92 *SF-36 physical functioning: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	–2.2	–5.4	1.0
Ery. + BP bd – oxytetracycline	–2.2	–5.5	1.0
Ery. + BP bd – minocycline	–0.1	–3.3	3.1
Ery. od + BP od – ery. + BP bd	0.1	–3.1	3.3
Benzoyl peroxide – oxytetracycline	–1.8	–5.0	1.4
Benzoyl peroxide – minocycline	0.4	–2.8	3.6
Benzoyl peroxide – ery. + BP bd	0.4	–2.8	3.7
Ery. od + BP od – oxytetracycline	–2.1	–5.3	1.1
Ery. od + BP od – minocycline	0.0	–3.1	3.2
Ery. od + BP od – benzoyl peroxide	–0.3	–3.5	2.9

The baseline by treatment interaction was significant ($p = 0.0001$), but further analyses by severity were not performed.

Role – physical

This scale measures the extent of disability in everyday activities due to physical problems. Role – physical scores were high (good) to start (a mean of 93–95/100, and median of 100 in all groups). There was little change in scores over the study (*Table 93*).

TABLE 93 *Mean SF-36 role – physical*

Treatment group	*n*	Week			LSmean	95% CI
		0	18	18–0		
Oxytetracycline	125	95.4	92.9	–2.5	–1.9	(–5.1 to 1.4)
Minocycline	129	94.8	94.0	–0.8	–0.6	(–3.8 to 2.6)
Benzoyl peroxide	127	93.4	92.0	–1.4	–1.6	(–4.8 to 1.7)
Ery. + BP bd	124	93.3	93.5	0.2	–0.1	(–3.4 to 3.2)
Ery. od + BP od	128	93.3	92.6	–0.7	–1.0	(–4.3 to 2.2)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 94*.

Ranking of treatments for role – physical:

oxytetracycline < benzoyl peroxide < ery. od + BP od < minocycline < ery. + BP bd

TABLE 94 *SF-36 role – physical: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	1.2	–3.4	5.8
Ery. + BP bd – oxytetracycline	1.8	–2.9	6.4
Ery. + BP bd – minocycline	0.5	–4.1	5.1
Ery. od + BP od – ery. + BP bd	–0.9	–5.6	3.7
Benzoyl peroxide – oxytetracycline	0.3	–4.3	4.9
Benzoyl peroxide – minocycline	–1.0	–5.5	3.6
Benzoyl peroxide – ery. + BP bd	–1.5	–6.1	3.1
Ery. od + BP od – oxytetracycline	0.8	–3.8	5.4
Ery. od + BP od – minocycline	–0.4	–5.0	4.1
Ery. od + BP od – benzoyl peroxide	0.5	–4.0	5.1

The baseline by treatment interaction was not significant ($p = 0.072$), so data were not analysed separately for differing severity.

Bodily pain

This scale focuses on the severity of bodily pain and resulting limitations in activities. There was little change in pain scores during the study, and around half of participants had no pain at all (*Table 95*).

TABLE 95 *Mean SF-36 bodily pain*

Treatment group		Week 0		Week 18		Week 18–0	
	n	Mean	Median	Mean	Median	Mean difference	LSmean (95% CI)
Oxytetracycline	127	83.1	84.0	86.0	100.0	2.9	2.7 (0.0 to 5.3)
Minocycline	129	83.9	84.0	84.8	100.0	0.9	0.8 (–1.9 to 3.4)
Benzoyl peroxide	127	84.4	84.0	83.6	84.0	–0.8	–0.6 (–3.2 to 2.0)
Ery. + BP bd	125	85.7	100.0	89.4	100.0	3.7	4.7 (2.0 to 7.3)
Ery. od + BP od	128	82.5	84.0	82.9	84.0	0.4	–0.1 (–2.8 to 2.5)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 96*.

Ranking of treatments for bodily pain:

benzoyl peroxide < ery. od + BP od < minocycline < oxytetracycline < ery. + BP bd

TABLE 96 *SF-36 bodily pain: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	–1.9	–5.6	1.8
Ery. + BP bd – oxytetracycline	2.0	–1.7	5.8
Ery. + BP bd – minocycline	3.9	0.2	7.6
Ery. od + BP od – ery. + BP bd	–4.8	–8.5	–1.1
Benzoyl peroxide – oxytetracycline	–3.3	–7.0	0.5
Benzoyl peroxide – minocycline	–1.4	–5.1	2.3
Benzoyl peroxide – ery. + BP bd	–5.3	–9.0	–1.5
Ery. od + BP od – oxytetracycline	–2.8	–6.5	0.9
Ery. od + BP od – minocycline	–0.9	–4.6	2.8
Ery. od + BP od – benzoyl peroxide	0.5	–3.2	4.2

The baseline by treatment interaction was significant ($p = 0.018$), but no further analysis by differing baseline severity was carried out.

General health

A mid-range score is obtained by reporting no unfavourable evaluations of health in general, so average health was good. There was a very small decrease in general health scores in all groups (*Table 97*).

TABLE 97 *SF-36 general health*

Treatment group	*n*	Week			LSmean	95% CI
		0	18	18–0		
Oxytetracycline	126	74.7	74.3	–0.3	–0.6	(–2.5 to 1.4)
Minocycline	129	78.4	77.9	–0.5	–0.3	(–2.2 to 1.7)
Benzoyl peroxide	127	76.5	74.8	–1.7	–1.7	(–3.6 to 0.2)
Ery. + BP bd	124	76.4	74.8	–1.6	–1.6	(–3.6 to 0.4)
Ery. od + BP od	128	77.1	76.4	–0.8	–0.7	(–2.7 to 1.2)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 98*.

Ranking of treatments for general health:

benzoyl peroxide < ery. + BP bd < ery. od + BP od < oxytetracycline < minocycline

TABLE 98 *SF-36 general health: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	0.3	–2.4	3.1
Ery. + BP bd – oxytetracycline	–1.0	–3.8	1.8
Ery. + BP bd – minocycline	–1.3	–4.1	1.4
Ery. od + BP od – ery. + BP bd	0.8	–1.9	3.6
Benzoyl peroxide – oxytetracycline	–1.1	–3.9	1.6
Benzoyl peroxide – minocycline	–1.4	–4.2	1.3
Benzoyl peroxide – ery. + BP bd	–0.1	–2.9	2.7
Ery. od + BP od – oxytetracycline	–0.2	–2.9	2.6
Ery. od + BP od – minocycline	–0.5	–3.2	2.3
Ery. od + BP od – benzoyl peroxide	–1.0	–1.8	3.7

The baseline by treatment interaction was not significant ($p = 0.856$), so data were not analysed separately for differing severity.

Vitality

A mid-range score is reported by those who do not report feeling tired or worn out; a score of 100, in addition to an absence of these symptoms, is earned by those who report feeling full of pep and energy all of the time. Mean vitality was above the mid-range. There was a very small decrease in vitality scores in all groups (*Table 99*).

TABLE 99 *Mean SF-36 vitality*

Treatment group	*n*	Week			LSmean	95% CI
		0	18	18–0		
Oxytetracycline	126	65.5	65.4	–0.1	–0.4	(–2.9 to 2.1)
Minocycline	129	68.4	66.4	–2.0	–1.6	(–4.0 to 0.9)
Benzoyl peroxide	127	68.2	66.0	–2.1	–1.6	(–4.1 to 0.9)
Ery. + BP bd	124	66.3	65.0	–1.2	–1.4	(–3.9 to 1.1)
Ery. od + BP od	128	65.1	64.6	–0.5	–1.1	(–3.6 to 1.4)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 100*.

Ranking of treatments for vitality:

benzoyl peroxide = minocycline < ery. + BP bd < ery. od + BP od < oxytetracycline

TABLE 100 *SF-36 vitality: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	–1.2	–4.7	2.4
Ery. + BP bd – oxytetracycline	–1.0	–4.6	2.6
Ery. + BP bd – minocycline	0.2	–3.4	3.7
Ery. od + BP od – ery. + BP bd	0.3	–3.3	3.8
Benzoyl peroxide – oxytetracycline	–1.3	–4.8	2.3
Benzoyl peroxide – minocycline	–0.1	–3.6	3.4
Benzoyl peroxide – ery. + BP bd	–0.3	–3.8	3.3
Ery. od + BP od – oxytetracycline	–0.7	–4.2	2.8
Ery. od + BP od – minocycline	0.5	–3.0	4.0
Ery. od + BP od – benzoyl peroxide	0.6	–3.0	4.1

The baseline by treatment interaction was not significant ($p = 0.801$), so data were not analysed separately for differing severity.

Social functioning

A score of 100 on this scale indicates no limitations or disability due to personal problems. There was a small increase in the mean social functioning score for the ery. + BP bd group, but little change for the other groups (*Table 101*). Median scores were 100 at weeks 0 and 18 for all groups. This was probably the scale most likely to show changes owing to needing a smaller sample size,[47] but perhaps the acne was too mild in this population.

TABLE 101 *Mean SF-36 social functioning*

Treatment group	*n*	Week			LSmean	95% CI
		0	18	18–0		
Oxytetracycline	127	86.5	86.4	–0.1	–0.1	(–2.7 to 2.5)
Minocycline	129	87.3	88.2	0.9	1.2	(–1.4 to 3.8)
Benzoyl peroxide	127	87.5	85.8	–1.7	–1.4	(–4.0 to 1.2)
Ery. + BP bd	125	84.9	90.4	5.5	4.6	(2.0 to 7.2)
Ery. od + BP od	128	85.7	86.9	1.2	1.0	(–1.6 to 3.6)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 102*.

Ranking of treatments for social functioning:

benzoyl peroxide < oxytetracycline < ery. od + BP od < minocycline < ery. + BP bd

TABLE 102 *SF-36 social functioning: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	1.3	–2.4	5.0
Ery. + BP bd – oxytetracycline	4.7	1.0	8.4
Ery. + BP bd – minocycline	3.4	–0.3	7.1
Ery. od + BP od – ery. + BP bd	–3.6	–7.3	0.1
Benzoyl peroxide – oxytetracycline	–1.3	–5.0	2.4
Benzoyl peroxide – minocycline	–2.6	–6.3	1.1
Benzoyl peroxide – ery. + BP bd	–6.0	–9.7	–2.3
Ery. od + BP od – oxytetracycline	1.1	–2.6	4.8
Ery. od + BP od – minocycline	–0.2	–3.9	3.5
Ery. od + BP od – benzoyl peroxide	2.4	–1.3	6.1

The baseline by treatment interaction was significant ($p = 0.004$), but no further analysis by baseline severity was carried out.

Role – emotional

A score of 100 on this scale indicates no limitations or disability due to emotional problems. There was little change in mean role – emotional scores for any group (*Table 103*). Median scores were 100 at both weeks 0 and 18 in all groups.

TABLE 103 *Mean SF-36 role – emotional*

Treatment group	*n*	Week			LSmean	95% CI
		0	18	18–0		
Oxytetracycline	126	81.2	81.5	0.3	–1.3	(–5.4 to 2.9)
Minocycline	129	89.4	86.8	–2.6	–1.1	(–5.2 to 3.0)
Benzoyl peroxide	127	85.6	87.1	1.6	1.7	(–2.4 to 5.8)
Ery. + BP bd	124	86.8	87.1	0.3	0.8	(–3.4 to 4.9)
Ery. od + BP od	128	83.1	83.6	0.5	–0.0	(–4.1 to 4.1)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 104*.

Ranking of treatments for role – emotional:

oxytetracycline < minocycline < ery. od + BP od < ery. + BP bd < benzoyl peroxide

TABLE 104 *SF-36 role – emotional: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	0.1	–5.7	6.0
Ery. + BP bd – oxytetracycline	2.0	–3.8	7.9
Ery. + BP bd – minocycline	1.9	–3.9	7.7
Ery. od + BP od – ery. + BP bd	–0.8	–6.7	5.0
Benzoyl peroxide – oxytetracycline	2.9	–2.9	8.8
Benzoyl peroxide – minocycline	2.8	–3.0	8.6
Benzoyl peroxide – ery. + BP bd	0.9	–4.9	6.8
Ery. od + BP od – oxytetracycline	1.2	–4.6	7.1
Ery. od + BP od – minocycline	1.1	–4.7	6.9
Ery. od + BP od – benzoyl peroxide	–1.7	–7.6	4.1

The baseline by treatment interaction was not significant ($p = 0.280$), so data were not analysed separately for differing severity.

Mental health

This is a bipolar scale, and mid-range scores are earned by those reporting no symptoms of psychological stress; a score of 100 requires reports of frequently feeling happy, calm and peaceful. Mean mental health was above the mid-range. There was little change in mean mental health scores in any group (*Table 105*).

TABLE 105 *Mean SF-36 mental health*

Treatment group	*n*	Week			LSmean	95% CI
		0	18	18–0		
Oxytetracycline	126	72.7	72.3	–0.4	–0.6	(–2.8 to 1.7)
Minocycline	128	73.3	71.7	–1.6	–1.5	(–3.7 to 0.8)
Benzoyl peroxide	127	73.9	72.1	–1.8	–1.6	(–3.9 to 0.7)
Ery. + BP bd	124	73.3	73.8	0.5	0.6	(–1.7 to 2.9)
Ery. od + BP od	128	71.9	71.3	–0.5	–0.8	(–3.1 to 1.4)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 105*.

Ranking of treatments for mental health:

benzoyl peroxide < minocycline < ery. od + BP od < oxytetracycline < ery. + BP bd

TABLE 106 *SF-36 mental health: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	–0.9	–4.1	2.3
Ery. + BP bd – oxytetracycline	1.1	–2.1	4.4
Ery. + BP bd – minocycline	2.0	–1.2	5.2
Ery. od + BP od – ery. + BP bd	–1.4	–4.6	1.8
Benzoyl peroxide – oxytetracycline	–1.0	–4.2	2.2
Benzoyl peroxide – minocycline	–0.1	–3.3	3.1
Benzoyl peroxide – ery. + BP bd	–2.2	–5.4	1.1
Ery. od + BP od – oxytetracycline	–0.3	–3.5	3.0
Ery. od + BP od – minocycline	0.6	–2.6	3.8
Ery. od + BP od – benzoyl peroxide	0.8	–2.4	4.0

The baseline by treatment interaction was not significant ($p = 0.052$), so data were not analysed separately for differing severity.

DLQI analysis

TABLE 107 *Mean total DLQI*

Treatment group	*n*	Week					LSmean	95% CI
		0	6	12	18	18–0		
Oxytetracycline	93	5.4	4.1	4.3	3.9	–1.5	–1.4	(–2.0 to –0.8)
Minocycline	82	4.6	3.0	2.7	2.1	–2.4	–2.6	(–3.2 to –2.0)
Benzoyl peroxide	97	4.5	4.1	3.7	3.9	–0.6	–0.7	(–1.3 to –0.1)
Ery. + BP bd	90	4.9	3.6	3.1	2.7	–2.2	–2.2	(–2.8 to –1.6)
Ery. od + BP od	97	5.2	4.3	3.4	3.2	–2.0	–1.9	(–2.4 to –1.3)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 108*.

Ranking of treatments for DLQI total score:

benzoyl peroxide < oxytetracycline < ery. od + BP od < ery. + BP bd < minocycline

TABLE 108 *DLQI: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	–1.2	–2.1	–0.3
Ery. + BP bd – oxytetracycline	–0.8	–1.6	0.0
Ery. + BP bd – minocycline	0.4	–0.5	1.3
Ery. od + BP od – ery. + BP bd	0.3	–0.5	1.2
Benzoyl peroxide – oxytetracycline	0.7	–0.1	1.5
Benzoyl peroxide – minocycline	1.9	1.1	2.8
Benzoyl peroxide – ery. + BP bd	1.5	0.7	2.3
Ery. od + BP od – oxytetracycline	–0.5	–1.3	0.3
Ery. od + BP od – minocycline	0.7	–0.1	1.6
Ery. od + BP od – benzoyl peroxide	–1.2	–2.0	–0.4

The baseline by treatment interaction was significant ($p = 0.0002$), but owing to small numbers of participants, the data were not split up further for analysis by baseline.

CDLQI analysis

TABLE 109 *Mean CDLQI*

Treatment group	*n*	Week					LSmean	95% CI
		0	6	12	18	18–0		
Oxytetracycline	34	3.7	2.9	2.8	3.3	–0.4	–0.4	(–1.4 to 0.5)
Minocycline	45	3.9	3.0	2.6	2.6	–1.3	–1.4	(–2.2 to –0.6)
Benzoyl peroxide	27	4.7	3.9	3.2	2.7	–2.0	–1.6	(–2.6 to –0.5)
Ery. + BP bd	35	4.5	3.0	3.0	3.3	–1.2	–1.1	(–2.0 to –0.1)
Ery. od + BP od	30	3.2	2.5	2.3	2.5	–0.7	–1.1	(–2.1 to –0.1)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 110*.

Ranking of treatments for CDLQI total score:

oxytetracycline < ery. + BP bd = ery. od + BP od < minocycline < benzoyl peroxide

TABLE 110 *CDLQI: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	–1.0	–2.2	0.3
Ery. + BP bd – oxytetracycline	–0.7	–2.0	0.7
Ery. + BP bd – minocycline	0.3	–0.9	1.5
Ery. od + BP od – ery. + BP bd	–0.0	–1.4	1.3
Benzoyl peroxide – oxytetracycline	–1.1	–2.6	0.3
Benzoyl peroxide – minocycline	–0.2	–1.5	1.1
Benzoyl peroxide – ery. + BP bd	–0.5	–1.9	0.9
Ery. od + BP od – oxytetracycline	–0.7	–2.1	0.7
Ery. od + BP od – minocycline	0.3	–1.0	1.6
Ery. od + BP od – benzoyl peroxide	0.5	–1.0	1.9

The baseline by treatment interaction was not significant ($p = 0.091$), so data were not analysed separately for differing baseline score.

DQOLS analysis

Psychosocial scale

TABLE 111 *Mean DQOL psychosocial scale*

Treatment group	*n*	Week					LSmean	95% CI
		0	6	12	18	18–0		
Oxytetracycline	129	25.4	20.4	17.5	17.7	–7.7	–8.0	(–10.3 to –5.7)
Minocycline	129	23.0	16.6	12.7	13.4	–9.6	–11.3	(–13.6 to –9.0)
Benzoyl peroxide	127	27.6	20.3	19.2	19.9	–7.6	–7.1	(–9.5 to –4.8)
Ery. + BP bd	126	27.5	18.5	14.1	14.8	–12.7	–12.0	(–14.4 to –9.7)
Ery. od + BP od	128	27.2	20.9	16.6	16.3	–10.9	–10.4	(–12.7 to –8.1)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 113*.

Ranking of treatments for DQOL psychosocial scale:

benzoyl peroxide < oxytetracycline < ery. od + BP od < minocycline < ery. + BP bd

Medians are also given in *Table 112*, as raw data are not normally distributed (although differences from baseline are close enough to a normal distribution for usual methods of analysis).

TABLE 112 *Medians for DQOL psychosocial scale*

Treatment group	Week				
	0	6	12	18	18–0
Oxytetracycline	19.1	13.2	10.3	10.3	–2.9
Minocycline	14.7	11.8	7.4	8.8	–4.4
Benzoyl peroxide	22.1	14.7	11.8	13.2	–2.9
Ery. + BP bd	25.0	14.7	8.8	8.8	–9.6
Ery. od + BP od	22.1	11.8	9.6	8.1	–8.8

TABLE 113 *DQOL psychosocial scale: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	–3.3	–6.6	–0.0
Ery. + BP bd – oxytetracycline	–4.1	–7.4	–0.8
Ery. + BP bd – minocycline	–0.7	–4.0	2.6
Ery. od + BP od – ery. + BP bd	1.7	–1.6	5.0
Benzoyl peroxide – oxytetracycline	0.8	–2.4	4.1
Benzoyl peroxide – minocycline	4.2	0.9	7.5
Benzoyl peroxide – ery. + BP bd	4.9	1.6	8.2
Ery. od + BP od – oxytetracycline	–2.4	–5.7	0.9
Ery. od + BP od – minocycline	0.9	–2.4	4.2
Ery. od + BP od – benzoyl peroxide	–3.3	–6.6	0.0

The baseline by treatment interaction was significant ($p = 0.015$), but data were not split for further analysis by severity.

Activities scale

TABLE 114 *Mean DQOL activities scale*

Treatment group	*n*	Week					LSmean	95% CI
		0	6	12	18	18–0		
Oxytetracycline	129	11.7	8.6	8.2	7.5	–4.2	–4.1	(–5.7 to –2.6)
Minocycline	129	9.3	7.6	6.0	6.0	–3.3	–4.3	(–5.8 to –2.7)
Benzoyl peroxide	127	11.8	9.7	9.8	9.9	–2.0	–1.8	(–3.4 to –0.3)
Ery. + BP bd	126	12.2	9.4	6.9	6.9	–5.3	–5.1	(–6.6 to –3.5)
Ery. od + BP od	128	12.8	9.1	6.9	7.1	–5.7	–5.2	(–6.8 to –3.6)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 116*.

Ranking of treatments for DQOL activities scale:

benzoyl peroxide < oxytetracycline < minocycline < ery. + BP bd < ery. od + BP od

Medians are also given in *Table 115*, as raw data do not appear to be normally distributed (although differences from baseline are close enough to a normal distribution for ANOVA).

TABLE 115 *Median DQOL activities scale*

Treatment group	Week				
	0	6	12	18	18–0
Oxytetracycline	6.3	2.1	2.1	2.1	0.0
Minocycline	4.2	4.2	2.1	2.1	0.0
Benzoyl peroxide	4.2	2.1	2.1	2.1	0.0
Ery. + BP bd	6.3	3.1	2.1	2.1	–2.1
Ery. od + BP od	7.3	4.2	2.1	2.1	–2.1

TABLE 116 *DQOL activities scale: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	–0.2	–2.4	2.0
Ery. + BP bd – oxytetracycline	–0.9	–3.2	1.3
Ery. + BP bd – minocycline	–0.8	–3.0	1.4
Ery. od + BP od – ery. + BP bd	–0.1	–2.4	2.1
Benzoyl peroxide – oxytetracycline	2.3	0.1	4.5
Benzoyl peroxide – minocycline	2.5	0.3	4.7
Benzoyl peroxide – ery. + BP bd	3.2	1.0	5.4
Ery. od + BP od – oxytetracycline	–1.1	–3.3	1.1
Ery. od + BP od – minocycline	–0.9	–3.1	1.3
Ery. od + BP od – benzoyl peroxide	–3.4	–5.6	–1.2

The baseline by treatment interaction was not significant ($p = 0.665$), so data were not analysed separately for differing baseline.

Symptoms scale

TABLE 117 *Mean DQOL symptoms scale*

Treatment group	*n*	Week					LSmean	95% CI
		0	6	12	18	18–0		
Oxytetracycline	129	25.8	20.4	16.8	18.4	–7.3	–7.4	(–10.1 to –4.8)
Minocycline	129	23.7	17.5	15.2	13.9	–9.8	–11.2	(–13.8 to –8.5)
Benzoyl peroxide	127	26.0	22.2	21.1	20.0	–6.0	–5.9	(–8.5 to –3.2)
Ery. + BP bd	126	27.6	23.1	16.8	18.0	–9.6	–8.8	(–11.5 to –6.2)
Ery. od + BP od	128	27.8	22.9	18.1	17.5	–10.3	–9.6	(–12.3 to –7.0)

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Table 119*.

Ranking of treatments for DQOL symptoms scale:

benzoyl peroxide < oxytetracycline < ery. + BP bd < ery. od + BP od < minocycline

Medians are also given in *Table 118*, as raw data are not normally distributed (although differences from baseline are close enough to a normal distribution for ANOVA).

TABLE 118 *Median DQOL symptoms scale*

Treatment group	Week				
	0	6	12	18	18–0
Oxytetracycline	20.8	14.6	10.4	10.4	–4.2
Minocycline	18.8	12.5	10.4	10.4	–4.2
Benzoyl peroxide	18.8	16.7	14.6	14.6	–2.1
Ery. + BP bd	22.9	16.7	11.5	12.5	–6.3
Ery. od + BP od	22.9	15.6	11.5	10.4	–6.3

TABLE 119 *DQOL symptoms scale: confidence intervals for differences between treatments*

Treatment comparison	Difference in LSmeans	Lower 95% CL	Upper 95% CL
Minocycline – oxytetracycline	–3.7	–7.4	–0.0
Ery. + BP bd – oxytetracycline	–1.4	–5.1	2.3
Ery. + BP bd – minocycline	2.3	–1.4	6.0
Ery. od + BP od – ery. + BP bd	–0.8	–4.5	2.9
Benzoyl peroxide – oxytetracycline	1.6	–2.1	5.3
Benzoyl peroxide – minocycline	5.3	1.6	9.0
Benzoyl peroxide – ery. + BP bd	3.0	–0.7	6.7
Ery. od + BP od – oxytetracycline	–2.2	–5.9	1.5
Ery. od + BP od – minocycline	1.5	–2.2	5.2
Ery. od + BP od – benzoyl peroxide	–3.8	–7.5	–0.0

The adjusted means produce a different ordering of the data to the raw means.

The baseline by treatment interaction was not significant ($p = 0.417$), so data were not analysed separately for differing baseline scores.

Appendix 14

Additional utility and cost-effectiveness information

Numbers in utility summaries

TABLE 120 *Numbers of participants included in utility summaries*

	Week 0		Week 18			
Treatment group	**Q. 1**	**Q. 2**	**Q. 1**	**Q. 2**	**Q. 3**	**Q. 4**
Oxytetracycline	120 (122)	91 (101)	86 (88)	84 (89)	86 (88)	80 (90)
Minocycline	124 (125)	98 (108)	87 (89)	83 (90)	87 (89)	76 (88)
Benzoyl peroxide	122 (123)	89 (107)	87 (89)	83 (89)	86 (88)	75 (87)
Ery. + BP bd	119 (120)	88 (100)	94 (95)	92 (97)	94 (95)	83 (97)
Ery. od + BP od	122 (124)	85 (105)	90 (90)	78 (89)	87 (89)	77 (87)

Numbers in parentheses include >£10,000 category as £10,000.

Further cost-effectiveness analyses

TABLE 121 *Ratio of patient global at week 18 to cost of weeks on treatment (weekly cost × number of weeks on treatment)*

Treatment group	***n***	**Mean**	**Median**	**SD**	**Min.**	**Max.**	**Rank**
Oxytetracycline	131	0.0240	0.0307	0.0257	0.00	0.07	3
Minocycline	130	0.0059	0.0089	0.0056	0.00	0.01	5
Benzoyl peroxide	130	0.0634	0.0437	0.0806	0.00	0.21	1
Ery. + BP bd	127	0.0153	0.0196	0.0120	0.00	0.03	4
Ery. od + BP od	131	0.0376	0.0356	0.0389	0.00	0.10	2

TABLE 122 *Ratio of lesion count change at week 18 to cost of weeks on treatment*

Treatment group	***n***	**Mean**	**Median**	**SD**	**Min.**	**Max.**	**Rank (median)**
Oxytetracycline	131	–0.796	–0.460	1.269	–5.42	2.33	3 (4)
Minocycline	130	–0.250	–0.189	0.332	–1.72	0.45	5 (5)
Benzoyl peroxide	129	–1.900	–1.094	3.169	–17.90	3.50	1 (1)
Ery. + BP bd	127	–0.556	–0.509	0.737	–5.19	2.48	4 (3)
Ery. od + BP od	131	–1.510	–0.926	1.890	–8.83	0.80	2 (2)

TABLE 123 *Ratio of WTP (week 18) to cost of weeks on treatment*

Treatment group	***n***	**Mean**	**Median**	**SD**	**Min.**	**Max.**	**Rank (median)**
Oxytetracycline	88	18.99	1.17	102.52	0.00	685.87	2 (3)
Minocycline	89	3.27	0.32	15.31	0.00	102.88	5 (5)
Benzoyl peroxide	89	34.77	2.19	129.00	0.00	1028.81	1 (1)
Ery. + BP bd	95	6.88	0.75	28.48	0.00	195.62	4 (4)
Ery. od + BP od	90	7.98	1.78	20.35	0.00	158.53	3 (2)

TABLE 124 *Ratio of WTA (week 18) to cost of weeks on treatment*

Treatment group	n	Mean	Median	SD	Min.	Max.	Rank
Oxytetracycline	89	89.70	15.35	160.22	0.00	685.87	3
Minocycline	90	22.83	2.30	39.33	0.00	126.26	5
Benzoyl peroxide	89	192.55	21.87	402.04	0.00	2057.61	1
Ery. + BP bd	97	56.19	9.78	93.70	0.00	301.93	4
Ery. od + BP od	89	137.25	17.81	223.26	0.00	992.06	2

Benzoyl peroxide was consistently the most cost-effective and minocycline the least, whichever way the data were analysed. The order of the other three treatments varied slightly depending on the analysis or summary statistic.

TABLE 125 *Summary of WTP at week 18 by patient global categories (£)*

Patient global	*n*	Mean	SD	Median	Min.	Max.	Q1	Q3
Worse	11	77.3	146.82	25.0	0	500	0	100
No improvement	17	10.3	14.41	5.0	0	50	0	25
Slight improvement	52	64.8	175.58	5.0	0	1,000	5	25
Moderate improvement	173	139.9	556.31	25.0	0	5,000	25	50
Excellent improvement	184	243.3	976.13	50.0	0	10,000	25	100
Completely cleared	7	171.4	226.12	25.0	25	500	25	500

Q1, lower quartile; Q3, upper quartile.

TABLE 126 *Summary of WTP at week 0 by baseline Burke and Cunliffe grade (£)*

B&C grade	*n*	Mean	SD	Median	Min.	Max.	Q1	Q3
0.05–0.11	18	126.1	245.41	50.0	5	1,000	25	100
0.25	79	264.4	811.47	50.0	5	5,000	25	100
0.5–0.55	123	450.8	1654.18	50.0	5	10,000	25	100
0.7–0.75	25	150.0	287.46	25.0	5	1,000	25	100
1	133	156.1	473.54	25.0	5	5,000	25	100
1.25–1.5	111	244.6	1067.45	25.0	5	10,000	25	100
1.75	39	133.6	250.38	25.0	5	1,000	25	100
2	38	492.2	1782.93	25.0	5	10,000	25	100
2.25–2.5	28	42.1	34.25	25.0	5	100	25	50
2.75–3	12	196.3	226.21	75.0	5	500	25	500

Q1, lower quartile; Q3, upper quartile.

Appendix 15

Microbiology analysis results

Patient global assessment by baseline erythromycin resistance status

The baseline erythromycin resistance by treatment interaction was not significant at week 18 (difference in χ^2 statistic =9.176 on 5 df, $p > 0.1$, only significant ratio was oxytetracycline to minocycline with $p = 0.012$) or week 12 (χ^2 difference = 2.036 on 5 df, $p > 0.8$).

The baseline severity by treatment interaction was not significant for any analysis (differences in χ^2 statistics varied from 0.165 for with erythromycin resistance at week 12, $p > 0.005$ on 4 df, to 7.162 for no erythromycin resistance at week 12, $p > 0.1$ on 4 df, and only the minocycline to oxytetracycline ratio at week 12 was significant, $p = 0.036$).

TABLE 127 *Estimates from logistic regression for patient global assessment at week 18, by baseline erythromycin resistance status*

Erythromycin resistance:	Without (n = 347)			With (n = 301)		
Treatment comparison	**Estimate of OR**	**Lower 95% CL**	**Upper 95% CL**	**Estimate of OR**	**Lower 95% CL**	**Upper 95% CL**
Minocycline vs oxytetracycline	1.772	0.881	3.565	0.473	0.224	1.001
Ery. + BP bd vs oxytetracycline	1.939	0.953	3.946	1.346	0.632	2.867
Ery. + BP bd vs minocycline	1.094	0.529	2.263	2.846	1.330	6.090
Ery. od + BP od vs ery. + BP bd	0.993	0.477	2.066	0.702	0.330	1.495
Benzoyl peroxide vs oxytetracycline	1.471	0.743	2.914	0.902	0.426	1.911
Benzoyl peroxide vs minocycline	0.830	0.412	1.673	1.907	0.899	4.046
Benzoyl peroxide vs ery. + BP bd	0.759	0.373	1.544	0.670	0.313	1.436
Ery. od + BP od vs oxytetracycline	1.925	0.951	3.897	0.946	0.450	1.987
Ery. od + BP od vs minocycline	1.086	0.531	2.221	2.000	0.954	4.191
Ery. od + BP od vs benzoyl peroxide	1.309	0.645	2.655	1.048	0.497	2.212

TABLE 128 *Estimates from logistic regression for patient global assessment at week 12, by baseline erythromycin resistance status*

Erythromycin resistance:	Without (n = 347)			With (n = 301)		
Treatment comparison	**Estimate of OR**	**Lower 95% CL**	**Upper 95% CL**	**Estimate of OR**	**Lower 95% CL**	**Upper 95% CL**
Minocycline vs oxytetracycline	1.412	0.715	2.789	1.034	0.497	2.149
Ery. + BP bd vs oxytetracycline	2.263	1.120	4.571	1.959	0.940	4.082
Ery. + BP bd vs minocycline	1.602	0.792	3.241	1.895	0.904	3.973
Ery. od + BP od vs ery. + BP bd	0.809	0.396	1.652	0.625	0.300	1.302
Benzoyl peroxide vs oxytetracycline	1.166	0.597	2.277	1.089	0.524	2.266
Benzoyl peroxide vs minocycline	0.826	0.422	1.617	1.054	0.504	2.205
Benzoyl peroxide vs ery. + BP bd	0.515	0.258	1.031	0.556	0.264	1.170
Ery. od + BP od vs oxytetracycline	1.831	0.918	3.650	1.224	0.594	2.521
Ery. od + BP od vs minocycline	1.296	0.652	2.575	1.184	0.574	2.444
Ery. od + BP od vs benzoyl peroxide	1.570	0.793	3.107	1.124	0.541	2.332

Patient global assessment by baseline tetracycline resistance status

The baseline tetracycline resistance by treatment interaction was not significant at week 18 (difference in χ^2 statistic =9.593 on 5 df, $p > 0.075$, only significant ratio was minocycline to ery. + BP bd, $p = 0.044$) or week 12 (difference in χ^2 statistic = 7.992 on 5 df, $p > 0.15$, only significant ratio was minocycline to benzoyl peroxide, $p = 0.033$).

The baseline severity by treatment interaction was not significant for any analysis (differences in χ^2 statistics varied from 2.545 for with tetracycline resistance at week 12, $p > 0.6$ on 4 df, to 5.254 for no tetracycline resistance at week 18, $p > 0.2$ on 4 df), and only the benzoyl peroxide to minocycline ratio no tetracycline resistance at week 18 was significant, $p = 0.030$). No further analyses were carried out.

TABLE 129 *Estimates from logistic regression for patient global assessment at week 18, by baseline tetracycline resistance status*

Tetracycline resistance:	Without (*n* = 534)			With (*n* = 114)		
Treatment comparison	**Estimate of OR**	**Lower 95% CL**	**Upper 95% CL**	**Estimate of OR**	**Lower 95% CL**	**Upper 95% CL**
Minocycline vs oxytetracycline	1.114	0.643	1.929	0.547	0.134	2.229
Ery. + BP bd vs oxytetracycline	1.527	0.855	2.727	3.648	0.994	13.383
Ery. + BP bd vs minocycline	1.371	0.761	2.469	6.667	1.814	24.504
Ery. od + BP od vs ery. + BP bd	0.896	0.495	1.622	0.593	0.179	1.963
Benzoyl peroxide vs oxytetracycline	1.086	0.634	1.860	2.450	0.571	10.511
Benzoyl peroxide vs minocycline	0.974	0.563	1.687	4.479	1.020	19.667
Benzoyl peroxide vs ery. + BP bd	0.711	0.398	1.270	0.672	0.177	2.548
Ery. od + BP od vs oxytetracycline	1.369	0.787	2.382	2.164	0.560	8.363
Ery. od + BP od vs minocycline	1.229	0.701	2.152	3.956	1.022	15.310
Ery. od + BP od vs benzoyl peroxide	1.261	0.724	2.195	0.883	0.218	3.576

TABLE 130 *Estimates from logistic regression for patient global assessment at week 12, by baseline tetracycline resistance status*

Tetracycline resistance:	Without (*n* = 347)			With (*n* = 301)		
Treatment comparison	**Estimate of OR**	**Lower 95% CL**	**Upper 95% CL**	**Estimate of OR**	**Lower 95% CL**	**Upper 95% CL**
Minocycline vs oxytetracycline	1.242	0.725	2.130	1.474	0.371	5.865
Ery. + BP bd vs oxytetracycline	2.139	1.205	3.797	3.751	1.032	13.630
Ery. + BP bd vs minocycline	1.722	0.963	3.078	2.544	0.771	8.399
Ery. od + BP od vs ery. + BP bd	0.687	0.384	1.230	0.625	0.196	1.998
Benzoyl peroxide vs oxytetracycline	0.927	0.547	1.571	5.263	1.165	23.770
Benzoyl peroxide vs minocycline	0.746	0.436	1.276	3.570	0.831	15.325
Benzoyl peroxide vs ery. + BP bd	0.433	0.244	0.768	1.403	0.368	5.344
Ery. od + BP od vs oxytetracycline	1.470	0.856	2.524	2.345	0.606	9.082
Ery. od + BP od vs minocycline	1.183	0.686	2.042	1.591	0.441	5.737
Ery. od + BP od vs benzoyl peroxide	1.586	0.926	2.718	0.446	0.108	1.841

Lesion counts by baseline erythromycin resistance status

Baseline resistance by treatment interaction was not significant ($p = 0.557$ week 18, $p = 0.393$ week 12). The baseline count by treatment interaction was significant at week 18 for with erythromycin resistance ($p = 0.005$) and week 12 ($p = 0.001$), but not for no erythromycin resistance ($p = 0.300$ week 18, $p = 0.861$ week 12). Further subanalyses were not carried out.

TABLE 131 *Estimates from ANOVA for lesion counts at week 18, by baseline erythromycin resistance status*

Erythromycin resistance:	Without (*n* = 347)			With (*n* = 301)		
Treatment comparison	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**
Minocycline – oxytetracycline	–6.5	–13.9	0.8	–0.4	–7.7	6.9
Ery. + BP bd – oxytetracycline	–6.3	–13.8	1.2	–9.0	–16.3	–1.7
Ery. + BP bd – minocycline	0.2	–7.2	7.7	–8.6	–15.9	–1.2
Ery. od + BP od – ery. + BP bd	–4.1	–11.7	3.4	2.2	–5.1	9.5
Benzoyl peroxide – oxytetracycline	–4.2	–11.5	3.1	–3.4	–10.7	3.9
Benzoyl peroxide – minocycline	2.3	–5.0	9.6	–2.9	–10.3	4.4
Benzoyl peroxide – ery. + BP bd	2.1	–5.3	9.5	5.6	–1.8	13.0
Ery. od + BP od – oxytetracycline	–10.4	–17.9	–3.0	–6.8	–14.0	0.4
Ery. od + BP od – minocycline	–3.9	–11.3	3.5	–6.4	–13.6	0.8
Ery. od + BP od – benzoyl peroxide	–6.2	–13.6	1.2	–3.5	–10.7	3.8

TABLE 132 *Estimates from ANOVA for lesion counts at week 12, by baseline erythromycin resistance status*

Erythromycin resistance:	Without (*n* = 347)			With (*n* = 301)		
Treatment comparison	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**
Minocycline – oxytetracycline	–10.3	–16.8	–3.7	–4.6	–11.9	2.8
Ery. + BP bd – oxytetracycline	–6.6	–13.2	0.0	–11.3	–18.6	–4.1
ery. + BP bd – minocycline	3.7	–2.9	10.3	–6.8	–14.2	0.6
Ery. od + BP od – ery. + BP bd	–2.7	–9.4	4.0	2.5	–4.7	9.8
Benzoyl peroxide – oxytetracycline	–4.0	–10.4	2.5	–4.6	–11.9	2.7
Benzoyl peroxide – minocycline	6.3	–0.1	12.8	–0.1	–7.5	7.3
Benzoyl peroxide – ery. + BP bd	2.7	–3.9	9.2	6.7	–0.7	14.1
Ery. od + BP od – oxytetracycline	–9.4	–16.0	–2.7	–8.8	–16.0	–1.6
Ery. od + BP od – minocycline	0.9	–5.6	7.5	–4.3	–11.5	3.0
Ery. od + BP od – benzoyl peroxide	–5.4	–11.9	1.1	–4.2	–11.5	3.1

Lesion counts by baseline tetracycline resistance status

Baseline resistance by treatment interaction was significant at week 18 ($p = 0.036$), but not at week 12 ($p = 0.183$). The baseline count by treatment interaction was significant at week 12 ($p = 0.010$), but not at week 18 ($p = 0.093$) with tetracycline resistance, and was not significant at either week 12 ($p = 0.483$) or week 18 ($p = 0.191$) without resistance. Further subanalyses were not carried out.

TABLE 133 *Estimates from ANOVA for lesion counts at week 18, by baseline tetracycline resistance status*

Tetracycline resistance:	Without (n = 534)			With (n = 114)		
Treatment comparison	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**
Minocycline – oxytetracycline	–3.4	–9.2	2.3	–7.4	–19.7	4.9
Ery. + BP bd – oxytetracycline	–4.4	–10.3	1.6	–23.1	–34.5	–11.8
Ery. + BP bd – minocycline	–0.9	–6.9	5.1	–15.8	–26.6	–4.9
Ery. od + BP od – ery. + BP bd	–2.2	–8.2	3.8	3.0	–7.9	14.0
Benzoyl peroxide – oxytetracycline	–1.9	–7.6	3.7	–17.4	–30.6	–4.2
Benzoyl peroxide – minocycline	1.5	–4.2	7.2	–10.0	–22.9	2.9
Benzoyl peroxide – ery. + BP bd	2.4	–3.5	8.3	5.7	–6.2	17.7
Ery. od + BP od – oxytetracycline	–6.5	–12.3	–0.8	–20.1	–32.5	–7.7
Ery. od + BP od – minocycline	–3.1	–8.9	2.7	–12.7	–24.6	–0.9
Ery. od + BP od – benzoyl peroxide	–4.6	–10.3	1.1	–2.7	–15.6	10.2

TABLE 134 *Estimates from ANOVA for lesion counts at week 12, by baseline tetracycline resistance status*

Tetracycline resistance:	Without (n = 534)			With (n = 114)		
Treatment comparison	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**
Minocycline – oxytetracycline	–7.7	–12.9	–2.5	–6.5	–20.0	6.9
Ery. + BP bd – oxytetracycline	–7.1	–12.6	–1.7	–18.1	–30.6	–5.5
Ery. + BP bd – minocycline	0.6	–4.9	6.0	–11.5	–23.6	0.5
Ery. od + BP od – ery. + BP bd	–0.4	–5.9	5.0	3.9	–8.4	16.2
Benzoyl peroxide – oxytetracycline	–2.6	–7.8	2.5	–13.4	–27.8	0.9
Benzoyl peroxide – minocycline	5.1	–0.1	10.3	–6.9	–20.9	7.1
Benzoyl peroxide – ery. + BP bd	4.5	–0.9	9.9	4.6	–8.6	17.9
Ery. od + BP od – oxytetracycline	–7.6	–12.8	–2.3	–14.1	–27.7	–0.6
Ery. od + BP od – minocycline	0.1	–5.1	5.4	–7.6	–20.5	5.3
Ery. od + BP od – benzoyl peroxide	–4.9	–10.1	0.3	–0.7	–14.7	13.3

Burke and Cunliffe grade by baseline erythromycin resistance status

Baseline erythromycin resistance was not a statistically significant factor in the analysis of Burke and Cunliffe grade (p = 0.287 at week 12 and p = 0.091 at week 18), neither were interactions between baseline erythromycin resistance and treatment (p = 0.099 at week 12 and p = 0.151 at week 18). The baseline by treatment interaction was significant at week 18 for no erythromycin resistance (p = 0.0002) and week 12 (p = 0.002), but further subanalyses were not carried out (with erythromycin resistance, p = 0.481 at week 12 and p = 0.139 at week 18).

TABLE 135 *Mean (and 95% CI) Burke and Cunliffe grade, by baseline erythromycin resistance status*

Erythromycin resistance: Treatment group	Week 12		Week 18	
	Without (*n* = 347)	With (*n* = 300)	Without (*n* = 347)	With (*n* = 300)
Oxytetracycline	–0.257 (–0.352 to –0.161)	–0.346 (–0.468 to –0.224)	–0.378 (–0.486 to –0.270)	–0.483 (–0.605 to –0.362)
Minocycline	–0.541 (–0.636 to –0.445)	–0.371 (–0.495 to –0.248)	–0.626 (–0.734 to –0.518)	–0.444 (–0.567 to –0.320)
Benzoyl peroxide	–0.419 (–0.513 to –0.326)	–0.411 (–0.537 to –0.286)	–0.503 (–0.609 to –0.397)	–0.444 (–0.569 to –0.319)
Ery. + BP bd	–0.497 (–0.595 to –0.399)	–0.584 (–0.706 to –0.462)	–0.583 (–0.695 to –0.472)	–0.616 (–0.738 to –0.495)
Ery. od + BP od	–0.560 (–0.657 to –0.463)	–0.518 (–0.639 to –0.397)	–0.660 (–0.770 to –0.550)	–0.620 (–0.740 to –0.499)

The confidence intervals in this table refer to changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Tables 136* and *137*.

Ranking of treatments with respect to Burke and Cunliffe grade and baseline erythromycin resistance:

No resistance, weeks 12 and 18:
oxytetracycline < benzoyl peroxide < ery. + BP bd < minocycline < ery. od + BP od

Resistance, week 12:
oxytetracycline < minocycline < benzoyl peroxide < ery. od + BP od < ery. + BP bd

Resistance, week 18:
minocycline = benzoyl peroxide < oxytetracycline < ery. + BP bd < ery. od + BP od

TABLE 136 *Estimates from ANOVA for Burke and Cunliffe grade at week 18, by baseline erythromycin resistance status*

Erythromycin resistance:	Without (*n* = 347)			With (*n* = 301)		
Treatment comparison	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**
Minocycline – oxytetracycline	–0.248	–0.402	–0.095	0.039	–0.134	0.213
Ery. + BP bd – oxytetracycline	–0.206	–0.361	–0.050	–0.133	–0.304	0.038
Ery. + BP bd – minocycline	0.043	–0.112	0.198	–0.173	–0.346	0.001
Ery. od + BP od – ery. + BP bd	–0.077	–0.234	0.080	–0.003	–0.175	0.168
Benzoyl peroxide – oxytetracycline	–0.125	–0.277	0.026	0.039	–0.135	0.213
Benzoyl peroxide – minocycline	0.123	–0.029	0.275	–0.001	–0.176	0.175
Benzoyl peroxide – ery. + BP bd	0.080	–0.073	0.234	0.172	0.002	–0.346
Ery. od + BP od – oxytetracycline	–0.282	–0.437	–0.128	–0.136	–0.308	0.035
Ery. od + BP od – minocycline	–0.034	–0.188	0.120	–0.176	–0.348	–0.004
Ery. od + BP od – benzoyl peroxide	–0.157	–0.310	–0.004	–0.175	–0.349	–0.002

TABLE 137 *Estimates from ANOVA for Burke and Cunliffe grade at week 12, by baseline erythromycin resistance status*

Erythromycin resistance:	Without (*n* = 347)			With (*n* = 301)		
Treatment comparison	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**
Minocycline – oxytetracycline	–0.284	–0.419	–0.149	–0.026	–0.200	0.149
Ery. + BP bd – oxytetracycline	–0.241	–0.378	–0.104	–0.238	–0.411	–0.066
Ery. + BP bd – minocycline	0.044	–0.093	0.181	–0.213	–0.387	–0.039
Ery. od + BP od – ery. + BP bd	–0.063	–0.201	0.075	0.066	–0.106	0.239
Benzoyl peroxide – oxytetracycline	–0.163	–0.296	–0.029	–0.066	–0.241	0.109
Benzoyl peroxide – minocycline	0.121	–0.012	0.255	–0.040	–0.216	0.137
Benzoyl peroxide – ery. + BP bd	0.078	–0.057	0.213	0.173	–0.002	0.348
Ery. od + BP od – oxytetracycline	–0.304	–0.440	–0.167	–0.172	–0.344	0.000
Ery. od + BP od – minocycline	–0.019	–0.155	0.116	–0.146	–0.319	0.027
Ery. od + BP od – benzoyl peroxide	–0.141	–0.276	–0.006	–0.106	–0.281	0.068

Burke and Cunliffe grade by baseline tetracycline resistance status

Baseline tetracycline resistance was a statistically significant factor in the analysis of Burke and Cunliffe grade at week 12 ($p = 0.021$), but not quite at week 18 ($p = 0.056$); interactions between baseline tetracycline resistance and treatment were not significant ($p = 0.327$ at week 12, $p = 0.188$ at week 18). There were smaller decreases in score for most treatment groups in the resistant group, these differences being greatest in the minocycline group.

The baseline by treatment interaction was significant at week 18 for no tetracycline resistance ($p = 0.018$), but no further subanalyses were carried out. Interactions at week 12 were not significant ($p = 0.066$ without and $p = 0.676$ with resistance), nor was the interaction at week 18 with resistance ($p = 0.164$).

TABLE 138 *Mean (and 95% CI) Burke and Cunliffe grade, by baseline tetracycline resistance*

Tetracycline resistance: Treatment group	Week 12		Week 18	
	Without (*n* = 533)	With (*n* = 114)	Without (*n* = 533)	With (*n* = 114)
Oxytetracycline	–0.319 (–0.402 to –0.236)	–0.245 (–0.449 to –0.042)	–0.451 (–0.540 to –0.363)	–0.295 (–0.506 to –0.084)
Minocycline	–0.500 (–0.585 to –0.416)	–0.273 (–0.460 to –0.086)	–0.581 (–0.671 to –0.490)	–0.358 (–0.552 to –0.165)
Benzoyl peroxide	–0.400 (–0.482 to –0.318)	–0.526 (–0.744 to –0.307)	–0.484 (–0.572 to –0.397)	–0.444 (–0.671 to –0.218)
Ery. + BP bd	–0.549 (–0.640 to –0.459)	–0.490 (–0.642 to –0.337)	–0.573 (–0.670 to –0.476)	–0.680 (–0.839 to –0.522)
Ery. od + BP od	–0.556 (–0.640 to –0.471)	–0.452 (–0.638 to –0.266)	–0.643 (–0.733 to –0.553)	–0.599 (–0.792 to –0.406)

The confidence intervals in this table refer to changes from baseline for each treatment separately. For treatment comparison confidence intervals see *Tables 139* and *140*.

Ranking of treatments with respect to Burke and Cunliffe grade by baseline tetracycline resistance:

No resistance, week 12:
oxytetracycline < benzoyl peroxide < minocycline < ery. + BP bd < ery. od + BP od

No resistance, week 18:
oxytetracycline < benzoyl peroxide < ery. + BP bd < minocycline < ery. od + BP od

Resistance, week 12:
oxytetracycline < minocycline < ery. od + BP od < ery. + BP bd < benzoyl peroxide

Resistance, week 18:
oxytetracycline < minocycline < benzoyl peroxide < ery. od + BP od < ery. + BP bd

TABLE 139 *Estimates from ANOVA for Burke and Cunliffe grade at week 18, by baseline tetracycline resistance status*

Tetracycline resistance:	Without (*n* = 534)			With (*n* = 114)		
Treatment comparison	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**
Minocycline – oxytetracycline	–0.130	–0.256	–0.003	–0.063	–0.351	0.225
Ery. + BP bd – oxytetracycline	–0.122	–0.253	0.009	–0.385	–0.653	–0.117
Ery. + BP bd – minocycline	0.008	–0.125	0.140	–0.322	–0.572	–0.072
Ery. od + BP od – ery. + BP bd	–0.070	–0.202	0.063	0.081	–0.172	0.334
Benzoyl peroxide – oxytetracycline	–0.033	–0.157	0.091	–0.149	–0.457	0.158
Benzoyl peroxide – minocycline	0.097	–0.030	0.223	–0.086	–0.386	0.213
Benzoyl peroxide – ery. + BP bd	0.089	–0.041	0.220	0.236	–0.042	0.514
Ery. od + BP od – oxytetracycline	–0.192	–0.319	–0.065	–0.304	–0.591	–0.017
Ery. od + BP od – minocycline	–0.062	–0.190	0.065	–0.241	–0.515	0.033
Ery. od + BP od – benzoyl peroxide	–0.159	–0.285	–0.033	–0.155	–0.453	0.143

TABLE 140 *Estimates from ANOVA for Burke and Cunliffe grade at week 12, by baseline tetracycline resistance status*

Tetracycline resistance:	Without (*n* = 534)			With (*n* = 114)		
Treatment comparison	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**	**Difference in LSmeans**	**Lower 95% CL**	**Upper 95% CL**
Minocycline – oxytetracycline	–0.182	–0.300	–0.063	–0.028	–0.305	0.250
Ery. + BP bd – oxytetracycline	–0.231	–0.353	–0.108	–0.244	–0.502	0.014
Ery. + BP bd – minocycline	–0.049	–0.173	0.075	–0.217	–0.457	0.024
Ery. od + BP od – ery. + BP bd	–0.006	–0.130	0.118	0.038	–0.207	0.282
Benzoyl peroxide – oxytetracycline	–0.081	–0.198	0.035	–0.280	–0.576	0.016
Benzoyl peroxide – minocycline	0.100	–0.018	0.218	–0.252	–0.541	0.036
Benzoyl peroxide – ery. + BP bd	0.149	0.027	0.272	–0.036	–0.304	0.232
Ery. od + BP od – oxytetracycline	–0.237	–0.356	–0.118	–0.207	–0.484	0.070
Ery. od + BP od – minocycline	–0.055	–0.175	0.064	–0.179	–0.443	0.085
Ery. od + BP od – benzoyl peroxide	–0.156	–0.274	–0.037	0.073	–0.214	0.360

TABLE 141 *Change from baseline in mean growth score at week 18 for total viable propionibacterial load*

Treatment group	Change	SD	*n*	*p*-Value
Oxytetracycline	–0.5	1.30	131	<0.001
Minocycline	–0.8	1.35	129	<0.001
Benzoyl peroxide	–0.9	1.46	130	<0.001
Ery. + BP bd	–1.5	1.88	127	<0.001
Ery. od + BP od	–1.4	1.55	131	<0.001

TABLE 142 *Change from baseline in mean growth score at week 18 for prevalence of clindamycin-resistant propionibacteria*

Treatment group	Change	SD	*n*	*p*-Value
Oxytetracycline	–0.0	1.17	131	1.000
Minocycline	–0.2	1.31	129	0.085
Benzoyl peroxide	–0.5	1.35	130	<0.001
Ery. + BP bd	–0.4	1.61	127	0.006
Ery. od + BP od	–0.6	1.40	131	<0.001

TABLE 143 *Change from baseline in mean growth score at week 18 for prevalence of erythromycin-resistant propionibacteria*

Treatment group	Change	SD	*n*	*p*-Value
Oxytetracycline	–0.1	1.25	131	0.362
Minocycline	–0.2	1.46	129	0.122
Benzoyl peroxide	–0.5	1.43	130	<0.001
Ery. + BP bd	–0.5	1.69	127	0.001
Ery. od + BP od	–0.5	1.53	131	<0.001

TABLE 144 *Change from baseline in mean growth score at week 18 for prevalence of tetracycline-resistant propionibacteria*

Treatment group	Change	SD	*n*	*p*-Value
Oxytetracycline	–0.0	1.13	131	1.000
Minocycline	–0.0	1.21	129	1.000
Benzoyl peroxide	–0.3	1.12	130	0.003
Ery. + BP bd	–0.5	1.58	127	0.001
Ery. od + BP od	–0.4	1.14	131	<0.001

Owing to the very small number of participants with propionibacteria that grew on medium containing 5 mg l^{-1} of minocycline at baseline, and the finding that this breakpoint was too high, these data have not been analysed statistically.

Appendix 16

Concomitant medications

TABLE 145 *Concomitant medication details*

Patient ID	Week	Medication	Reason	Quantity/ frequency	Start date	Stop date
Oxytetracycline						
0008	0	Paroxetine	Depression	1 daily	May 98	Ongoing
0020	12	Prozac	Depression	20 mg od	25/11/98	
0026	0	Microgynon	Contraception	1 tablet daily	1991	Ongoing
	0	Bricanyl (terbutaline)	Asthma	occasional	1991	Ongoing
0042	6	Paracetamol	Pain relief	? ?	?	?
0127	0	Nytol	Sleep disturbance	1 tablet nocte	14/06/99	23/06/99
0153	6	Paracetamol	Cold			
0165	0	Microgynon	Contraception			
0174	0	Microgynon	Contraception	1 tablet per day	March 98	Ongoing
	12	Canestan pessary	Vaginal thrush			
0188	0	Aerolin	Wheezing	When needed	13.5 yrs ago	Ongoing
	0	Ventolin	Asthma	When needed		Ongoing
	0	Hydrocortizone	Eczema	When needed		Ongoing
	0	Flucloxacillin	Abscess		15/09/98	22/09/98
0237	0	Paramax	Migraine	3 tabs prn	1997	Ongoing
0257	6	Herbal remedy (Chinese)	Stomach cramps		27/12/98	27/12/98
0293	6	Piriton	Hayfever	prn		
0327	0	Clarityn	Hayfever, allergies to dust	1 od	Used on and off for about a year	Ongoing
	6	Zirtek	Hayfever	1 tablet as required		
0352	12	Paracetamol	Headache	500 mg one occasion	06/12/98	06/12/98
0371	0	Priadel (lithium carbonate)	Mild depression	400 mg bd	03/97	Ongoing
	6	Antibiotics (for tonsillitis)	Tonsillitis			
0400	0	Ventolin inhaler	Asthma	2 puffs as required	Several years ago	Ongoing
	0	Becotide inhaler	Asthma	2 puffs bd	Several years ago	Ongoing
0423	12	Eardrops (sodium bicarbonate)	Excess ear wax in right ear	3 drops tds	18/08/99	Ongoing
0437	6	Paracetamol	Headaches	2 × 500 mg tabs od	13/07/99	14/07/99
	12	Boots travel sickness pills	Precaution against sea-sickness	1 tablet prn	16/07/99	16/07/99
0447	0	Zirtek (cetirizine)	Hayfever	od	05/99	Ongoing
	12	Penicillin	Throat infection	250 mg 4 × daily	03/08/99	17/08/99

continued

TABLE 145 *Concomitant medication details (cont'd)*

Patient ID	Week	Medication	Reason	Quantity/ frequency	Start date	Stop date
Oxytetracycline						
0477	6	Remegel	Indigestion	1 tablet as required	25/09/99	25/09/99
0511	12	M? (for candida)	Candida infection	od		
0520	0	Humalog (insulin)	Diabetes	16, 16, 30 (units?) 3 times daily	12 yrs ago	Ongoing
	0	Isophane (insulin)	Diabetes	55 1 nocte		Ongoing
0589	6	Betnovate	Topical for contact dermatitis on hand	Sparingly bd	23/11/99	01/12/99
0597	6	Amoxycillin	Cough	250 mg tds	20/11/99	24/11/99
0610	0	Azathiaprine	Hepatitis	100 mg od	Feb 96	April 2000
0634	0	Coproxamol	Back pain	qds	13/11/99	Ongoing
0713	0	Salbutamol	Asthma	2 puffs prn	Unknown	Ongoing
0803	0	Imipramine	Depression	25 mg bd	1987	Ongoing
	6	Imipramine	Depression	8 × 25 mg bd	14/03/00	Ongoing
	6	Citalopram	Depression	2 × 20 mg bd	31/03/00	Ongoing
	12	Citalopram	Depression	2 × 20 mg bd	31/03/00	Ongoing
	12	Imipramine	Depression	8 × 25 mg bd	14/03/00	Ongoing
0818	12	Canestan	Thrush		30/04/00	03/05/00
	18	Sudocream	To help acne	once	15/06/00	Ongoing
0870	0	Beconase (eye drops & nose spray)	Hayfever		About 3 wks ago	
0919	0	Microgynon	Contraception		2 yrs ago	Ongoing
0982	0	Becotide	Asthma	2 puffs once a day		
	0	Ventolin	Asthma	prn		
1017	0	Blisteze	Herpes sores on lips		Since childhood (birth)	Ongoing
1037	0	Ibuprofen	Ankle pain	prn		
	0	Amoxycillin	Ear infection	250 mg tds	07/01/00	13/01/00
1063	0	Penicillin (or amoxycillin?)	For dentistry	250 mg	07/02/00	14/02/00
	18	Canestan pessaries	Thrush	1 nocti	26/05/00	03/06/00
1119	0	Cipramil	Antidepressant		Since 2 yrs ago	Ongoing
	0	Depo injections	Contraception			
1155	0	Mesalazine	Colitis	400 mg × 2 twice a day	4 yrs ago	Ongoing
1186	6	Paracetamol	Headaches	500 mg bd	07/04/00	Ongoing
	6	Meningitis vaccine	Immunisation for meningitis		06/04/00	N/A
1202	6	Ibruprofen	Period pain & headache (not used regularly)	2 × 200 mg tabs as required	20/06/99	As required (see diary card)
	12	Ibuprofen	Cold symptoms & period pains	2 × 200 mg tabs prn	As required	
	18	Ibuprofen	Period pain	400 mg as required	About 4 days duration	
1215	12	Migraine tablets (name unknown)	Migraine	2 capsules prn	Long time ago	Ongoing (as & when required)

continued

TABLE 145 *Concomitant medication details (cont'd)*

Patient ID	Week	Medication	Reason	Quantity/ frequency	Start date	Stop date
Oxytetracycline						
1241	6	Cough syrup for catarrh as well	Cold symptoms	1 tsp 4 × daily	17/12/99	20/12/99
1257	12	Homeopathic remedy for athletes foot	Athletes foot		19/02/00	21/02/00
1267	18	Nytol	Sleepless nights	2 tablets as required	04/03/00	Used occasionally since then
1288	6	Lemsip	Cold symptoms	1 sachet as required (used 3 times)	Can't remember exact dates	
	18	Diclofenac	Back pain	N/K as required		
1306	6	Canestan cream	Thrush	Cover area thinly twice daily	05/03/00	08/03/00
	12	Canestan cream	Vaginal thrush	Applied to affected areas 2 times daily	29/04/00	03/05/00
	18	Canestan cream	Vaginal thrush	Applied to affected areas 2–3 × daily	01/06/00	10/06/00
1311	6	Meningitis vaccine	Immunisation against meningitis		03/04/00	–
1325	6	Aspirin	Period cramps & migraine	3 × 300 mg tabs as required	No dates given	
	6	Paracetamol	Period cramps & migraine	2 × 500 mg tabs as required	No dates given	
1340	0	Ventolin inhaler	Asthma on exertion	2 puffs prn (3–4 times per wk on average	About 3 yrs ago	Ongoing
	0	Zirtek	Hayfever	1 tablet od	30/04/00	Ongoing
	0	Prescribed eyedrops (name N/K)	Hayfever	2 drops twice daily	30/04/00	Ongoing
	6	Zirtek	Hayfever symptoms	1 tablet once daily	16/05/00	Ongoing
	6	Ventolin inhaler	Asthma on exertion	2 puffs as required	About 2 yrs ago	Ongoing
1409	12	Clarityn	Hayfever	10 mg od	13/06/00	Ongoing
	12	Amoxycillin	Sinuses (related to hayfever)	250 mg tds	13/06/00	20/06/00
	12	Beconase nasal spray	Hayfever	2 puffs qds	13/06/00	Ongoing
	18	Clarityn	Hayfever	10 mg od	14/06/00	25/06/00
	18	Triludan	Hayfever	60 mg bd	26/06/00	28/07/00
1474	6	Ibuprofen	Pain-killer for sprained ankle	200 mg tds	15/04/00	19/04/00
	18	Nasobec inhaler	Hayfever	2 puffs prn	19/06/00	Ongoing
	18	Clarityn	Hayfever	1 tablet od	19/06/00	Ongoing
1493	6	Ibuprofen	Temperature	200 mg qds	15/04/00	16/04/00
	6	Meningitis vaccine	Inoculation against meningitis		?	
Minocycline						
0015	0	Epilim	Epilepsy	500 mg 2 daily	Sept 97	Currently
	6	Epilim	Epilepsy	1000 mg bd	28/10/98	Ongoing
	12	Epilim	Epilepsy	1000 mg bd	15/12/98	Ongoing

continued

TABLE 145 *Concomitant medication details (cont'd)*

Patient ID	Week	Medication	Reason	Quantity/ frequency	Start date	Stop date
Minocycline						
0072	0	Microgynon	Contraception	1 tablet daily	5 yrs ago	Ongoing
0106	0	Spasmonal	Irritable bowel	3 tablets/day prn		Ongoing
	6	Spasmonal	IBS	Reduced dose (unknown) prn	N/K	Ongoing
0124	0	Voltarol	Pain killer	50 mg prn	N/A	
	12	Prozac	Depression	5 mg od	10/8/99	? 6 months
0189	18	Ventolin inhaler	Asthma		18/01/99	Ongoing
	18	Becotide inhaler	Asthma		18/01/99	Ongoing
0227	6	Paracetamol	Headache		22/10/98	30/10/98
0246	0	Aloe vera	To improve immune system		Jan 98	Ongoing
	0	Spirolena	To improve immune system		Jan 98	Ongoing
0320	0	Vitamins	Rheumatoid arthritis			
	0	Maxitrol	Rheumatoid arthritis		5 yrs ago	Ongoing
0337	6	Pain killers given at hospital (don't know what)	Broken toe	2 tablets daily	17/10/98	20/10/98
	18	Nurofen cold & flu	Flu symptoms	As recommended	11/01/99	18/01/99
0342	6	Paracetamol	Headache	500 mg bd	12/10/98 (not sure)	12/10/98
0398	12	Paracetamol	Headaches	2 × 500 mg prn	Various occasions	Ongoing
	18	Beecham's powder capsules	Cold symptoms	2 capsules prn	03/10/99	Ongoing
0417	18	Aspirin	Headache due to hangover	600 mg prn	On 2 occasions – dates unknown	
0424	6	? (for throat infection)	Throat infection			
0470	12	Paracetamol	Cold symptoms	2 × 500 mg prn	Taken occasionally – no dates available	
	18	Paracetamol	Cold symptoms	2 × 500 mg tabs prn	Last week	Took for 2 nights
0475	0	Contraceptive pill (unknown)	Contraception			Ongoing
	6	Paracetamol	Headaches	2 × 500 mg tabs as required	20/09/99	Ongoing
0485	0	Cilest	Contraception	1 daily		
0502	18	Iron tablets	Anaemia	200 mg daily	21/12/99	Ongoing
0536	0	Beconase	Sinus problem	prn	Aug 99	Ongoing
0543	0	Cipramil	Depression	10 mg every other day	1997	?
	12	Cipramil	Depression	60 mg tds	07/12/99	1 yr
0554	6	Canestan suppository	Thrush	1 once only	10/10/99	10/10/99
	6	Canestan cream	Thrush	As needed bd	10/10/99	17/10/99
0625	6	Paracetamol	Influenza	2 × 4 × daily	03/11/99	10/11/99
	6	Lemsip	Influenza	1 sachet occasional	03/11/99	10/11/99

continued

TABLE 145 *Concomitant medication details (cont'd)*

Patient ID	Week	Medication	Reason	Quantity/ frequency	Start date	Stop date
Minocycline						
0625	6	Lemsip	Cold	1 sachet every 4 hours	12/12/99	Ongoing
	18	Diclofenac	Sprained ankle	50 mg tds-od	09/02/00	Ongoing
0636	0	Pseudoephedrine hydrochloride	Decongestant	tds	11/11/99	18/11/99
	6	Penicillin	Flu	250 mg qds	15/11/99	22/11/99
0643	0	Ventolin	Asthma	2 puffs prn	N/K	Ongoing
	0	Becotide	Asthma	2 puffs prn	N/K	Ongoing
0655	0	Unknown contraceptive	Contraception			Ongoing
0672	0	Logynon	Contraception	1 tablet od	N/K	Ongoing
0723	0	Lithium	Manic depression	800 mg od	10/11/99	Ongoing
	12	Venlafaxine	Depression	bd	15/02/00	Ongoing
0765	18	Canestan pessaries	Thrush	200 mg od	01/06/00	03/06/00
0813	6	Canestan cream	Candida infection	bd	30/03/00	01/04/00
	12	Diflucan	Thrush	1 od	11/05/00	11/05/00
	18	Diflucan	Thrush	? once only	11/05/00	11/05/00
0842	0	Amoxycillin	Ear infection	3 capsules	25/05/99	Not sure
0861	18	Penicillin	Chest infection	500 mg 4qds	03/10/99	17/10/99
0873	0	Alispone	Stomach wind	prn		
0963	0	Ibruprofen	Painful knees (work related)	1 bd	2 months ago	Ongoing
0999	0	Ibuprofen	Bad back		6 months ago	Ongoing
	0	Paracetamol	Bad back		6 months ago	Ongoing
	0	Seroxat	Post-natal depression		4 months ago	Ongoing
1006	0	Vaccination	Meningitis immunisation		07/12/99	Not available
1045	0	Inderal polypropylene (?)	Stomach migraine (?)		About 8 months	To be reviewed soon
1091	0	Paracetamol	Back pain	prn		
1117	0	Ventolin	Asthma	Once daily	June 1999	Ongoing
	0	Easy breathe	Asthma	Once daily	June 1999	Ongoing
	0	Becloforte	Asthma	Twice daily	June 1999	Ongoing
1233	12	Verruca/wart treatment	Verruca on foot	Apply to affected area once nightly	07/02/00	Ongoing
1282	18	Paracetamol	Headache	2 × 500 mg taken once	05/04/00	05/04/00
1309	6	Aspirin	Headache	600–900 mg as required	Uses occasionally	
	6	Paracetamol	Headache	1000 mg as required	Uses occasionally	
	18	Morning after pill	Post-coital contraception?		19/06/00	19/06/00
1313	0	St. John's wort	General health benefit	900 μg once daily	Feb 99	Ongoing

continued

TABLE 145 *Concomitant medication details (cont'd)*

Patient ID	Week	Medication	Reason	Quantity/ frequency	Start date	Stop date
Minocycline						
1313	0	Ginkgo biloba	General health benefits & memory benefits	? once daily	Feb 99	Ongoing
1321	0	Carbamazapine (Tegretol Retard)	Epilepsy	1 tablet: 300 mg 2 × daily	Used for about 1 yr	Ongoing
1336	6	Hep A & typhoid vaccines	Holiday immunisations		09/06/00	09/06/00
1381	0	Ventolin	Asthma	prn	1 yr	Ongoing
1425	6	Zirtek	Hayfever	10 mg od	10/05/00	Ongoing
	12	Zirtek	Hayfever	10 mg od	?	20/06/00
	18	Zirtek (citirazine)	Hayfever	10 mg (1 tablet) od	Ongoing	16/07/00?
1480	18	Ibuprofen	Ankle injury	200 mg tds	15/07/00	29/07/00
1504	0	Marvelon	Contraception	od	09/03/00	Ongoing
1515	12	Paracetamol	Headache		16/05/00	17/05/00
Benzoyl peroxide						
0017	0	Telfast TC (Fexofenadine hydrochloride)	Asthma	120 mg 1 daily	July 98	Ongoing
0049	12	Amoxycillin	Chest infection	250 mg tds	12/01/99	17/01/99
0086	0	Contraceptive pill (unknown)	Contraception	1 tablet daily	Recently	
0095	12	Cephalexin	Kidney infection	500 mg tds	09/09/99	16/09/99
	18	Trimethoprim	Kidney infection	bd	01/09/99	06/09/99
0100	6	Hayfever tablets (name unknown)	Hayfever		?	25/06/99
0130	0	Cocodamol	Pain in knees	500 mg prn		
0136	0	Prozac	Depression	20 mg od	19/05/99	Ongoing
0146	0	Ventolin	Asthma	2 puffs prn		
0157	12	Flucloxacillin	Antibiotic for ingrowing toenail	250 mg qds	05/10/99	12/10/99
0176	0	Ventolin	Asthma	200 mg bds	17 yrs ago	Ongoing
	0	Becotide	Asthma	prn		Ongoing
0183	0	Inhaler	Asthma, when out of breath during sports		About 2 yrs ago	
0190	0	Ventolin	Asthma	When needed	12 yrs ago	
0202	0	Ventolin inhaler	Asthma	Nightly	18 months ago	Ongoing
	12	Sudocreme	Burning by medication	Daily	21/11/98	30/11/98
0217	0	Ventolin inhaler	Asthma	Twice a day prn	2 yrs ago	Ongoing
0232	0	Baclofen	Muscle relaxant	60 mg (10 mg tablets) tds	3–4 yrs ago	Ongoing
0261	0	Not known (see AE)	Migraine	? ?	pre 09/04/00	?
0261	6	Not known	Vomiting, headaches, dizziness (in hospital)		09/04/00	Ongoing
0287	0	Ventolin inhaler	Asthma	prn		Ongoing
0328	18	Paracetamol (as Lemsip max strength)	Cold/flu	1000 mg bd	09/01/99	Ongoing

continued

TABLE 145 *Concomitant medication details (cont'd)*

Patient ID	Week	Medication	Reason	Quantity/ frequency	Start date	Stop date
Benzoyl peroxide						
0363	18	Paracetamol	Flu symptoms	1000 mg prn	29/01/99	Ongoing
	18	Unknown cough linctus	To ease coughing	10 ml qid	29/01/99	Ongoing
0406	6	'Boots own' hayfever tablets	Hayfever got worse	1 tablet od	14/06/99	06/07/99
	6	Clarityn	Hayfever			Ongoing
	12	Clarityn	Hayfever	1 tablet prn		Ongoing
0412	0	Bricanyl	Asthma – mild, occasional	1 puff od	3 yrs ago	Ongoing
	6	Paracetamol	Headaches	2 × 500 mg as required	See comments	
	12	Paracetamol	Headache	1 × 500 mg tab prn	16/07/99	Ongoing
	18	Paracetamol	Headache	500 mg prn	On several occasions	
0421	0	Ovenite	Contraception	od	10 months ago	Ongoing
0444	0	Cilest	Contraception			Ongoing
0455	0	Zirtek	Hayfever	One tablet od as required	June 99	Ongoing
	0	Clarityn	Hayfever	One tablet od as required	June 99	Ongoing
	6	Zirtek or Clarityn	Hayfever	1 tablet as required	10/07/99	Ongoing
	6	Paracetamol	Backpain & headache	2 × 500 mg tablets as required	14/07/99	Ongoing
	12	Paracetamol	Sore throat & back pain	2 × 500 mg prn	15/09/99	Ongoing
	12	Simple linctus (for sore throat)	Sore throat	2 tsp prn	06/09/99	Ongoing
	18	Paracetamol	Pain in shoulder	2 × 500 mg 1 dose taken	03/11/99	03/11/99
0463	18	Calpol (paracetamol)	Sore throat & temperature	1–2 tsps twice daily	30/10/99	04/11/99
0514	18	Zolpidem hermitartate	Sleep difficulties (depression)	5 mg nocte	06/01/00	04/02/00
0521	18	Beechams	Flu	1 tds/prn	?	?
	18	Lemsip	Flu	1 tds/prn	?	?
0617	12	Antibiotics (unknown – for tooth infection)	Tooth infection	1 tablet tds	03/02/00	10/02/00
	12	Ibuprofen	Painkiller for toothache	200 mg prn	03/02/00	prn
0632	6	Loratidine	Facial rash	10 mg od	13/11/99	20/11/99
	6	Hydrocortisone 1%	Facial rash	tds as needed	16/11/99	19/11/99
0640	0	Ventolin	Asthma	2 puffs prn	N/K	Ongoing
	0	Ibuprofen	Aching joints	200 mg prn	N/K	Ongoing
	0	Codeine phosphate	Migraines	30 mg prn	N/K	Ongoing
0666	6	Trimethoprim	Cystitis	200 mg bd	12/01/00	17/01/00
	6	Microgynon	Contraception	1 od	Unknown	Ongoing
0698	0	Paroxetine	Antidepressant	30 mg od	Aug 99	Ongoing

continued

TABLE 145 *Concomitant medication details (cont'd)*

Patient ID	Week	Medication	Reason	Quantity/ frequency	Start date	Stop date
Benzoyl peroxide						
0720	6	Painkillers (unknown)	Pain	od	28/12/99	07/01/00
0742	0	Flixotide	Asthma	2 puffs od	Age 2	Ongoing
	0	Serevent	Asthma	2 puffs od	Age 2	Ongoing
	0	Salbutamol	Asthma	1 prn	Age 2	Ongoing
	12	Benadryl	Asthma	1 ? prn	Unknown	Ongoing
0750	0	Marvelon	Contraception	od	Oct 95	Ongoing
	12	Ciprofloxacin	Sinusitis	250 mg bd	27/03/00	29/03/00
0825	0	Steroid cream	Eczema		18/05/99	25/05/99
	12	Paracetamol	Headaches	500 mg bd	07/07/99	08/07/99
	18	Paracetamol	Headaches	500 mg bd	20/09/99	24/09/99
0910	0	Microgynon	Contraception			
0926	0	Antihistamin	Influenza		02/09/99	Ongoing
	6	Domperidone	Flu, antihistamine	10 mg 3 × 1 day	23/10/99	7/11/99
	6	Pantoprazole	Flu, antihistamine	40 mg 1 nocte	23/10/99	7/11/99?
	6	Panadol	Flu, antihistamine	? ?	23/10/99?	7/11/99?
0977	0	Amoxycillin	Cold/chest infection	500 mg tds	1 week only	
	0	Antidepressant	Depression	1 bd	2 weeks ago	2 weeks more
1033	0	Becotide	Asthma	twice a day		
	0	Ventolin	Asthma	prn		
1048	0	Bricanyl	Asthma	bd	Since 5 yrs old	Ongoing
1067	0	Colpamine	Irritable bowel	prn		
1075	0	Efamast	Mastitis			
	0	Voltare	Analgesic			
1171	0	Ibuprofen	Cyst on back of knee to be surgically removed	1 tds	1 yr	Ongoing
1208	6	Paracetamol	Cold symptoms	2 × 500 mg as required	06/10/99	08/10/99
	6	Penicillin	Cold symptoms	1 capsule 3 × daily	06/10/99	08/10/99
	12	Zirtek	Rash on arms	1 tablet 1 × daily	10/12/99	Ongoing
1213	0	Phentermine/ Phenylpromed?	Appetite suppressant	1 tablet twice daily	3 weeks ago	Ongoing
1228	6	Cold relief tablets containing paracetamol	Flu symptoms	2 tablets 4 × daily	20/12/99	23/12/99
	18	Asda's cold relief tablets (contain paracetamol)	Cold symptoms	2 tabs as required	09/03/00	11/03/00
1236	12	Penicillin V	Tonsillitis	250 mg tablets 4 times daily	19/01/00	24/01/00
	18	Paracetamol	Cold symptoms	2 × 500 mg 4 times daily	15/03/00	18/03/00
1254	6	Aspirin	Cold symptoms	Up to 3 × 300 mg Up to 3 × daily	Don't know (as required)	
1303	6	Aspirin	Headache	3 × 300 mg tablets as required (3–4 times)	Dates not known	

continued

TABLE 145 *Concomitant medication details (cont'd)*

Patient ID	Week	Medication	Reason	Quantity/ frequency	Start date	Stop date
Benzoyl peroxide						
1303	12	Aspirin	Headache	1 × 250 mg prn – couple of times since last visit	No dates available	
1329	18	Famvir (famciclovir)	Shingles	250 mg 3 × daily	07/07/00	14/07/00
	18	Pain killers (strong ones from GP)	Shingles	? ?	17/07/00	21/07/00
1333	6	Meningitis C vaccination	Immunisation against meningitis		17/05/00	17/05/00
	6	Cetirizine hydrochloride	Fell in nettle patch!	10 mg once	16/05/00	16/05/00
	18	Penicillin VK tablets	Tonsillitis	250 mg 4 × daily	07/07/00	14/07/00
	18	Paracetamol	Tonsillitis	500 mg as required		
1343	6	Aerolin	Asthma	2 puffs prn – only occasional use	10 yrs ago	Ongoing
1411	12	Clarityn	Hayfever	10 mg od	14/06/00	Ongoing
	18	Clarityn	Hayfever	10 mg once daily	From previous	13/07/00
	18	Clarityn	Hayfever	10 mg once daily	From previous	13/07/00
Ery. + BP bd						
0007	0	Terfenadine	Hayfever	Per day		Aug 98
0040	6	Paracetamol	Pain relief	? ?	?	?
0080	0	Daktacort	Fungal infection to (R) wrist	N/A bd	25/05/99	02/06/99
0107	0	Microgynon	Contraception	1 tablet daily		
	0	Salbutamol	Asthma	2 puffs prn		
	0	Triludan	Hayfever	1 tablet prn		
	6	Ibuprofen	Pain killer	prn		
0167	0	Becotide	Asthma	bd	6 months ago	Ongoing
	0	Ventolin	Asthma	?	6 months ago?	Ongoing
	0	Triludan + unknown follow-up	Hayfever	12 times this year	10 yrs ago	prn
0205	0	Beconase inhaler	Hayfever	Not often		Last used mid-August
	0	Clarityn	Hayfever	Not often		Last used mid-August
0361	0	Ventolin	Mild asthma	2 puffs as required	Used for 1 yr	Ongoing
0405	0	Zirtek (Cetirizine)	Hayfever	10 mg od	2 yrs ago	Ongoing
	6	Local anaesthesia	Trapped finger in door needed stitches		04/07/99	04/07/99
0418	6	Hayfever tablets – possibly Triludan	Hayfever	1 tablet od	05/07/99	Ongoing
	18	Boots cold & flu relief tablets	Cold symptoms	2 tablets once	One occasion about 2 wks ago	
0426	0	Paracetamol	Cold	2 × 500 mg tabs od	30/05/99	Ongoing
	6	Erythromycin	Ear & throat/chest infection	250 mg qd	10/06/99	16/06/99
	6	Paracetamol	Ear & throat/chest infection	2 × 500 mg as required	10/06/99	16/06/99

continued

TABLE 145 *Concomitant medication details (cont'd)*

Patient ID	Week	Medication	Reason	Quantity/ frequency	Start date	Stop date
Ery. & BP bd						
0449	0	Migraleve (pink & yellow)	Migraine	As required		Ongoing
0461	6	Hayfever tablets	Hayfever	1 tablet od as required	?	Ongoing
	6	Opticrom eye drops (sodium chromoglycate 2%)	Hayfever	1 drop per eye qd	01/08/99	Ongoing
	12	Tranexamic acid tabs	Heavy periods	1000 mg 3 × daily	24/09/99	27/09/99
	12	Paracetamol	Pain	1000 mg prn	On several occasions as needed	
0473	6	Movelat cream	Sprained ankle	3 × daily	05/10/99	Ongoing
	12	Cyclizine	Stomach upset	2 tablets daily	10/11/99	17/11/99
0474	12	Itraconazole	Nail fungal infection		19/11/99	Ongoing
	18	Itraconazole	Nail fungal infection	2 tablets 1 × daily	14/09/99	Ongoing
0508	6	Marvelon	To help periods	1 tablet daily	29/10/99	?
0525	0	Cilest	Contraception	1 nocte	?Sept 98	Ongoing
0534	18	Amoxycillin	Ear infection	? 3 × daily	17/01/00	24/01/00
0578	0	Mefenamic acid	Period pain	prn		
	18	Amoxycillin	Ear infection	400 mg? tds	06/03/00	13/03/00
	18	Amoxycillin	Ear infection	400 mg? tds	06/03/00	13/03/00
0599	6	Amoxicillin	Influenza	250 mg tds	26/11/99	02/12/99
	18	Eumovate cream	Eczema to groin	1 tds	02/01/00	'til resolves
0620	6	Erythromycin	Tonsillitis	250 mg tds	29/11/99	07/12/99
0702	0	Microgynon	Contraception	1 od	Nov 98	Ongoing
0735	18	Creation (weight-training supplement)	For energy	5 g od	17/04/00	Ongoing
0761	0	Fucibet	Eczema	As needed tds	10/01/00	Ongoing
0800	12	Zirtek	Hayfever	10 mg od	19/05/00	Ongoing
0820	18	Steroid cream	Pityriasis rosacea	Small dabs prn	04/07/00	Ongoing
0868	0	Tablets (not known) for blotches	Blotches on face	2 tablets twice daily	Feb 99	Ongoing
0889	0	Amino acid tabs	Herpes		May 99	Ongoing
0897	0	Prozac	Depression	20 mg bd		Ongoing
	0	Solian (amisulpride)	Depression			Ongoing
	0	Precyclodine	To minimise side effects of Solian			Ongoing
0916	0	Sanomigran	Migraine			Ongoing
0961	0	Ibugel	Pain in shoulder			
0990	0	Celeste	Contraception			
0995	0	Antibiotics & eardrops	Ear infection		01/12/99	05/12/99
1004	0	Salbutamol	Asthma	(Inhaler) prn		
1026	0	Paramax	Migraine	prn		
1108	6	Metronidazole	Pelvic inflammation	500 mg tds	30/03/00	03/04/00
1167	0	Penicillin	Dental infection		22/03/00	25/03/00

continued

TABLE 145 *Concomitant medication details (cont'd)*

Patient ID	Week	Medication	Reason	Quantity/ frequency	Start date	Stop date
Ery. & BP bd						
	0	Pain killer (unknown – for dental infection)	Dental infection		22/03/00	25/03/00
1203	6	Tesco's cold remedy caps	Felt cold coming on	2 capsules twice daily	24/10/99	24/10/99
	12	Ibuprofen	Cold symptoms	2 tablets 200 mg 3 times daily	15/11/99	18/11/99
	18	Beechams capsules	Cold symptoms	1 capsule as required	Over Xmas (no exact dates)	
1224	18	Paracetamol	Headache/hangover	2 × 500 mg tabs as required	On several occasions – no dates	
1243	12	Ibuprofen	Headache			
	12	Cold & flu capsules	Cold symptoms			
	18	Ibuprofen	Period pain	2 × 200 mg tabs 3 x daily	17/03/00	17/03/00
	18	Hepatitis B vaccine	Immunisation		20/03/00	20/03/00
1245	0	Microgynon	Contraception	1 tablet 1 × daily	Sep 99	Ongoing
	0	Ventolin inhaler	Asthma	2 puffs as required	June 98	Ongoing
	6	Paracetamol	Headache	1000 mg as required	Various times	
	6	Ibuprofen	Headache	400 mg as required	Various times	
	6	Decadaine throat lozenges	Sore throat			
	12	Paracetamol	Headaches	2 × 500 mg prn	Occasional use	Ongoing
	12	Typhoid & hepatitis A immunisation	Immunisation for typhoid & hepatitis A		End Jan 2000	
	18	Paracetamol	Headache	2 × 500 mg tabs as required – occasional	No dates	
1256	6	Ibuprofen	Headache	1 × 200 mg tabs as required	Taken once since last seen, but not sure when	
	18	Ibuprofen	Period pain/headache	2 tablets 200 mg as required	No dates given	
1273	12	Amoxycillin	Throat infection	1 cap twice daily	11/02/00	16/02/00
	12	Erythromycin	Throat infection	2 tablets twice daily	18/02/00	Ongoing
1293	6	Paracetamol	Headaches	1 × 500 mg as required (taken several occasions)	Can't remember exact dates	
	12	Paracetamol	Sore throat	2 × 500 mg prn	03/04/00	Ongoing
	12	Meningitis vaccine	Prophylaxis/ immunisation for meningitis	1 injection	31/03/00	31/03/00
	18	Paracetamol	Headache, earache	2 × 500 mg as required	06/05/00	13/05/00
	18	Sodium bicarbonate eardrops	Ear blockage		06/05/00	13/05/00
1316	12	Piriton	Hayfever symptoms	1 tablet once daily	06/05/00	10/05/00
	18	Piriton tablets	Hayfever	1 × 4 mg tablets as required		

continued

TABLE 145 *Concomitant medication details (cont'd)*

Patient ID	Week	Medication	Reason	Quantity/ frequency	Start date	Stop date
Ery. od & BP bd						
1346	6	Paracetamol tablets	Cold symptoms	2 × 500 mg qid	?	06/06/00
	6	Sudafed tablets	Cold symptoms	1 tablet qid	?	06/06/00
1410	18	Co-proxamol?	Pain in ankle	? tds	As before	21/06/00
	18	Ibuprofen	Pain in ankle	400 mg tds	As before	21/06/00
1485	6	Folic acid	Pregnancy	400 mg od	25/04/00	Ongoing
1500	18	?Painkiller for back	Back pain	50 mg bd	30/05/00	Ongoing
Ery. od + BP od						
0019	0	Colofac	IBS	2 tabs prn	Jan 1998	Ongoing
0028	0	Diclofenac	Neck injury	50 mg tds	25/09/98	Ongoing
	0	Paracetamol	Neck injury	1 g qds	25/09/98	Ongoing
	0	Diazepam	Neck injury	2 mg bd	01/10/98	Ongoing
	6	Diazepam	Neck injury		01/10/98	Since last visit
	6	Diclofenac	Neck injury		25/09/98	Since last visit
	12	Clarityn	Hayfever	10 mg 1 daily		
0036	0	Salbutamol	Asthma	2 puffs prn	Childhood	Ongoing
	0	Becotide	Asthma		Childhood	Ongoing
	12	Amitryptyline	Migraine prophylaxis	10 mg od	09/12/99	
	12	Naramig	Migraine	2.5 mg prn	09/12/99	
0102	0	Clarityn	Hayfever	1 tablet prn	as required	
0134	0	Thyroxine	Inactive thyroid gland	200 mg daily	1997	Ongoing
0144	0	Telfast	Hayfever	160 g daily	prn (not known)	As required
0162	0	Pain killers (name not given)	For pains due to gall bladder problems			24/09/98
0177	18	Paracetamol	Headaches & stomach cramps		3 days duration	
0212	0	Desmopressin	Urinary incontinence	200 mg 1 at night		
0250	0	Ventolin	Asthma	100 mg once/month		Ongoing
0254	0	Aerolin	Asthma			Ongoing
	0	Aerobic	Asthma			Ongoing
0340	18	Polio vaccination	Immunisation		08/01/99	
0346	6	Prochlorperazine	Migraine	3 tablets daily	02/11/98	04/11/98
0359	6	Amoxycillin	Chest infection	250 mg td	13/10/98	18/10/98
	6	Paracetamol	Chest infection	1000 mg qd	13/10/98	20/10/98
0364	12	Fluconazole	Vaginal thrush	150 mg once	09/12/98	09/12/98
	18	Fluconazole	Suspected vaginal thrush	1 capsule once	Between T12 & Xmas	Between T12 & Xmas
0386	6	Paracetamol	Cold & flu symptoms & headaches	2 × 500 mg tabs qd	Various	
0404	6	Triludan	Hayfever	1 tablet od	21/06/99	24/06/99
	6	Paracetamol	Headaches	2 × 500 mg tabs as required		
0419	0	Ovysmen	Contraception	od	6 months ago	Ongoing
	0	Benadryl	Hayfever	od	3 weeks ago	Ongoing
0443	6	Clarityn	Hayfever	1 tablet od	15/06/99	30/06/99

continued

TABLE 145 *Concomitant medication details (cont'd)*

Patient ID	Week	Medication	Reason	Quantity/ frequency	Start date	Stop date
Ery. od & BP od						
0443	6	Piriton	Hayfever	1 tablet od	26/06/99	13/07/99
	12	Safeway's cold & flu remedy (contains paracetamol)	Relief of cold symptoms	2 capsules prn	24/08/99	Ongoing
	18	Otrivine nasal spray (Xylometazoline 0.1%)	To clear nose & prevent infection after operation	2 doses each nostril twice daily	30/09/99	04/10/99
	18	General anaesthetic	Operation?		29/09/99	29/09/99
0469	12	Paracetamol	Headache	2 tablets prn	Used on & off as required	
	18	Benylin – chesty cough	Cold symptoms	2 tsp 3 times daily	06/12/99	10/12/99
	18	Solpadeine	Cold symptoms	2 tablets prn	As required	
	18	Sudafed tablets	Cold symptoms	1 tablet once daily	10/12/99	12/12/99
	18	Sudafed liquid – chesty coughs	Cold symptoms	2 tsp 3 times daily	10/12/99	12/12/99
0483	0	Salbutamol inhaler	Asthma	1 puff 1 × daily	10 yrs old	Ongoing
	6	Sodium chromoglycate (Boots hayfever relief drops)	Eye infection	1 drop per eye as required	18/10/99	Ongoing
	6	Beconase nasal spray	Rhinitis (allergic)	1 spray per nostril od	28/10/99	Ongoing
	18	Loratidine	Swelling & inflammation around eyes	1 tablet one occasion	25/12/99	25/12/99
0489	0	Flixotide	Asthma	2 puffs prn		
	0	Salbutamol	Asthma	2 puffs prn		
0505	0	Cilest	Contraception	1 daily		
0512	6	Ibuprofen	Pain in hand from ligament	200 mg tds	27/09/99	As needed
0530	0	Thyroxine	Underactive thyroid	150 mcg daily	Jan 99	Ongoing
0540	12	Meningitis jab	Vaccination against meningitis	Once only	15/12/99	15/12/99
0591	18	Laxative	Constipation	tds		Ongoing
0605	0	Loratidine	Urticaria	10 mg od (prn)	?	Ongoing
	18	Cephalexin (antibiotic)	Broken leg	500 mg tds	28/12/99	03/03/00
	18	Microgynon	Contraception	150 mg/300 mcg od	02/03/00	Ongoing
0635	6	Hydrocortisone ointment	Skin inflamed (eczematous)	bd	17/11/99	24/11/99
0715	0	Salbutamol	Asthma	2 puffs prn		Ongoing
0756	0	Ovranette	Contraception	1 tablet od	4 yrs ago	N/A
0811	0	Insulin – Humalog	Diabetes	10 IU nocte	1996	Ongoing
	0	Mixatard	Diabetes	14 IU od	1996?	Ongoing
	0	Insulatard	Diabetes	23 IU nocte	1996?	Ongoing
0835	6	Antibiotics (for thrush)	Thrush			Ongoing
0876	0	Nicotine patches	To stop smoking			

continued

TABLE 145 *Concomitant medication details (cont'd)*

Patient ID	Week	Medication	Reason	Quantity/ frequency	Start date	Stop date
Ery. od & BP od						
0887	0	Hayfever tablets	Hayfever	prn		
0909	0	Brevinor	Contraceptive pills		1 yr ago	Ongoing
0935	12	Paracetamol	Headaches	500 mg bd	09/12/99	09/12/99
0944	0	Priadel	Manic depression	600 mg per day	9/98	?
	0	Venlafaxine	Depression	37.5 mg per day	5/99	?
	18	Cileste	Contraception		12/01/00	Ongoing
0969	0	Marvelon	Contraception			
	0	Zovirax	Cold sores			
	0	Antifungal	Athletes foot			
1041	0	Easy breathe inhalers	Asthma	4 times a day	About 1 yr ago	Ongoing
1083	0	Beconyl	Asthma	Every night	Since birth	
1164	0	Davonex	Psoriasis		Mar 2000	May 2000
1190	0	Aerolin	Asthma	prn	1 yr ago	Ongoing
1209	0	Thyroxine	Myxoedema	250mcg od	7 yrs ago	Ongoing
	0	Iron tablets	Hair loss	2 × 250 mg tablets od	2 yrs ago	Ongoing
	0	Colofac	Indigestion & trapped wind	1 tablet tid	4 yrs ago	Ongoing
1225	6	Paracetamol	Flu symptoms	2 × 500 mg tabs used once during flu	22/11/99	27/11/99
1239	6	Aspirin	Pain in thumb	1 tablet once daily	22/11/99	25/11/99
1246	6	Aspirin	Headache	Up to 3 × 300 mg tablets as required	As required	
1278	6	Lemsip (contains paracetamol)	Flu symptoms	1 sachet as required	Can't remember	
	12	Lemsip (1 g paracetamol per sachet)	Flu symptoms	1 sachet 4 × daily	21/02/00	25/02/00
1308	12	General anaesthetic	Dental operation		19/04/00	19/04/00
	12	Ibuprofen liquid	Pain relief		19/04/00	26/04/00
	12	Paracetamol	Pain relief		19/04/00	26/04/00
1317	18	Clarityn	Hayfever symptoms	1 tablet as required		
1422	0	Ventolin	Asthma	prn	N/K	Ongoing
	0	Becadisc	Asthma	2 pumps	N/K	Ongoing
	18	Tetanus vaccine	Booster immunisation for tetanus	once only	16/08/00	16/08/00
1431	0	Sudafed	Sinusitis	3 tablets prn	25/04/00	Ongoing
1533	18	Paracetamol	Migraine	100 mg bd	27/06/00	02/07/00

Details are printed from the database and are as reported by the participant.

IBS, irritable bowel syndrome; N/K, not known.

Appendix 17

Further details of adverse events and side-effects

TABLE 146 *Number of participants with adverse events by classification*

Week	Treatment group	Classification										
		NR	GI	CNS	Psych	Skin	Inf	M/S	Repro	Resp	Other	All
6	Oxytetracycline	0	22	11	2	5	7	0	0	0	1	48
	Minocycline	0	14	12	1	5	7	0	2	0	0	41
	Benzoyl peroxide	1	8	2	0	17	5	0	0	1	2	36
	Ery. + BP bd	0	8	4	0	11	5	0	1	0	2	31
	Ery. od + BP od	0	8	2	0	11	6	0	2	0	2	31
	All	1	60	31	3	49	30	0	5	1	7	187
12	Oxytetracycline	0	4	0	1	3	8	0	0	1	0	17
	Minocycline	0	8	5	1	4	1	3	0	0	0	22
	Benzoyl peroxide	0	3	2	0	2	6	1	0	0	1	15
	Ery. + BP bd	0	6	3	0	3	5	1	0	0	2	20
	Ery. od + BP od	0	4	1	0	4	6	1	0	0	1	17
	All	0	25	11	2	16	26	6	0	1	4	91
18	Oxytetracycline	0	1	1	1	1	2	0	0	1	0	7
	Minocycline	0	2	2	0	2	8	5	0	1	3	23
	Benzoyl peroxide	0	0	1	1	3	9	0	0	0	1	15
	Ery. + BP bd	0	4	2	1	2	2	2	0	1	2	16
	Ery. od + BP od	0	1	3	0	1	5	2	0	0	3	15
	All	0	8	9	3	9	26	9	0	3	9	76

CNS, central nervous system; GI, gastrointestinal; Inf, infections; M/S, musculoskeletal; NR, not recorded (adverse event occurred, but details are missing); Psych, psychiatric; Repro, reproductive system; Resp, respiratory system.

TABLE 147 *Adverse event details*

Pt ID	Week	Adverse event description	Class	Severity	Days	Outcome	Pt W/D	Trt rec
Oxytetracycline								
0026	6	Dry skin	Skin	Mild	.	Ongoing	No	No
	12	Itchy skin	Skin	Mild	.	Ongoing	No	No
0042	6	Headaches, nausea, dizziness	CNS	Moderate	4	Resolved	No	No
0174	12	Vaginal thrush	Inf	Mild	7	Resolved	No	Yes
	18	Rash on left arm	Skin	Mild	.	Resolved	No	No
0184	6	Headaches	CNS	Mild	.	Resolved	No	No
0188	6	Diarrhoea	GI	Mild	1	Resolved	No	No
0209	6	Diarrhoea	GI	Mild	.	Resolved	No	No
		Swelling	Other	Mild	.	Ongoing	No	No
	18	Stomach cramps	GI	Moderate	.	Ongoing	No	No
0257	6	Stomach cramps	GI	Mild	0	Resolved	No	Yes
0271	6	Exacerbation of acne on forehead	Skin	NR	.	Ongoing	No	No
0352	12	Felt sick & unwell	GI	Mild	2	Resolved	No	Yes
		Felt sick & unwell	GI	Mild	1	Resolved	No	No
0355	6	Bowel habit change – increase in frequency	GI	Mild	5	Resolved	No	No
0371	6	Very mild looseness of motions	GI	Mild	.	Ongoing	No	No
		Tonsillitis	Inf	Mild	.	Resolved	No	Yes
0411	6	Migraine	CNS	Severe	.	Referred to GP	Yes	No

continued

TABLE 147 *Adverse event details (cont'd)*

Pt ID	Week	Adverse event description	Class	Severity	Days	Outcome	Pt W/D	Trt rec
Oxytetracycline								
0437	6	Nausea	GI	Mild	2	Resolved	No	No
	12	Bad prickly heat – worse than ever before	Skin	Mild	14	Resolved	No	No
0447	12	Throat infection	Inf	Mild	15	Resolved	No	Yes
0459	6	Brief, sharp, stabbing pains in abdomen on & off	GI	Mild	.	Ongoing	No	No
0477	6	Constipation	GI	Mild	18	Resolved	No	No
0506	6	Stomach ache	GI	Mild	1	Resolved	No	No
0511	6	Nausea (occasional)	GI	Mild	.	Ongoing	No	No
	12	Candida infection	Inf	Moderate	7	Resolved	Yes	Yes
0533	6	Tiredness	CNS	Mild	.	Ongoing	No	No
0557	6	Stomach aches & diarrhoea	GI	Severe	17	Resolved	Yes	No
0622	6	Flu	Inf	NR	.	Resolved	No	No
0646	6	Headache	CNS	Mild	0	Resolved	No	No
0688	12	Indigestion, heart-burn & gastric reflux	GI	Mild	.	Ongoing	No	No
0713	6	Headache	CNS	Mild	0	Resolved	No	No
0718	6	V. sore red, dry skin	Skin	Severe	10	Resolved	Yes	No
		Rash & swelling to eyes	Skin	Severe	10	Resolved	Yes	No
0737	6	Thrush	Inf	Mild	2	Resolved	No	No
0741	6	Virus	Inf	NR	.	Resolved	No	No
0803	6	Depression – worsening	Psych	Severe	.	Hospitalised	No	Yes
	12	Exacerbation of depression	Psych	Severe	63	Hospitalised	No	Yes
	18	Depression (ongoing)	Psych	Moderate	.	Ongoing	No	No
0818	12	Constipation	GI	Moderate	.	Ongoing	No	No
		Thrush	Inf	Mild	3	Resolved	No	No
0851	6	Stomach cramps	GI	Mild	2	Resolved	No	No
		Skin irritation	Skin	Moderate	7	Resolved	No	No
1017	6	Loss of appetite	GI	Moderate	23	Resolved	No	No
		Influenza	Inf	NR	.	Resolved	No	No
	12	Loss of appetite	GI	Mild	3	Resolved	No	No
1063	18	Vaginal thrush	Inf	Moderate	.	Referred to GP	No	Yes
1088	6	Exacerbation of acne	Skin	Moderate	.	Referred to GP	Yes	No
1119	6	Abdominal pain	GI	Mild	1	Resolved	No	No
		Headache	CNS	Mild	2	Resolved	No	No
1130	6	Nausea	GI	Mild	2	Resolved	No	No
1186	6	Stomach cramps	GI	Mild	2	Resolved	No	No
		Headaches	CNS	Severe	.	Referred to GP	No	Yes
		Tiredness	CNS	NR	.	Referred to GP	No	No
		Nausea	GI	NR	.	Referred to GP	No	No
	12	Pneumonia	Inf	NR	.	Ongoing	Yes	Yes
1202	6	Feeling of queasiness & tiredness	CNS	Mild	28	Resolved	No	No
		On & off constipation	GI	Mild	28	Resolved	No	No
	12	Cold	Inf	Mild	6	Resolved	No	Yes
1241	6	Depression	Psych	Mild	22	Resolved	No	No
		Cold symptoms	Inf	Mild	4	Resolved	No	Yes
1247	6	Constipation & uncomfortable feeling with nausea	GI	Mild	.	Ongoing	No	No
1267	18	Not slept very well	CNS	Mild	.	Ongoing	No	Yes
1287	12	More hair loss than normal	Skin	Mild	.	Ongoing	No	No
1306	6	Nausea – occasional in morning, when without food	GI	Mild	.	Ongoing	No	No
		Thrush	Inf	Mild	3	Resolved	No	Yes
		Thrush	Inf	Mild	3	Resolved	No	Yes

continued

TABLE 147 *Adverse event details (cont'd)*

Pt ID	Week	Adverse event description	Class	Severity	Days	Outcome	Pt W/D	Trt rec
Oxytetracycline								
1306	12	Vaginal thrush	Inf	Moderate	8	Resolved	No	Yes
1306	18	Vaginal thrush	Inf	Mild	9	Resolved	No	Yes
		Vaginal thrush	Inf	Mild	3	Resolved	No	Yes
1409	6	Tiredness	CNS	Mild	14	Resolved	No	No
	12	Hayfever	Resp	Severe	.	Ongoing	No	Yes
	18	Hayfever	Resp	Severe	43	Ongoing	No	Yes
1421	6	Stomach churning	GI	Mild	2	Resolved	No	No
1432	12	Cough & cold	Inf	Mild	6	Resolved	No	No
1474	6	Stomach cramps	GI	Moderate	4	Referred to GP	No	No
1493	6	Fever & convulsions	CNS	Severe	1	Hospitalised	Yes	Yes
1502	6	Nausea	GI	Mild	1	Resolved	No	No
Minocycline								
0006	6	Nausea, vomiting and diarrhoea	GI	Moderate	.	Ongoing	No	No
0015	6	Epileptic fit	CNS	.	0	Resolved	No	No
	12	Epilepsy	CNS	.	.	Resolved	No	Yes
	18	Unstable epilepsy	CNS	Moderate	.	Ongoing	No	Yes
0038	6	Exacerbation of acne on back	Skin	Mild	.	Ongoing	No	No
0072	12	Nausea	GI	Mild	.	Ongoing	No	No
	18	Nausea	GI	.	.	Resolved	No	No
0106	6	Constipation	GI	Moderate	.	Ongoing	No	No
	12	Constipation	GI	Mild	.	Ongoing	No	No
0124	6	Stomach upset	GI	Mild	3	Resolved	No	No
	12	Depression	Psych	Mild	.	Ongoing	No	No
0139	6	Diarrhoea	GI	Moderate	9	Resolved	Yes	No
		Stomach cramps	GI	Moderate	11	Resolved	Yes	No
0159	6	Nausea	GI	Mild	13	Resolved	No	No
0179	6	Persistent headaches	CNS	Mild	3	Resolved	No	No
0189	12	Nausea (suspected stomach bug)	GI	Mild	1	Resolved	No	No
	18	Asthma (due to flu?)	Resp	Moderate	.	Referred to GP	No	Yes
		Flu	Inf	Moderate	.	Referred to GP	No	No
0227	6	Headaches	CNS	Mild	8	Resolved	No	Yes
0234	12	Unusual joint pain	M/S	Moderate	.	Referred to GP	No	No
0258	12	Nausea	GI	Mild	15	Resolved	No	No
		Stomach cramps	GI	Moderate	15	Resolved	No	No
		Headaches	CNS	Mild	4	Resolved	No	No
0283	6	Headaches	CNS	Mild	3	Resolved	No	No
0295	12	Dark blotches on skin (back)	Skin	Moderate	.	Ongoing	No	No
0337	18	Flu	Inf	Mild	7	Resolved	No	Yes
0390	6	Headaches	CNS	Moderate	31	Resolved	No	No
0398	18	Cold symptoms	Inf	Mild	.	Ongoing	No	No
0417	6	Nausea	GI	Mild	0	Resolved	No	No
0475	6	Bad headaches accompanied by dizziness	CNS	Moderate	.	Ongoing	No	Yes
0485	6	Depression	Psych	Mild	.	Ongoing	No	No
	12	Left leg, hip & knee ache – exacerbation	M/S	Mild	.	Ongoing	No	No
		Hair loss – moulting	Skin	Moderate	.	Ongoing	No	No
	18	Hair loss continues, hair brittle & weak	Skin		. .	Ongoing	No	No
0502	6	Nausea	GI	Mild	2	Resolved	No	No
0509	18	Ulcers on tongue	Other	Mild	.	Ongoing	No	No
		Flu (?)	Inf	NR	2	Resolved	No	No
0543	12	Diarrhoea & flatulence	GI	Mild	.	Ongoing	No	No
0554	6	Thrush	Inf	Severe	10	Resolved	No	Yes
0615	6	Headaches	CNS	Mild	2	Resolved	No	No

continued

TABLE 147 *Adverse event details (cont'd)*

Pt ID	Week	Adverse event description	Class	Severity	Days	Outcome	Pt W/D	Trt rec
Minocycline								
0615	18	Knee joint burning/aching sensation – exacerbation	M/S	Mild	.	Ongoing	No	No
0625	6	Influenza	Inf	Severe	7	Resolved	No	Yes
		Cold	Inf	Severe	.	Ongoing	No	Yes
	18	Sprained ankle	M/S	NR	.	Resolved	No	No
0636	6	Flu	Inf	NR	.	Resolved	No	Yes
0655	6	Breakthrough bleeding between periods	Repro	Mild	2	Resolved	Yes	No
		Breakthrough bleeding between periods	Repro	Mild	2	Resolved	Yes	No
0668	6	Nausea	GI	Mild	3	Resolved	No	No
	12	Joint pains in wrists, ankles & shoulders	M/S	Mild	.	Ongoing	No	No
	18	Joint pain	M/S	Mild	.	Resolved	No	No
0672	6	Pregnancy	Repro	NR	.	Referred to GP	Yes	No
0693	6	Dizzyness	CNS	Mild	1	Resolved	No	No
0765	18	Thrush	Inf	Mild	.	Ongoing	No	Yes
0789	12	Stomach ache	GI	Mild	.	Ongoing	No	No
0813	6	Thrush	Inf	Mild	2	Resolved	No	Yes
	12	Thrush	Inf	Severe	.	Ongoing	No	Yes
	18	Thrush	Inf	Moderate	.	Ongoing	Yes	Yes
0824	6	Feeling tired	CNS	Mild	.	Ongoing	No	No
	12	Exacerbation of acne	Skin	Moderate	.	Referred to GP	Yes	No
0861	6	Brownish pigments on cheek bones	Skin	Mild	.	Ongoing	No	No
	18	Chest infection	Inf	Moderate	14	Resolved	No	Yes
0955	6	Exacerbation of acne	Skin	NR	.	NR	No	No
0989	6	Stomach cramps	GI	Mild	7	Resolved	No	No
		Diarrhoea	GI	Mild	7	Resolved	No	No
		Influenza	Inf	NR	.	Resolved	No	No
0999	12	Diarrhoea	GI	Mild	5	Resolved	No	No
		Headaches	CNS	Mild	.	Ongoing	No	No
1015	6	Loss of appetite	GI	Moderate	19	Resolved	No	No
		Influenza	Inf	NR	.	Resolved	No	No
1015	12	Headaches	CNS	Moderate	2	Resolved	No	No
	18	Stomach cramps	GI	Mild	.	Ongoing	No	No
		Headaches	CNS	Mild	2	Resolved	No	No
1117	6	Headaches	CNS	Mild	1	Ongoing	No	No
1220	18	Skin itchy & sensitive all over	Skin	Moderate	2	Resolved	No	No
		Swelling inside of mouth	Other	Moderate	2	Resolved	No	No
1233	18	Possible fractured left wrist	M/S	Mild	.	Ongoing	No	No
1253	6	Tiredness – more mental than physical	CNS	Mild	.	Ongoing	No	No
1309	6	Stomach pain & diarrhoea	GI	Mild	5	Resolved	No	No
1313	6	Headache	CNS	Severe	.	Referred to GP	Yes	No
		Nausea	GI	NR	.	Referred to GP	Yes	No
		Rash	Skin	NR	.	Referred to GP	Yes	No
1419	6	Stomach cramps	GI	Mild	.	Resolved	No	No
	12	Dry, red skin	Skin	Mild	65	Resolved	No	No
1425	6	Rash to temples	Skin	Mild	3	Resolved	No	No
1480	18	Ankle injury - exacerbation	M/S	Mild	.	Ongoing	No	No
1494	6	Blood in urine? UTI	Inf	Moderate	0	Resolved	No	No
1504	6	Nausea & stomach cramps	GI	Severe	1	Resolved	No	No
	18	Very heavy cold with sinus problems	Inf	Moderate	.	Ongoing	No	No
		Nose bleeds & dizziness – intermittent	Other	Severe	.	Ongoing	No	No
1515	12	Headaches	CNS	Mild	1	Resolved	No	Yes
		Felt sick	GI	Mild	1	Resolved	No	No

continued

TABLE 147 *Adverse event details (cont'd)*

Pt ID	Week	Adverse event description	Class	Severity	Days	Outcome	Pt W/D	Trt rec
Benzoyl peroxide								
0004	6	Tightening of skin after using topical solution	Skin	Mild	19	Resolved	No	No
0049	6	Dry skin	Skin	Mild	15	Resolved	No	No
	12	Chest infection	Inf	NR	.	NR	No	Yes
0086	6	Rash? Acne worsening to face only	Skin	Severe	.	Referred to GP	Yes	No
0095	12	Kidney infection	Inf	NR	9	Resolved	No	Yes
	18	Kidney infection	Inf	Severe	37	Resolved	No	Yes
0100	6	Rash on legs, chest & arms	Skin	Severe	10	Referred to GP	Yes	No
0176	6	Diarrhoea	GI	NR	10	Resolved	No	No
		Breast pain	Other	NR	.	NR	No	No
0202	12	Blisters around mouth & burning	Other	Severe	22	Resolved	No	Yes
0253	6	Nausea	GI	Mild	5	Resolved	No	No
0261	6	Vomiting, headaches, dizziness	GI	NR	.	Hospitalised	Yes	Yes
0303	6	(Unknown – forgotten)	NR	Mild	5	Resolved	No	No
0328	18	Cold or flu symptoms	Inf	Mild	.	Ongoing	No	Yes
0363	6	Stomach ache & diarrhoea	GI	Mild	.	Ongoing	No	No
	18	Flu symptoms	Inf	Mild	.	Ongoing	No	Yes
0406	6	Worsening of hayfever symptoms	Resp	Mild	.	Ongoing	No	Yes
0421	6	Headaches (dull, non-localised)	CNS	Mild	13	Resolved	No	No
		Occasional nausea	GI	Mild	13	Resolved	No	No
0444	6	Felt sick & tired – generally unwell	GI	Mild	4	Resolved	No	No
0455	6	Diarrhoea	GI	Mild	4	Resolved	No	No
		Nausea	GI	Mild	4	Resolved	No	No
	12	Sore throat	Inf	Mild	.	Ongoing	No	Yes
0463	12	Feeling run-down (v. tired, no energy, depressed)	CNS	Mild	.	Ongoing	No	No
	18	Sore throat & enlarged glands in neck	Inf	Mild	4	Resolved	No	Yes
0514	18	Depression	Psych	Moderate	.	Ongoing	No	No
0521	18	Flu	Inf	NR	.	Ongoing	No	No
0548	6	Dry red skin	Skin	Severe	.	Ongoing	No	Yes
0552	6	Eczematous rash to face	Skin	Severe	7	Resolved	Yes	No
0590	6	Red, dry & flaky skin	Skin	Moderate	5	Ongoing	No	No
0600	6	Red,dry, itchy sore skin	Skin	Moderate	.	Ongoing	No	No
0611	6	Dry, itchy, sore skin	Skin	Severe	5	Ongoing	No	No
0632	6	?Allergic reaction – rash & swelling to face	Skin	Severe	.	Referred to GP	No	Yes
0640	6	Dry, sore, red itchy skin	Skin	Moderate	.	Ongoing	No	No
	18	Eczema around eyes – became increasingly active	Skin	Moderate	.	Ongoing	No	No
		Colds – 2 in last 4 weeks	Inf	NR	.	Resolved	No	No
0657	6	Severe dry skin	Skin	Severe	5	Referred to GP	Yes	Yes
		Rash	Skin	Severe	5	Referred to GP	Yes	Yes
		Swelling of eyes	Other	Severe	5	Referred to GP	Yes	Yes
0666	6	Cystitis	Inf	NR	.	Resolved	No	Yes
0675	12	Stomach cramp	GI	Mild	.	Ongoing	No	No
0750	12	Skin reaction (red & burning)	Skin	Severe	.	Ongoing	Yes	No
0780	18	Exacerbation of acne	Skin	Mild	.	Ongoing	Yes	No
0809	6	Red, dry, burning, itchy skin	Skin	Moderate	8	Resolved	No	No
0825	6	Persistent headaches	CNS	Mild	7	Resolved	No	No
	12	Persistent headaches	CNS	Moderate	4	Resolved	No	Yes
	18	Headaches	CNS	NR	4	Resolved	No	Yes
0837	6	Excessive facial dryness	Skin	Moderate	10	Resolved	No	No

continued

TABLE 147 *Adverse event details (cont'd)*

Pt ID	Week	Adverse event description	Class	Severity	Days	Outcome	Pt W/D	Trt rec
Benzoyl peroxide								
0926	6	Flu	Inf	NR	15	Resolved	No	Yes
0964	18	Unusual redness of face	Skin	Mild	2	Resolved	No	No
1048	12	Thrush	Inf	Mild	7	Resolved	No	No
1075	6	Diarrhoea	GI	Mild	0	Resolved	No	No
		Thrush	Inf	Mild	1	Resolved	No	No
1112	6	Sweating	Skin	Mild	.	Ongoing	No	No
		Extremely sore skin	Skin	Moderate	7	Resolved	No	No
1208	6	Cold	Inf	Mild	2	Resolved	No	Yes
	12	Rash on lower arms	Skin	Mild	.	Ongoing	No	Yes
1228	6	Flu	Inf	Mild	3	Resolved	No	No
1236	12	Tonsillitis	Inf	Mild	5	Resolved	No	Yes
	18	Cold symptoms	Inf	Mild	4	Resolved	No	Yes
1263	12	Sickness	GI	Moderate	4	Resolved	No	No
1310	12	Pain in RH lower back area	M/S	Mild	4	Resolved	No	No
1329	18	Shingles	Inf	Moderate	.	Ongoing to GP	No	Yes
1333	12	Stomach pain	GI	Mild	0	Resolved	No	No
	18	Tonsillitis	Inf	Mild	11	Resolved	No	Yes
1343	12	Stomach bug	Inf	Moderate	1	Resolved	No	No
1427	18	Nose running & eyes watering	Other	Moderate	.	Referred to GP	No	No
1498	6	Dry, red, itchy, sore skin	Skin	Severe	2	Resolved	No	No
1523	6	Sore, dry, red skin	Skin	Severe	22	Resolved	Yes	No
Ery. + BP bd								
0024	6	Rash on face only	Skin	Mild	4	Resolved	No	No
0089	18	Nausea & stomach ache	GI	Mild	2	Resolved	No	No
		Red, sore skin	Skin	Moderate	.	Ongoing	No	No
0125	6	Excessive dryness & burning sensation to skin	Skin	Severe	7	Resolved	Yes	No
0152	18	Itchy eyes	Other	Severe	.	Resolved	No	No
0167	6	Exacerbation of acne	Skin	Moderate	14	Ongoing	No	No
0187	6	Stomach cramps	GI	Mild	3	Resolved	No	No
0205	6	Tiredness & sleepy	CNS	Moderate	14	Resolved	No	No
	12	Pain in back of neck	M/S	Mild	.	Ongoing	No	No
	18	Headaches	CNS	NR	37	Resolved	No	No
0240	12	Stomach cramps	GI	Mild	1	Resolved	No	No
0269	12	Nausea & stomach cramps	GI	NR	.	Resolved	No	No
	18	Stomach cramps	GI	Mild	.	Ongoing	No	No
0301	6	Skin sore & tight	Skin	Mild	3	Resolved	No	No
	18	Migraine	CNS	Moderate	.	Ongoing	No	No
0366	18	Hyperventilating, panic attack	Psych	Mild	11	Resolved	No	No
0405	6	Headache	CNS	Mild	.	Ongoing	No	No
		Dizziness	CNS	Mild	.	Ongoing	No	No
0426	6	Ear, throat & chest infection	Inf	Mild	7	Resolved	No	Yes
0473	6	Flu symptoms	Inf	Mild	.	Ongoing	No	No
	12	Stomach upset	GI	Mild	.	Ongoing	No	Yes
		Headache	CNS	Mild	.	Ongoing	No	No
0474	12	Worsening nail fungal infection	Inf	Mild	.	Ongoing	No	Yes
0525	6	Redness, swelling & itching of eyes	Other	Severe	3	Resolved	No	No
0534	18	Ear infection	Inf	Mild	7	Resolved	No	No
0578	18	Ear infection	Inf	Mild	7	Resolved	No	No
0593	6	Dry skin	Skin	Moderate	.	Ongoing	No	No
0620	6	Red, dry skin	Skin	Moderate	.	Ongoing	No	No
		Tonsillitis	Inf	NR	.	Resolved	No	Yes
0682	12	Rash & swelling to face	Skin	Moderate	15	Resolved	Yes	No
0725	6	Itchiness	Skin	Moderate	.	Ongoing	No	No
0761	6	Poorly	Other	NR	.	Resolved	No	No

continued

TABLE 147 *Adverse event details (cont'd)*

Pt ID	Week	Adverse event description	Class	Severity	Days	Outcome	Pt W/D	Trt rec
Ery. & BP bd								
0771	6	Dry, sore, red skin	Skin	Moderate	.	Ongoing	No	No
	12	Red, sore dry skin – intermittent	Skin	Severe	.	Ongoing	No	No
		Swelling to eyes – intermittent	Other	NR	.	Ongoing	No	No
	18	Itchy, dry & red in patches to chin	Skin	Moderate	.	Ongoing	No	No
0800	6	Nausea & stomach ache	GI	Moderate	.	Ongoing	No	No
		Headaches & dizziness	CNS	Moderate	21	Resolved	No	No
0820	6	Rash in ankles	Skin	Mild	28	Resolved	No	No
	12	Dry skin to body	Skin	Severe	.	Ongoing	No	No
0872	6	Stomach cramps	GI	Mild	6	Resolved	No	No
		Nausea	GI	Mild	6	Resolved	No	No
0916	6	Diarrhoea	GI	Mild	3	Resolved	No	No
		Rash under eyes	Skin	Mild	2	Resolved	No	No
		Thrush	Inf	Mild	.	Resolved	No	No
		Headaches	CNS	NR	.	NR	No	No
	12	Stomach cramps	GI	Mild	5	Resolved	No	No
		Diarrhoea	GI	Mild	5	Resolved	No	No
	18	Diarrhoea	GI	Mild	3	Resolved	No	No
1072	6	Stomach cramps & diarrhoea	GI	Mild	1	Resolved	No	No
1108	6	Pelvic inflammation	Repro	Moderate	5	Resolved	No	No
1203	12	Cold	Inf	Mild	3	Resolved	No	Yes
1243	12	Cold symptoms	Inf	Mild	.	Resolved	No	Yes
		Headache	CNS	Mild	.	Resolved	No	Yes
1245	12	Nausea, tiredness after typhoid & Hep. A immunised	Other	Mild	3	Resolved	No	No
1273	6	Stomach upset	GI	Mild	7	Resolved	No	No
	12	Throat infection	Inf	Moderate	.	Ongoing	No	Yes
1293	6	Stomach ache	GI	Mild	2	Resolved	No	No
	12	Headache	CNS	Mild	1	Resolved	No	No
		Nausea	GI	Mild	1	Resolved	No	No
		Sore throat	Inf	Mild	.	Ongoing	No	Yes
	18	Ear pain – infection/wax blockage?	Other	Mild	7	Resolved	No	Yes
1316	18	Hayfever symptoms	Resp	Mild	.	Ongoing	No	Yes
1342	6	Nausea	GI	Mild	.	Resolved	No	No
	12	Nausea & diarrhoea	GI	Mild	.	Resolved	No	No
1346	6	Cold symptoms & sore throat	Inf	Mild	.	Ongoing	No	No
1410	18	Ankle fracture (ongoing)	M/S	Mild	.	Ongoing	No	No
1485	6	Severe skin reaction	Skin	Severe	5	Resolved	No	No
1490	18	Nausea	GI	Mild	1	Resolved	No	No
1500	18	Backache/pain (trapped nerve?)	M/S	Severe	.	Ongoing	No	Yes
Ery. od + BP od								
0003	6	Dry skin	Skin	Mild	.	Ongoing	No	No
0028	6	Excessive dry skin	Skin	Mild	.	Ongoing	No	No
0036	6	Headaches + (nosebleeds)	CNS	Moderate	.	Referred to GP	No	No
		Nosebleeds	Other		. .	.	No	No
	12	Nausea	GI	Mild	.	Ongoing	No	No
		Skin inflammation	Skin		. .	Ongoing	No	No
0085	12	Stomach cramps	GI	Moderate	7	Resolved	No	No
0090	6	Dry skin & discoloration	Skin	Severe	.	Resolved	Yes	No
0102	18	Bleached hair	Skin	Mild	.	Ongoing	No	No
0115	6	Diarrhoea	GI	Moderate	6	Resolved	No	No
0122	6	Skin tenderness	Skin	Moderate	6	Resolved	Yes	No
0144	6	Rash to face	Skin	Moderate	.	Ongoing	Yes	No
0177	18	Stomach cramps	GI	Mild	3	Resolved	No	No
		Headaches	CNS	Mild	3	Resolved	No	Yes
0238	12	Fever	Inf	Moderate	6	Resolved	No	No

continued

TABLE 147 *Adverse event details (cont'd)*

Pt ID	Week	Adverse event description	Class	Severity	Days	Outcome	Pt W/D	Trt rec
Ery. od & BP od								
0346	6	Migraine	CNS	Moderate	4	Resolved	No	Yes
0359	6	Chest infection	Inf	Moderate	7	Resolved	No	Yes
0364	12	Possible thrush	Inf	Mild	3	Resolved	No	Yes
	18	Suspected vaginal thrush	Inf	Mild	.	Resolved	No	Yes
0386	6	Influenza	Inf	Moderate	.	Resolved	No	Yes
0404	12	Throat infection	Inf	Mild	11	Resolved	No	No
0413	18	Insomnia	Other	Mild	.	Ongoing	No	No
		Headaches	CNS	Mild	.	Ongoing	No	No
		Sore throat	Inf	Mild	.	Ongoing	No	No
		Dizziness	CNS	Mild	.	Ongoing	No	No
0469	18	Cold symptoms	Inf	Mild	8	Resolved	No	Yes
0483	6	Eye infection	Inf	NR	.	Ongoing	No	Yes
	18	Swollen eyes (unspec. allergic reaction)	Other	Mild	.	Resolved	No	Yes
0523	12	V. dry red 'blotchy' skin	Skin	Severe	4	Resolved	Yes	No
0540	6	Weight gain	Other	Mild	.	Ongoing	No	No
	12	Joint pain left knee	M/S	Moderate	.	Ongoing	Yes	No
		Increased appetite	GI	Moderate	.	Ongoing	Yes	No
0579	6	Sore, dry red skin	Skin	Moderate	.	Ongoing	No	No
0591	6	Dry, red skin	Skin	Moderate	16	Ongoing	No	No
0605	6	Nausea & dizziness	GI	Mild	2	Resolved	No	No
	18	Fractured fibula	M/S	NR	.	Referred to GP	No	No
0619	6	Diarrhoea & sickness	GI	Moderate	3	Resolved	No	No
0635	6	Skin reaction/irritation	Skin	Severe	13	Referred to GP	Yes	Yes
0684	18	Eye irritation & swelling	Other	Mild	3	Resolved	No	No
0715	6	Redness & dry skin	Skin	Mild	.	Ongoing	No	No
0726	18	Joint pain in shoulders	M/S	Mild	.	Ongoing	No	No
0774	18	Cold	Inf	Mild	.	Resolved	No	No
0811	6	Severe skin reaction: red, dry, itch, swell, burn	Skin	Severe	7	Resolved	No	No
0835	6	Vaginal discharge	Repro	NR	10	Ongoing	No	Yes
0909	12	Exacerbation of acne	Skin	Severe	33	Resolved	No	No
0935	12	Headaches	CNS	Mild	0	Resolved	No	Yes
0944	6	Nausea	GI	Mild	7	Resolved	No	No
		Loss of appetite	GI	Mild	7	Resolved	No	No
0969	6	Cold sores	Inf	Mild	8	Resolved	No	No
1058	12	Stomach cramps	GI	Mild	2	Resolved	No	No
1106	6	Unusual early onset of period	Repro	Moderate	10	Resolved	No	No
1209	6	Sickness – 2 to 3 times daily	GI	Moderate	7	Resolved	No	No
	12	Flu symptoms	Inf	Mild	.	Ongoing	No	No
1225	6	Flu symptoms	Inf	Mild	5	Resolved	No	Yes
1246	6	Constipation & stomach ache	GI	Mild	7	Resolved	No	No
1268	18	Cold symptoms	Inf	Mild	.	Ongoing	No	No
1278	12	Flu symptoms	Inf	Moderate	5	Resolved	No	Yes
		Rash on neck	Skin	Moderate	3	Resolved	No	No
1296	6	Stomach ache	GI	Mild	2	Resolved	No	No
1308	12	Operation on tooth	Other	Mild	1	Resolved	No	Yes
1331	6	Stomach pain	GI	Mild	1	Resolved	No	Yes
	12	Cold symptoms	Inf	Mild	.	Ongoing	No	No
1417	6	Blotchy face	Skin	Mild	7	Resolved	No	No
1507	6	Thrush	Inf	Moderate	14	Resolved	Yes	No
1533	18	Migraine	CNS	Moderate	3	Resolved	No	Yes

Details are printed from the database and are as reported by the participant.
CNS, central nervous system; Days, duration in days; GI, gastrointestinal; Inf, infections; M/S, musculoskeletal; NR, not recorded (adverse event occurred, but details are missing); Psych, psychiatric; Pt W/D, patient withdrawn; Repro, reproductive system; Resp, respiratory system; Trt rec, treatment received.

TABLE 148 *Summary of participant assessment of moderate and severe stinging*

Week	Treatment group	None or mild		Moderate		Severe		All
0	Oxytetracycline	115	(88.5)	15	(11.5)	0	(0)	130
	Minocycline	117	(90.0)	11	(8.5)	2	(1.5)	130
	Benzoyl peroxide	119	(91.5)	10	(7.7)	1	(0.8)	130
	Ery. + BP bd	116	(91.3)	11	(8.7)	0	(0)	127
	Ery. od + BP od	116	(88.5)	13	(9.9)	2	(1.5)	131
0–2	Oxytetracycline	123	(94.6)	6	(4.6)	1	(0.8)	130
	Minocycline	119	(91.5)	11	(8.5)	0	(0)	130
	Benzoyl peroxide	102	(78.5)	16	(12.3)	12	(9.2)	130
	Ery. + BP bd	108	(85.0)	14	(11.0)	5	(3.9)	127
	Ery. od + BP od	106	(80.9)	19	(14.5)	6	(4.6)	131
2–4	Oxytetracycline	125	(96.2)	5	(3.8)	0	(0)	130
	Minocycline	124	(95.4)	6	(4.6)	0	(0)	130
	Benzoyl peroxide	118	(90.8)	7	(5.4)	5	(3.8)	130
	Ery. + BP bd	118	(92.9)	8	(6.3)	1	(0.8)	127
	Ery. od + BP od	124	(94.7)	5	(3.8)	2	(1.5)	131
4–6	Oxytetracycline	127	(97.7)	3	(2.3)	0	(0)	130
	Minocycline	125	(96.2)	5	(3.8)	0	(0)	130
	Benzoyl peroxide	124	(95.4)	2	(1.5)	4	(3.1)	130
	Ery. + BP bd	122	(96.1)	3	(2.4)	2	(1.6)	127
	Ery. od + BP od	126	(96.2)	3	(2.3)	2	(1.5)	131
12	Oxytetracycline	124	(95.4)	5	(3.8)	1	(0.8)	130
	Minocycline	126	(96.9)	4	(3.1)	0	(0)	130
	Benzoyl peroxide	119	(91.5)	5	(3.8)	6	(4.6)	130
	Ery. + BP bd	121	(95.3)	4	(3.1)	2	(1.6)	127
	Ery. od + BP od	125	(95.4)	4	(3.1)	2	(1.5)	131
18	Oxytetracycline	124	(95.4)	5	(3.8)	1	(0.8)	130
	Minocycline	126	(96.9)	4	(3.1)	0	(0)	130
	Benzoyl peroxide	120	(92.3)	4	(3.1)	6	(4.6)	130
	Ery. + BP bd	121	(95.3)	4	(3.1)	2	(1.6)	127
	Ery. od + BP od	127	(96.9)	2	(1.5)	2	(1.5)	131

Data are shown as *n* (%).

TABLE 149 *Summary of participant assessment of moderate and severe burning*

Week	Treatment group	None or mild		Moderate		Severe		All
0	Oxytetracycline	126	(96.9)	3	(2.3)	1	(0.8)	130
	Minocycline	128	(98.5)	2	(1.5)	0	(0)	130
	Benzoyl peroxide	125	(96.2)	5	(3.8)	0	(0)	130
	Ery. + BP bd	123	(96.9)	4	(3.1)	0	(0)	127
	Ery. od + BP od	130	(99.2)	1	(0.8)	0	(0)	131
0–2	Oxytetracycline	127	(97.7)	2	(1.5)	1	(0.8)	130
	Minocycline	125	(96.2)	5	(3.8)	0	(0)	130
	Benzoyl peroxide	106	(81.5)	13	(10.0)	11	(8.5)	130
	Ery. + BP bd	114	(89.8)	9	(7.1)	4	(3.1)	127
	Ery. od + BP od	111	(84.7)	15	(11.5)	5	(3.8)	131
2–4	Oxytetracycline	128	(98.5)	2	(1.5)	0	(0)	130
	Minocycline	128	(98.5)	2	(1.5)	0	(0)	130
	Benzoyl peroxide	120	(92.3)	6	(4.6)	4	(3.1)	130
	Ery. + BP bd	120	(94.5)	6	(4.7)	1	(0.8)	127
	Ery. od + BP od	127	(96.9)	3	(2.3)	1	(0.8)	131
4–6	Oxytetracycline	130	(100)	0	(0)	0	(0)	130
	Minocycline	128	(98.5)	2	(1.5)	0	(0)	130
	Benzoyl peroxide	124	(95.4)	3	(2.3)	3	(2.3)	130
	Ery. + BP bd	125	(98.4)	0	(0)	2	(1.6)	127
	Ery. od + BP od	128	(97.7)	2	(1.5)	1	(0.8)	131
12	Oxytetracycline	127	(97.7)	2	(1.5)	1	(0.8)	130
	Minocycline	129	(99.2)	1	(0.8)	0	(0)	130
	Benzoyl peroxide	121	(93.1)	4	(3.1)	5	(3.8)	130
	Ery. + BP bd	124	(97.6)	1	(0.8)	2	(1.6)	127
	Ery. od + BP od	128	(97.7)	2	(1.5)	1	(0.8)	131
18	Oxytetracycline	130	(100)	0	(0)	0	(0)	130
	Minocycline	130	(100)	0	(0)	0	(0)	130
	Benzoyl peroxide	122	(93.8)	3	(2.3)	5	(3.8)	130
	Ery. + BP bd	124	(97.6)	0	(0)	3	(2.4)	127
	Ery. od + BP od	128	(97.7)	2	(1.5)	1	(0.8)	131

Data are shown as *n* (%).

TABLE 150 *Summary of participant assessment of moderate and severe dryness*

Week	Treatment group	None or mild		Moderate		Severe		All
0	Oxytetracycline	108	(83.1)	21	(16.2)	1	(0.8)	130
	Minocycline	110	(84.6)	19	(14.6)	1	(0.8)	130
	Benzoyl peroxide	101	(77.7)	29	(22.3)	0	(0)	130
	Ery. + BP bd	102	(80.3)	24	(18.9)	1	(0.8)	127
	Ery. od + BP od	107	(81.7)	21	(16.0)	3	(2.3)	131
0–2	Oxytetracycline	108	(83.1)	20	(15.4)	2	(1.5)	130
	Minocycline	112	(86.2)	13	(10.0)	5	(3.8)	130
	Benzoyl peroxide	60	(46.2)	49	(37.7)	21	(16.2)	130
	Ery. + BP bd	69	(54.3)	48	(37.8)	10	(7.9)	127
	Ery. od + BP od	78	(59.5)	40	(30.5)	13	(9.9)	131
2–4	Oxytetracycline	116	(89.2)	14	(10.8)	0	(0)	130
	Minocycline	119	(91.5)	10	(7.7)	1	(0.8)	130
	Benzoyl peroxide	89	(68.5)	33	(25.4)	8	(6.2)	130
	Ery. + BP bd	91	(71.7)	34	(26.8)	2	(1.6)	127
	Ery. od + BP od	101	(77.1)	20	(15.3)	10	(7.6)	131
4–6	Oxytetracycline	124	(95.4)	6	(4.6)	0	(0)	130
	Minocycline	117	(90.0)	12	(9.2)	1	(0.8)	130
	Benzoyl peroxide	99	(76.2)	24	(18.5)	7	(5.4)	130
	Ery. + BP bd	107	(84.3)	18	(14.2)	2	(1.6)	127
	Ery. od + BP od	111	(84.7)	16	(12.2)	4	(3.1)	131
12	Oxytetracycline	118	(90.8)	12	(9.2)	0	(0)	130
	Minocycline	118	(90.8)	12	(9.2)	0	(0)	130
	Benzoyl peroxide	102	(78.5)	19	(14.6)	9	(6.9)	130
	Ery. + BP bd	100	(78.7)	25	(19.7)	2	(1.6)	127
	Ery. od + BP od	110	(84.0)	15	(11.5)	6	(4.6)	131
18	Oxytetracycline	125	(96.2)	5	(3.8)	0	(0)	130
	Minocycline	121	(93.1)	9	(6.9)	0	(0)	130
	Benzoyl peroxide	102	(78.5)	22	(16.9)	6	(4.6)	130
	Ery. + BP bd	106	(83.5)	20	(15.7)	1	(0.8)	127
	Ery. od + BP od	111	(84.7)	15	(11.5)	5	(3.8)	131

Data are shown as *n* (%).

TABLE 151 *Summary of participant assessment of moderate and severe erythema*

Week	Treatment group	None or mild		Moderate		Severe		All
0	Oxytetracycline	69	(53.1)	50	(38.5)	11	(8.5)	130
	Minocycline	74	(56.9)	46	(35.4)	10	(7.7)	130
	Benzoyl peroxide	77	(59.2)	44	(33.8)	9	(6.9)	130
	Ery. + BP bd	70	(55.1)	50	(39.4)	7	(5.5)	127
	Ery. od + BP od	72	(55.0)	52	(39.7)	7	(5.3)	131
0–2	Oxytetracycline	100	(76.9)	26	(20.0)	4	(3.1)	130
	Minocycline	96	(73.8)	29	(22.3)	5	(3.8)	130
	Benzoyl peroxide	73	(56.2)	37	(28.5)	20	(15.4)	130
	Ery. + BP bd	94	(74.0)	27	(21.3)	6	(4.7)	127
	Ery. od + BP od	93	(71.0)	25	(19.1)	13	(9.9)	131
2–4	Oxytetracycline	109	(83.8)	19	(14.6)	2	(1.5)	130
	Minocycline	105	(80.8)	24	(18.5)	1	(0.8)	130
	Benzoyl peroxide	93	(71.5)	27	(20.8)	10	(7.7)	130
	Ery. + BP bd	108	(85.0)	17	(13.4)	2	(1.6)	127
	Ery. od + BP od	107	(81.7)	18	(13.7)	6	(4.6)	131
4–6	Oxytetracycline	115	(88.5)	13	(10.0)	2	(1.5)	130
	Minocycline	111	(85.4)	19	(14.6)	0	(0)	130
	Benzoyl peroxide	104	(80.0)	18	(13.8)	8	(6.2)	130
	Ery. + BP bd	117	(92.1)	8	(6.3)	2	(1.6)	127
	Ery. od + BP od	116	(88.5)	10	(7.6)	5	(3.8)	131
12	Oxytetracycline	106	(81.5)	19	(14.6)	5	(3.8)	130
	Minocycline	109	(83.8)	21	(16.2)	0	(0)	130
	Benzoyl peroxide	100	(76.9)	19	(14.6)	11	(8.5)	130
	Ery. + BP bd	112	(88.2)	12	(9.4)	3	(2.4)	127
	Ery. od + BP od	113	(86.3)	13	(9.9)	5	(3.8)	131
18	Oxytetracycline	109	(83.8)	17	(13.1)	4	(3.1)	130
	Minocycline	107	(82.3)	22	(16.9)	1	(0.8)	130
	Benzoyl peroxide	103	(79.2)	18	(13.8)	9	(6.9)	130
	Ery. + BP bd	105	(82.7)	21	(16.5)	1	(0.8)	127
	Ery. od + BP od	111	(84.7)	14	(10.7)	6	(4.6)	131

Data are shown as *n* (%).

TABLE 152 *Summary of participant assessment of moderate and severe scale*

Week	Treatment group	None or mild		Moderate		Severe		All
0	Oxytetracycline	112	(86.2)	17	(13.1)	1	(0.8)	130
	Minocycline	116	(89.2)	13	(10.0)	1	(0.8)	130
	Benzoyl peroxide	119	(91.5)	11	(8.5)	0	(0)	130
	Ery. + BP bd	108	(85.0)	18	(14.2)	1	(0.8)	127
	Ery. od + BP od	118	(90.1)	12	(9.2)	1	(0.8)	131
0–2	Oxytetracycline	119	(91.5)	10	(7.7)	1	(0.8)	130
	Minocycline	124	(95.4)	5	(3.8)	1	(0.8)	130
	Benzoyl peroxide	95	(73.1)	25	(19.2)	10	(7.7)	130
	Ery. + BP bd	102	(80.3)	24	(18.9)	1	(0.8)	127
	Ery. od + BP od	109	(83.2)	18	(13.7)	4	(3.1)	131
2–4	Oxytetracycline	125	(96.2)	5	(3.8)	0	(0)	130
	Minocycline	128	(98.5)	2	(1.5)	0	(0)	130
	Benzoyl peroxide	114	(87.7)	14	(10.8)	2	(1.5)	130
	Ery. + BP bd	112	(88.2)	14	(11.0)	1	(0.8)	127
	Ery. od + BP od	117	(89.3)	9	(6.9)	5	(3.8)	131
4–6	Oxytetracycline	127	(97.7)	3	(2.3)	0	(0)	130
	Minocycline	128	(98.5)	2	(1.5)	0	(0)	130
	Benzoyl peroxide	117	(90.0)	10	(7.7)	3	(2.3)	130
	Ery. + BP bd	117	(92.1)	8	(6.3)	2	(1.6)	127
	Ery. od + BP od	120	(91.6)	8	(6.1)	3	(2.3)	131
12	Oxytetracycline	123	(94.6)	7	(5.4)	0	(0)	130
	Minocycline	126	(96.9)	4	(3.1)	0	(0)	130
	Benzoyl peroxide	116	(89.2)	10	(7.7)	4	(3.1)	130
	Ery. + BP bd	117	(92.1)	9	(7.1)	1	(0.8)	127
	Ery. od + BP od	120	(91.6)	9	(6.9)	2	(1.5)	131
18	Oxytetracycline	126	(96.9)	4	(3.1)	0	(0)	130
	Minocycline	125	(96.2)	5	(3.8)	0	(0)	130
	Benzoyl peroxide	120	(92.3)	8	(6.2)	2	(1.5)	130
	Ery. + BP bd	119	(93.7)	7	(5.5)	1	(0.8)	127
	Ery. od + BP od	122	(93.1)	8	(6.1)	1	(0.8)	131

Data are shown as *n* (%).

TABLE 153 *Summary of participant assessment of moderate and severe itching*

Week	Treatment group	None or mild		Moderate		Severe		All
0	Oxytetracycline	107	(82.3)	17	(13.1)	6	(4.6)	130
	Minocycline	106	(81.5)	23	(17.7)	1	(0.8)	130
	Benzoyl peroxide	104	(80.0)	19	(14.6)	7	(5.4)	130
	Ery. + BP bd	107	(84.3)	19	(15.0)	1	(0.8)	127
	Ery. od + BP od	111	(84.7)	17	(13.0)	3	(2.3)	131
0–2	Oxytetracycline	123	(94.6)	6	(4.6)	1	(0.8)	130
	Minocycline	115	(88.5)	14	(10.8)	1	(0.8)	130
	Benzoyl peroxide	104	(80.0)	15	(11.5)	11	(8.5)	130
	Ery. + BP bd	104	(81.9)	20	(15.7)	3	(2.4)	127
	Ery. od + BP od	109	(83.2)	16	(12.2)	6	(4.6)	131
2–4	Oxytetracycline	127	(97.7)	2	(1.5)	1	(0.8)	130
	Minocycline	122	(93.8)	8	(6.2)	0	(0)	130
	Benzoyl peroxide	117	(90.0)	11	(8.5)	2	(1.5)	130
	Ery. + BP bd	116	(91.3)	8	(6.3)	3	(2.4)	127
	Ery. od + BP od	123	(93.9)	6	(4.6)	2	(1.5)	131
4–6	Oxytetracycline	126	(96.9)	3	(2.3)	1	(0.8)	130
	Minocycline	122	(93.8)	7	(5.4)	1	(0.8)	130
	Benzoyl peroxide	120	(92.3)	8	(6.2)	2	(1.5)	130
	Ery. + BP bd	117	(92.1)	7	(5.5)	3	(2.4)	127
	Ery. od + BP od	125	(95.4)	4	(3.1)	2	(1.5)	131
12	Oxytetracycline	119	(91.5)	9	(6.9)	2	(1.5)	130
	Minocycline	123	(94.6)	6	(4.6)	1	(0.8)	130
	Benzoyl peroxide	115	(88.5)	11	(8.5)	4	(3.1)	130
	Ery. + BP bd	120	(94.5)	6	(4.7)	1	(0.8)	127
	Ery. od + BP od	123	(93.9)	5	(3.8)	3	(2.3)	131
18	Oxytetracycline	122	(93.8)	5	(3.8)	3	(2.3)	130
	Minocycline	122	(93.8)	8	(6.2)	0	(0)	130
	Benzoyl peroxide	121	(93.1)	7	(5.4)	2	(1.5)	130
	Ery. + BP bd	118	(92.9)	7	(5.5)	2	(1.6)	127
	Ery. od + BP od	120	(91.6)	7	(5.3)	4	(3.1)	131

Data are shown as *n* (%).

TABLE 154 *Summary of assessor assessment of moderate and severe dryness*

Week	Treatment group	None or mild		Moderate		Severe		All
0	Oxytetracycline	106	(80.9)	25	(19.1)	0	(0)	131
	Minocycline	116	(89.2)	14	(10.8)	0	(0)	130
	Benzoyl peroxide	110	(84.6)	20	(15.4)	0	(0)	130
	Ery. + BP bd	116	(91.3)	11	(8.7)	0	(0)	127
	Ery. od + BP od	114	(87.0)	17	(13.0)	0	(0)	131
6	Oxytetracycline	118	(90.1)	13	(9.9)	0	(0)	131
	Minocycline	119	(91.5)	11	(8.5)	0	(0)	130
	Benzoyl peroxide	94	(72.3)	35	(26.9)	1	(0.8)	130
	Ery. + BP bd	94	(74.0)	33	(26.0)	0	(0)	127
	Ery. od + BP od	108	(82.4)	21	(16.0)	2	(1.5)	131
12	Oxytetracycline	116	(88.5)	15	(11.5)	0	(0)	131
	Minocycline	118	(90.8)	12	(9.2)	0	(0)	130
	Benzoyl peroxide	103	(79.2)	27	(20.8)	0	(0)	130
	Ery. + BP bd	104	(81.9)	23	(18.1)	0	(0)	127
	Ery. od + BP od	112	(85.5)	17	(13.0)	2	(1.5)	131
18	Oxytetracycline	121	(92.4)	10	(7.6)	0	(0)	131
	Minocycline	118	(90.8)	12	(9.2)	0	(0)	130
	Benzoyl peroxide	104	(80.0)	25	(19.2)	1	(0.8)	130
	Ery. + BP bd	108	(85.0)	19	(15.0)	0	(0)	127
	Ery. od + BP od	117	(89.3)	13	(9.9)	1	(0.8)	131

Data are shown as *n* (%).

TABLE 155 *Summary of assessor assessment of moderate and severe erythema*

Week	Treatment group	None or mild		Moderate		Severe		All
0	Oxytetracycline	89	(67.9)	40	(30.5)	2	(1.5)	131
	Minocycline	83	(63.8)	42	(32.3)	5	(3.8)	130
	Benzoyl peroxide	85	(65.4)	41	(31.5)	4	(3.1)	130
	Ery. + BP bd	92	(72.4)	33	(26.0)	2	(1.6)	127
	Ery. od + BP od	92	(70.2)	37	(28.2)	2	(1.5)	131
6	Oxytetracycline	111	(84.7)	18	(13.7)	2	(1.5)	131
	Minocycline	104	(80.0)	25	(19.2)	1	(0.8)	130
	Benzoyl peroxide	96	(73.8)	32	(24.6)	2	(1.5)	130
	Ery. + BP bd	107	(84.3)	20	(15.7)	0	(0)	127
	Ery. od + BP od	108	(82.4)	22	(16.8)	1	(0.8)	131
12	Oxytetracycline	102	(77.9)	23	(17.6)	6	(4.6)	131
	Minocycline	106	(81.5)	23	(17.7)	1	(0.8)	130
	Benzoyl peroxide	99	(76.2)	27	(20.8)	4	(3.1)	130
	Ery. + BP bd	113	(89.0)	14	(11.0)	0	(0)	127
	Ery. od + BP od	111	(84.7)	19	(14.5)	1	(0.8)	131
18	Oxytetracycline	104	(79.4)	24	(18.3)	3	(2.3)	131
	Minocycline	109	(83.8)	18	(13.8)	3	(2.3)	130
	Benzoyl peroxide	104	(80.0)	22	(16.9)	4	(3.1)	130
	Ery. + BP bd	106	(83.5)	20	(15.7)	1	(0.8)	127
	Ery. od + BP od	114	(87.0)	15	(11.5)	2	(1.5)	131

Data are shown as *n* (%).

TABLE 156 *Summary of assessor assessment of moderate and severe scale*

Week	Treatment group	None or mild		Moderate		Severe		All
0	Oxytetracycline	126	(96.2)	5	(3.8)	0	(0)	131
	Minocycline	124	(95.4)	6	(4.6)	0	(0)	130
	Benzoyl peroxide	124	(95.4)	6	(4.6)	0	(0)	130
	Ery. + BP bd	121	(95.3)	6	(4.7)	0	(0)	127
	Ery. od + BP od	121	(93.1)	9	(6.9)	0	(0)	130
6	Oxytetracycline	129	(98.5)	2	(1.5)	0	(0)	131
	Minocycline	128	(98.5)	2	(1.5)	0	(0)	130
	Benzoyl peroxide	116	(89.2)	12	(9.2)	2	(1.5)	130
	Ery. + BP bd	118	(92.9)	9	(7.1)	0	(0)	127
	Ery. od + BP od	120	(92.3)	10	(7.7)	0	(0)	130
12	Oxytetracycline	128	(97.7)	3	(2.3)	0	(0)	131
	Minocycline	126	(96.9)	4	(3.1)	0	(0)	130
	Benzoyl peroxide	118	(90.8)	12	(9.2)	0	(0)	130
	Ery. + BP bd	118	(92.9)	9	(7.1)	0	(0)	127
	Ery. od + BP od	121	(93.1)	9	(6.9)	0	(0)	130
18	Oxytetracycline	127	(96.9)	4	(3.1)	0	(0)	131
	Minocycline	123	(94.6)	7	(5.4)	0	(0)	130
	Benzoyl peroxide	117	(90.0)	13	(10.0)	0	(0)	130
	Ery. + BP bd	118	(92.9)	9	(7.1)	0	(0)	127
	Ery. od + BP od	126	(96.9)	4	(3.1)	0	(0)	130

Data are shown as *n* (%).

TABLE 157 *Mean changes from baseline (and standard deviations) for overall irritation scores*

		Week				
	Treatment group	0–2	2–4	4–6	12	18
Patient index (max. = 18)	Oxytetracycline	–1.3 (2.94)	–2.2 (2.85)	–2.6 (2.67)	–1.7 (2.77)	–2.2 (2.67)
	Minocycline	–1.1 (2.79)	–1.9 (2.66)	–2.1 (2.74)	–2.0 (2.44)	–2.1 (2.68)
	Benzoyl peroxide	1.8 (4.46)	–0.3 (3.65)	–1.0 (3.36)	–0.5 (3.64)	–0.9 (3.51)
	Ery. + BP bd	0.5 (3.30)	–0.8 (2.88)	–1.6 (2.92)	–1.3 (2.94)	–1.6 (2.86)
	Ery. od + BP od	0.9 (3.68)	–0.8 (3.33)	–1.6 (3.14)	–1.3 (3.09)	–1.5 (3.27)
Assessor index (max. = 9)	Oxytetracycline	–	–	–0.6 (1.55)	–0.4 (1.49)	–0.7 (1.52)
	Minocycline	–	–	–0.5 (1.27)	–0.5 (1.53)	–0.7 (1.65)
	Benzoyl peroxide	–	–	0.2 (1.45)	–0.0 (1.56)	–0.3 (1.75)
	Ery. + BP bd	–	–	0.1 (1.39)	–0.1 (1.49)	–0.3 (1.80)
	Ery. od + BP od	–	–	–0.3 (1.53)	–0.4 (1.68)	–0.8 (1.77)
Patient index (max. = 9)	Oxytetracycline	–1.0 (1.99)	–1.4 (1.90)	–1.8 (1.75)	–1.2 (1.88)	–1.5 (1.79)
	Minocycline	–0.8 (1.87)	–1.3 (1.78)	–1.5 (1.86)	–1.4 (1.69)	–1.4 (1.83)
	Benzoyl peroxide	1.0 (2.43)	–0.2 (2.05)	–0.5 (1.94)	–0.4 (2.09)	–0.5 (2.01)
	Ery. + BP bd	0.1 (2.10)	–0.6 (1.95)	–1.2 (2.00)	–0.8 (1.98)	–1.1 (1.98)
	Ery. od + BP od	0.3 (2.18)	–0.5 (2.07)	–1.0 (1.89)	–0.9 (1.99)	–1.0 (2.01)

The assessor index was not recorded at weeks 0–2 and 2–4. Numbers per treatment groups were 130, 130, 130, 127 and 131, respectively.

Appendix 18

Discontinued treatment groups

Baseline characteristics

These were similar between the six groups (*Table 158*). Most baseline characteristics were similar to the five main groups, except that the proportions of fair and medium complexion were reversed, and virtually all participants had previously had prescription medicines (these groups did not include recruitment from colleges).

TABLE 158 *Baseline characteristics for discontinued groups*

Characteristic	*n*	Mean	SD	Range
Age (years)	112	18.9	6.18	12–39
BMI (kg/m^2)	111	22.3	2.89	16–36
Age of onset (years)	112	13.4	2.89	7–24
Duration of acne (years)	112	5.6	5.15	0–26
Time since sought help (years)	109	3.7	4.26	0.2–24
Baseline severity (B&C grade)	111	0.91	0.734	0.1–3.0

Gender	53 (47.3%) Male	59 (52.7%) Female		
Ethnic group	105 (95.5%) Caucasian	4 (3.6%) Asian	1 (0.9%) Afro-Caribbean	0 other
Skin complexion	32 (29.4%) Fair	73 (67.0%) Medium	4 (3.7%) Dark	
Other acne affected site(s)	18 (16.1%) Neck	71 (63.4%) Back	35 (31.3%) Chest	8 (7.1%) Other
Family history	77 (69%) Yes	35 (31%) No		
Previous treatment	94 (83.9%) OTC	108 (96.4%) Prescription	75 (67.0%) Oral	99 (88.4%) Topical

	Numbers of participants with and without baseline propionibacteria resistant to:					
	Erythromycin		Tetracycline		Clindamycin	
Treatment group	Without	With	Without	With	Without	With
Erythromycin	8	11	16	3	9	10
Top. erythromycin	8	12	15	5	8	12
Clindamycin	7	11	15	3	9	9
Ery. + zinc acetate	9	9	15	3	10	8
Tetracycline + oxtet.	11	9	15	5	12	8
BP + oxytet.	10	7	16	1	10	7
All	53	59	92	20	58	54

n = 112; data are missing for some participants.

Some imbalance of baseline characteristics may be due to small numbers per group. There were some gender imbalances between groups (two-thirds of topical erythromycin and BP + oxytet groups and one-third of clindamycin group are female).

The majority (91%) of participants answered 'yes' to the question 'are you fit and healthy?'. *Table 159* gives details for those who answered 'no', none of which is considered serious. No participants reported liver, kidney or heart problems. One participant reported other serious disease: diabetes and asthma. Twenty-four participants (21%) reported sensitivities or allergies, the details of which are given in *Table 160*.

TABLE 159 *Discontinued groups: fit and healthy at baseline*

Treatment group	Patient	Fit?	Details
Erythromycin	0326	No	Mild sore throat – no medication as it is going now
	0354	No	Has asthma (mild) for which he uses Ventolin inhaler about 4 × a week
	0372	No	Sore throat & blocked left ear, otherwise fit & well
Top. erythromycin	0163	No	On some days gets breathless due to hayfever
Clindamycin	0211	No	Hurt back, seeing physio. Hopes to be discharged in 2 weeks
Ery. + zinc acetate	0349	No	Currently has dislocated right elbow 6.9.98 fell off rope attached to tree. No current medication for this. In cast – to be removed hopefully 1.10.98
Tetracycline + oxytet.	0203	No	?Sinuses, difficulty breathing. Hurt back at work 1 week, on osteotherapy
	0330	No	Asthma, irritable bowel syndrome, depression
	0356	No	He has asthma for which he uses inhalers
BP + oxytet.	0027	No	Back pain
	0172	Yes	(Reasonably so)
	0239	Yes	Thinks might have a 'stomach bug'. No diarrhoea, not taking any meds yet

Details are printed from the database and are as reported by the participant.

TABLE 160 *Discontinued groups: details of sensitivities at baseline*

Treatment group	Patient	No.	Sensitivity	Treatment received for sensitivity?	Date treatment stopped
Erythromycin	0025	1	Asthma	Yes	.
	0171	1	Minocin MR (acne)	Yes	09/09/97
	0195	1	Penicillin	.	.
	0216	1	Co-codamol	Yes	24/03/98
	0348	1	Penicillin allergy	.	.
Top. erythromycin	0163	1	Hayfever allergy	Yes	15/05/98
	0169	1	Unspecified allergy during holidays	Yes	08/07/98
	0181	1	Biactol (rash in nose area)	.	12/09/95
	0329	1	Amitriptylline	.	.
Clindamycin	0029	1	Grass causes itching	.	.
		2	Nylon – contact allergy	.	.
	0043	1	Penicillin	.	.
Ery. + zinc acetate	0186	1	Hayfever	Yes	.
	0207	1	Penicillin	Yes	18/09/94
	0213	1	Cannot remember the tablets. It was ages ago	.	.
	0231	1	Paracetamol	.	.
	0331	1	Dust	.	.
	0357	1	(Septrin) Cotrimoxazole	.	.
Tetracycline + oxytet.	0011	1	Penicillin	No	.
	0014	1	Penicillin	No	.
	0203	1	Penicillin	.	.
		2	Most antibiotics tend to cause stomach cramps	.	.
	0235	1	Ibuprofen	.	.
	0252	1	Penicillin	.	.
BP + oxytet.	0045	1	Aspirin	.	.
	0247	1	Thrush, antibiotics	Yes	26/11/93

Details are printed from the database and are as reported by the participant.

Half of the participants thought there was something that made their acne worse. When specifically asked, 62% of females reported premenstrual flare of acne. Ninety-three per cent of participants reported some degree of facial oiliness, with 24% very oily. For those with oily faces, 62% were bothered by it, but only 11% were extremely bothered.

Numbers analysed

ITT numbers analysed were 19, 20, 18, 18, 20, 17 in the erythromycin, topical erythromycin, clindamycin, erythromycin + zinc acetate, tetracycline + oxytetracycline and benzoyl peroxide + oxytetracycline groups, respectively. Since numbers in all these groups were very small, presentation of these data should be considered in an exploratory fashion.

Patient global assessment of facial acne

In all but the erythromycin and clindamycin groups, maximum improvement was seen at week 18 (*Table 161*). The erythromycin improvement rate was particularly low compared with all of the other ten groups in the study. Improvement in all but the clindamycin and ery. + zinc acetate groups was lower at week 6 compared with the main five treatment groups.

TABLE 161 *Discontinued groups: percentage of participants rating their facial acne as at least moderately improved*

Treatment group	Week			95% CI	Rank
	6	12	18		
Erythromycin	26.3	36.8	31.6	(10.7 to 52.5)	6
Top. erythromycin	20.0	45.0	55.0	(33.2 to 76.8)	2
Clindamycin	44.4	38.9	44.4	(21.4 to 67.4)	5
Ery. + zinc acetate	44.4	44.4	50.0	(26.9 to 73.1)	=3
Tetracycline + oxytet.	30.0	45.0	50.0	(28.1 to 71.9)	=3
BP + oxytet.	35.3	41.2	58.8	(35.4 to 82.2)	1

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately, not treatment comparisons.

Facial inflamed lesion counts

TABLE 162 *Discontinued groups: mean inflamed lesion counts*

Treatment group	Week					LSmean 95% CI	Rank
	0	6	12	18	18–0		
Erythromycin	57.2	51.8	48.7	44.3	–12.9	–8.3 (–17.5 to 0.9)	6
Top. erythromycin	46.7	35.4	32.7	28.9	–17.8	–19.0 (–28.0 to –9.9)	3
Clindamycin	41.3	34.6	29.6	29.3	–12.1	–17.7 (–27.3 to –8.2)	4
Ery. + zinc acetate	53.6	47.9	35.8	31.2	–22.4	–20.0 (–29.4 to –10.6)	2
Tetracycline + oxytet.	46.8	48.3	40.7	37.6	–9.2	–10.6 (–19.6 to –1.7)	5
B.P. + oxytet.	48.8	33.1	29.4	26.8	–22.1	–20.6 (–30.3 to –10.9)	1

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately, not treatment comparisons.

At baseline the majority (100 or 89%) of participants were nodule free. Using ITT data, there was little change in numbers of participants with nodules throughout the study in any group. Of those with nodules (24 at some time in the study) most only had one nodule, a few had two or three and only two

participants had four nodules at any time in the study. Of the participants with nodules, 13/24 completed the study. Of the 11 withdrawals, four were known to be due to exacerbation of acne (two in the erythromycin group, week 12; one in clindamycin group, week 18; and one in the BP + oxytetracycline group, week 12). A further participant in the BP + oxytet. group withdrew at week 6 owing to facial skin irritation, despite reducing application of the topical to once a day.

Burke and Cunliffe facial acne grade

An improvement in grade over time was seen in all treatment groups.

TABLE 163 *Discontinued groups: mean Burke and Cunliffe grade*

Treatment group	Week					LSmean 95% CI	Rank
	0	6	12	18	18–0		
Erythromycin	0.924	0.913	0.866	0.779	–0.145	–0.132 (–0.345 to 0.080)	6
Top. erythromycin	1.000	0.778	0.663	0.583	–0.418	–0.355 (–0.565 to –0.144)	4
Clindamycin	0.885	0.691	0.571	0.497	–0.367	–0.405 (–0.636 to –0.175)	2
Ery. + zinc acetate	1.056	0.889	0.692	0.594	–0.461	–0.368 (–0.587 to –0.149)	3
Tetracycline + oxytet.	0.858	0.743	0.730	0.640	–0.218	–0.256 (–0.465 to –0.047)	5
BP + oxytet.	0.691	0.621	0.488	0.391	–0.300	–0.424 (–0.651 to –0.196)	1

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately, not treatment comparisons.

Assessor global assessment of facial acne

TABLE 164 *Discontinued groups: percentage of participants with at least moderate improvement in facial acne severity according to the assessor*

Treatment group	Week				Rank
	6	12	18	95% CI	
Erythromycin	5.3	26.3	26.3	16.2 to 36.4	6
Top. erythromycin	30.0	45.0	40.0	29.0 to 51.0	3
Clindamycin	33.3	33.3	38.9	27.4 to 50.4	4
Ery. + zinc acetate	22.2	50.0	33.3	22.2 to 44.4	5
Tetracycline + oxytet.	20.0	25.0	50.0	38.8 to 61.2	2
BP + oxytet.	23.5	52.9	64.7	53.1 to 76.3	1

Maximum improvement was seen at week 12 in the erythromycin, topical erythromycin and ery. + zinc acetate groups, and at week 18 in the other groups (1) (*Table 164*). The erythromycin improvement rate was low compared with all of the other ten groups in the study, particularly at week 6. Improvement in all groups was lower at week 6 compared with the main five treatment groups.

CASS

The CASS improved over time for all treatment groups.

TABLE 165 *Discontinued groups: mean CASS*

Treatment group	Week					LSmean 95% CI	Rank
	0	6	12	18	18–0		
Erythromycin	21.3	18.6	17.7	17.5	–3.8	–3.1 (–6.3 to 0.1)	6
Top. erythromycin	20.4	15.8	13.6	12.3	–8.1	–8.0 (–11.2 to –4.9)	1
Clindamycin	19.3	14.7	13.3	13.2	–6.1	–6.6 (–10.0 to –3.3)	3
Ery. + zinc acetate	22.7	19.3	16.0	14.8	–7.8	–6.2 (–9.5 to –2.9)	4
Tetracycline + oxytet.	18.3	18.2	16.9	15.5	–2.8	–4.5 (–7.6 to –1.3)	5
BP + oxytet.	19.5	15.1	11.9	12.4	–7.1	–7.1 (–10.5 to –3.7)	2

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately, not treatment comparisons.

DLQI

The numbers analysed in each group were 12, 13, 14, 8, 15 and 10, respectively. There was a small improvement in the total DLQI score for all but the erythromycin group (*Table 166*).

TABLE 166 *Discontinued groups: mean total DLQI*

Treatment group	Week					LSmean 95% CI	Rank
	0	6	12	18	18–0		
Erythromycin	3.4	2.9	3.7	3.9	0.5	0.4 (–1.0 to 1.8)	6
Top. erythromycin	2.9	2.2	2.2	2.1	–0.8	–2.1 (–3.6 to –0.5)	1
Clindamycin	5.4	4.2	4.7	4.9	–0.5	–0.8 (–2.2 to 0.6)	5
Ery. + zinc acetate	4.5	3.6	3.0	2.3	–2.3	–2.0 (–3.7 to –0.3)	2
Tetracycline + oxytet.	2.8	2.6	1.7	1.7	–1.1	–1.5 (–3.0 to –0.0)	=3
BP + oxytet.	5.7	4.1	4.3	2.8	–2.9	–1.5 (–3.0 to 0.1)	=3

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately, not treatment comparisons.

CDLQI

The numbers analysed in each group were 8, 8, 7, 11, 8 and 8, respectively. There was a small improvement in the total CDLQI score for all groups (*Table 167*).

TABLE 167 *Discontinued groups: mean total CDLQI*

Treatment group	Week					LSmean	Rank
	0	6	12	18	18–0		
Erythromycin	3.0	1.8	2.3	2.3	–0.8	–1.1 (–2.8 to 0.6)	5
Top. erythromycin	5.4	3.8	4.0	3.1	–2.3	–1.3 (–3.0 to 0.5)	4
Clindamycin	4.4	3.9	3.3	3.1	–1.3	–1.0 (–2.8 to 0.9)	6
Ery. + zinc acetate	2.2	1.5	1.4	1.4	–0.5	–1.4 (–3.0 to 0.1)	3
Tetracycline + oxytet.	3.3	2.6	2.8	2.4	–0.9	–1.6 (–3.4 to 0.1)	2
BP + oxytet.	5.5	3.0	2.3	1.6	–3.9	–2.7 (–4.5 to –1.0)	1

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately, not treatment comparisons.

DQOLS

For all three DQOL scales n = 19, 20, 18, 18, 20, 17 for the treatment groups; the remaining participants did not have DQOLS data at any visit.

Psychosocial scale

There was improvement in the DQOL psychosocial scale by week 6, then little change for remaining weeks (*Table 168*).

TABLE 168 *Discontinued groups: mean DQOL psychosocial scale*

Treatment group	Week					LSmean 95% CI	Rank
	0	6	12	18	18–0		
Erythromycin	23.1	14.6	14.5	15.7	–7.4	–8.3 (–14.0 to –2.7)	4
Top. erythromycin	26.6	19.9	16.8	15.8	–10.8	–10.0 (–15.6 to –4.5)	3
Clindamycin	30.7	22.6	27.0	23.5	–7.2	–7.3 (–13.2 to –1.3)	5
Ery. + zinc acetate	17.6	13.6	12.7	14.7	–2.9	–6.0 (–12.2 to 0.3)	6
Tetracycline + oxytet.	22.1	12.7	12.4	11.9	–10.2	–11.8 (–17.5 to –6.1)	2
BP + oxytet.	33.8	22.5	17.1	15.7	–18.2	–12.5 (–18.7 to –6.3)	1

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately, not treatment comparisons.

Medians are also given in *Table 169*, as raw data are not normally distributed (although differences from baseline are close enough to a normal distribution).

TABLE 169 *Discontinued groups: median DQOL psychosocial scale*

Treatment group	Week				
	0	6	12	18	18–0
Erythromycin	13.2	8.8	8.8	8.8	–5.9
Top. erythromycin	20.6	12.5	9.6	9.6	–8.8
Clindamycin	14.7	11.8	11.8	10.3	–5.9
Ery. + zinc acetate	8.1	5.9	5.9	7.4	–1.5
Tetracycline + oxytet.	18.4	11.0	9.6	9.6	–10.3
BP + oxytet.	20.6	10.3	8.8	10.3	–2.9

Activities scale

Activity scores were low at baseline, as expected for healthy young people. There was a small improvement in mean scores post week 0, the largest improvement being in the BP + oxytet. group (*Table 170*).

TABLE 170 *Discontinued groups: mean DQOL activities scale*

Treatment group	Week					LSmean 95% CI	Rank
	0	6	12	18	18–0		
Erythromycin	9.3	5.6	6.7	6.9	–2.4	–3.4 (–7.2 to 0.4)	5
Top. erythromycin	9.4	7.2	5.6	4.6	–4.8	–5.1 (–8.8 to –1.3)	3
Clindamycin	16.9	11.6	11.5	10.8	–6.1	–3.1 (–7.2 to 0.9)	6
Ery. + zinc acetate	6.0	5.3	5.2	5.4	–0.6	–3.6 (–7.6 to 0.3)	4
Tetracycline + oxytet.	9.0	4.5	5.3	3.9	–5.1	–6.3 (–10.0 to –2.5)	2
BP + oxytet.	15.3	6.0	7.0	4.3	–11.0	–8.2 (–12.3 to –4.2)	1

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately, not treatment comparisons.

Medians are also given in *Table 171*, as raw data do not appear to be normally distributed (although differences from baseline are close enough to a normal distribution to use ANOVA).

TABLE 171 *Discontinued groups: median DQOL activities scale*

Treatment group	Week				
	0	6	12	18	18–0
Erythromycin	4.2	2.1	2.1	2.1	0.0
Top. erythromycin	4.2	1.0	2.1	2.1	–2.1
Clindamycin	10.4	4.2	2.1	1.0	–2.1
Ery. + zinc acetate	1.0	1.0	0.0	1.0	0.0
Tetracycline + oxytet.	8.3	2.1	1.0	2.1	–3.1
BP + oxytet.	2.1	0.0	0.0	0.0	0.0

Symptoms scale

The majority of the improvement in the DQOL symptom scale occurred by week 6, although mean counts for all groups improved further at week 12 (*Table 172*). It was perhaps surprising that the mean symptom score did not increase at week 6, as a result of side-effects, compared with baseline.

TABLE 172 *Discontinued groups: mean DQOL symptoms scale*

Treatment group	Week					LSmean 95% CI	Rank
	0	6	12	18	18–0		
Erythromycin	22.6	15.4	12.4	14.3	–8.3	–9.8 (–16.0 to –3.5)	4
Top. erythromycin	27.4	23.3	19.2	16.6	–10.8	–9.0 (–15.2 to –2.9)	5
Clindamycin	26.4	19.8	19.2	18.5	–7.9	–7.5 (–14.1 to –1.0)	6
Ery. + zinc acetate	20.6	14.1	11.0	10.6	–10.0	–12.7 (–19.1 to –6.2)	1
Tetracycline + oxytet.	21.8	15.8	13.5	13.2	–8.5	–10.0 (–16.2 to –3.9)	3
BP + oxytet.	31.3	24.0	20.7	15.2	–16.1	–12.3 (–19.0 to –5.7)	2

The confidence intervals in this table refer to week 18 changes from baseline for each treatment separately, not treatment comparisons.

Medians are also given in *Table 173*, as raw data are not normally distributed (although differences from baseline are close enough to a normal distribution).

TABLE 173 *Discontinued groups: median DQOL symptoms scale*

Treatment group	Week				
	0	6	12	18	18–0
Erythromycin	18.8	8.3	8.3	10.4	–4.2
Top. erythromycin	22.9	18.8	13.5	12.5	–2.1
Clindamycin	14.6	12.5	9.4	10.4	–5.2
Ery. + zinc acetate	11.5	6.3	3.1	6.3	–6.3
Tetracycline + oxytet.	19.8	11.5	10.4	10.4	–8.3
BP + oxytet.	27.1	18.8	12.5	8.3	–12.5

Utility questionnaires

About half of the participants did not receive question 2 (WTA – cure) at week 0.

TABLE 174 *Discontinued groups: utility questionnaires: median (mean) amount participants were WTP or WTA at baseline and after 18 weeks of treatment*

	Week 0 (£)	
Treatment group (n)	**WTP – cure**	**WTA – cure**
Erythromycin (18, 7)	100 (434)	1000 (3025)
Topical erythromycin (20, 8)	38 (177)	275 (2579)
Clindamycin (16, 2)	75 (757)	3000 (3000)
Ery. + zinc acetate (16, 6)	25 (352)	2550 (3352)
Tetracycline + oxytet. (20, 8)	38 (384)	3000 (4075)
BP + oxytet. (17, 8)	100 (115)	300 (2657)

	Week 18 (£)			
Treatment group (n)	**WTP – treatment received**	**WTA – treatment received**	**WTP – cure**	**WTA – cure**
Erythromycin (9, 9, 8, 7)	100 (706)	1000 (3572)	550 (2675)	1000 (4714)
Topical erythromycin (14, 12, 14, 12)	25 (179)	38 (1363)	300 (431)	750 (3584)
Clindamycin (10, 10, 9, 8)	75 (191)	263 (256)	100 (878)	3000 (4069)
Ery. + zinc acetate (12, 10, 11, 10)	5 (54)	100 (2133)	50 (176)	1000 (4220)
Tetracycline + oxytet. (13, 13, 12, 12)	50 (154)	500 (2247)	300 (459)	1000 (2792)
BP + oxytet. (12, 12, 12, 12)	75 (205)	1000 (4060)	300 (369)	5000 (5292)

Responses in the >£10,000 category have been excluded from the calculations.
Numbers in parentheses after treatment group are *n* for each question.

Worst aspect

TABLE 175 *Discontinued groups: percentage of participants with at least moderate improvement in worst aspect*

Treatment group	Week 18	Rank
Erythromycin	31.6	6
Top. erythromycin	40.0	=3
Clindamycin	38.9	5
Ery. + zinc acetate	55.6	2
Tetracycline + oxytet.	40.0	=3
BP + oxytet.	58.8	1

Adverse events

Overall, 34% of participants in the discontinued groups reported at least one adverse event in the study. The number of participants reporting an adverse event at week 6 was 33/98 (34%) at week 6, decreasing to 9/69 (13%) at week 12 and 10/71 (14%) at week 18. Numbers were similar in each group.

At week 6 the most frequent classification was gastrointestinal (18 participants overall), followed by infections (8), then skin (7). Frequencies were similar between treatment groups.

Withdrawals

TABLE 176 *Discontinued groups: cumulative withdrawal rate (%) by week*

Treatment group	Week			
	0	6	12	18
Erythromycin	0.0	0.0	36.8	52.6
Top. erythromycin	0.0	10.0	20.0	30.0
Clindamycin	0.0	5.6	27.8	44.4
Ery. + zinc acetate	0.0	5.6	11.1	33.3
Tetracycline + oxytet.	0.0	20.0	25.0	35.0
BP + oxytet.	0.0	11.8	23.5	29.4
All	0.0	8.9	24.1	37.5

The overall dropout rate improved later in the study (*Table 176*), which may have been due to the assessors' improved confidence, or may have been due to discontinuing less popular/successful treatment groups, although discontinuation of these treatments was not based on dropout rates or participant preference.

Irritation

The most noticeable change was an increase in overall irritation at 0–2 weeks in the BP + oxytetracycline group, in particular participant-reported burning, dryness, scale and stinging. There was also a transient rise in stinging and burning in the tetracycline + oxytetracycline group, and more dryness in the topical erythromycin group.

Participant-assessed irritation

Stinging increased in all groups at 0–2 weeks, and was back to baseline in all but the tetracycline + oxytet. and BP + oxytet. groups, which returned to baseline by week 18. These latter two groups also had more moderate/severe ratings at week 0–2. Burning showed an increase in the erythromycin and ery. + zinc acetate groups at week 0–2, in the BP + oxytet. groups until 2–4 weeks and in the tetracycline + oxytet. group until week 18. These latter two groups also had more moderate/severe ratings for weeks 0–2.

Dryness decreased in the erythromycin, clindamycin and ery. + zinc acetate groups (probably due to use of moisturiser), and increased in the BP + oxytet. group until week 4–6 with more moderate/severe ratings until week 18.

Erythema decreased in all groups, but less so in the tetracycline + oxytet. and BP + oxytet. groups.

Scale decreased in the clindamycin group over the study, and increased at week 0–2 in the BP + oxytet. group, returning to baseline.

Itching decreased in the clindamycin and tetracycline + oxytet. groups at week 0–2, and in the BP + oxytet. group by week 18.

Assessor appraisal of irritation

Dryness increased in the BP + oxytet. group.

Erythema decreased in all groups, except the BP + oxytet. group, where it increased from week 6, returning to less than baseline by week 18.

Scale was variable in all groups.

Differences between assessor and participant severity rating

For the three categories assessed by both the assessor and participant, the same severity was recorded in 57%, 46% and 60% of cases for dryness, erythema and scale, respectively. The assessor recorded greater severity in 21%, 23% and 15% of cases, and the participant recorded greater severity in 22%, 31% and 25% of cases for dryness, erythema and scale, respectively. The discrepancy was by two or three categories in 4%, 14% and 6% of cases, respectively.

Early withdrawal versus irritation

Greater severity (moderate or severe rating) of erythema and participant-reported scale and itch at week 6 was related to more likelihood of not completing the study.

Worst case analysis of irritation scores

TABLE 177 *Discontinued groups: percentage of participants whose worst case over the study was either moderate or severe*

Treatment group	Assessor			Participant					
	Dryness	Erythema	Scale	Stinging	Burning	Dryness	Erythema	Scale	Itching
Erythromycin	10.5	31.6	15.8	15.8	10.5	21.1	36.8	10.5	21.1
Top. erythromycin	25.0	40.0	20.0	20.0	5.0	30.0	45.0	5.0	25.0
Clindamycin	33.3	33.3	5.6	27.8	5.6	16.7	33.3	5.6	11.1
Ery. + zinc acetate	27.8	33.3	5.6	22.2	11.1	27.8	33.3	11.1	22.2
Tetracycline + oxytet.	5.0	25.0	5.0	40.0	30.0	15.0	40.0	15.0	25.0
BP + oxytet.	29.4	11.8	5.9	52.9	47.1	64.7	70.6	41.2	29.4
Cochran-Mantel-Haenszel test for difference between treatment groups									
p-Value	0.205	0.537	0.463	0.128	0.004	0.014	0.221	0.025	0.854

TABLE 178 *Discontinued groups: mean irritation scores*

		Week					
	Treatment group	0	0–2	2–4	4–6	12	18
Patient index (max. = 18)	Erythromycin	4.2	3.9	3.5	2.7	3.2	3.4
	Top. erythromycin	5.1	4.2	3.6	3.2	3.1	3.4
	Clindamycin	4.5	3.3	3.1	2.7	2.9	2.4
	Ery. + zinc acetate	5.0	3.8	3.5	2.3	2.3	2.9
	Tetracycline + oxytet.	5.6	5.6	4.7	3.9	3.5	3.2
	BP + oxytet.	5.1	7.5	5.5	3.9	4.9	3.9
Assessor index (max. = 9)	Erythromycin	1.8	–	–	2.1	2.1	2.5
	Top. erythromycin	2.2	–	–	2.3	2.1	2.6
	Clindamycin	2.1	–	–	1.9	2.1	1.7
	Ery. + zinc acetate	2.1	–	–	2.1	2.0	1.6
	Tetracycline + oxytet.	2.2	–	–	2.1	1.8	2.0
	BP + oxytet.	1.6	–	–	2.2	1.9	1.6
Patient index (max. = 9)	Erythromycin	3.1	2.1	1.9	1.7	2.2	2.3
	Top. erythromycin	3.5	2.4	2.1	1.9	2.1	2.2
	Clindamycin	2.8	1.8	1.6	1.5	1.9	1.3
	Ery. + zinc acetate	3.5	1.8	2.1	1.7	1.7	2.1
	Tetracycline + oxytet.	3.5	2.3	2.3	2.0	1.8	2.0
	BP + oxytet.	3.5	4.5	3.4	2.7	3.1	2.7

Overall irritation increased above baseline in the BP + oxytet. group in the first 2 weeks, then decreased to less than baseline levels by weeks 4–6 (*Table 178*). There were overall decreases in participant assessed irritation, but little change in assessor rated over time.

Patient global assessment by baseline erythromycin resistance status

Baseline erythromycin resistance was not a statistically significant factor in the analysis of patient global improvement ($p = 0.122$ at week 18, $p = 0.226$ at week 12), but numbers of participants were small (53 in total without resistance and 59 with, i.e. only four or five per treatment group). The only striking difference was between those with and without erythromycin resistance in the clindamycin group: a much higher success rate in those with resistance (both weeks 12 and 18) (*Table 179*).

TABLE 179 *Discontinued groups: percentage of participants rating their acne at least moderately improved, with and without erythromycin resistance at baseline*

	Week 12				Week 18			
Erythromycin resistance:	**Without (*n* = 53)**		**With (*n* = 59)**		**Without (*n* = 53)**		**With (*n* = 59)**	
Treatment group	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**
Erythromycin	37.5	=4	36.4	6	37.5	5	27.3	6
Top. erythromycin	37.5	=4	50.0	2	50.0	=1	58.3	3
Clindamycin	0.0	6	63.6	1	14.3	6	63.6	2
Ery. + zinc acetate	44.4	2	44.4	=3	44.4	4	55.6	=4
Tetracycline + oxytet.	45.5	1	44.4	=3	45.5	3	55.6	=4
BP + oxytet.	40.0	3	42.9	5	50.0	=1	71.4	1

Patient global assessment by baseline tetracycline resistance status

Baseline tetracycline resistance was not a significant factor in the analysis of patient global improvement (week 18 $p = 0.491$, week 12 $p = 0.682$) (*Table 180*). Numbers with tetracycline resistance were very small (one to five per treatment group). Of the three participants with tetracycline resistance at baseline, none was successful on erythromycin.

TABLE 180 *Discontinued groups: percentage of participants rating their acne at least moderately improved, with and without tetracycline resistance at baseline*

	Week 12				Week 18			
Tetracycline resistance:	**Without (*n* = 92)**		**With (*n* = 20)**		**Without (*n* = 92)**		**With (*n* = 20)**	
Treatment group	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**
Erythromycin	43.8	3	0.0	6	37.5	5	0.0	6
Top. erythromycin	46.7	=1	40.0	3	53.3	=2	60.0	=3
Clindamycin	40.0	=4	33.3	=4	33.3	6	100.0	=1
Ery. + zinc acetate	46.7	=1	33.3	=4	53.3	=2	33.3	5
Tetracycline + oxytet.	40.0	=4	60.0	2	46.7	4	60.0	=3
BP + oxytet.	37.5	6	100.0	1	56.3	1	100.0	=1

Patient global assessment by baseline clindamycin resistance status

Baseline clindamycin resistance was not a significant factor in the analysis of patient global improvement (week 18 $p = 0.297$, week 12 $p = 0.821$). There was a higher proportion of successes for those with rather than without clindamycin resistance in the clindamycin group (*Table 181*).

TABLE 181 *Discontinued groups: percentage of participants rating their acne at least moderately improved, with and without clindamycin resistance at baseline*

	Week 12				Week 18			
Clindamycin resistance:	**Without (*n* = 58)**		**With (*n* = 54)**		**Without (*n* = 58)**		**With (*n* = 54)**	
Treatment group	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**
Erythromycin	44.4	3	30.0	6	33.3	5	30.0	6
Top. erythromycin	50.0	=1	41.7	4	50.0	=1	58.3	3
Clindamycin	22.2	6	55.6	1	22.2	6	66.7	2
Ery. + zinc acetate	50.0	=1	37.5	5	50.0	=1	50.0	=4
Tetracycline + oxytet.	41.7	4	50.0	2	50.0	=1	50.0	=4
BP + oxytet.	40.0	5	42.9	3	50.0	=1	71.4	1

Lesion counts by baseline erythromycin resistance status

Baseline erythromycin resistance was not a statistically significant factor in the analysis of lesion counts (week 12 $p = 0.842$, week 18 $p = 0.500$). Baseline by treatment interaction was significant for week 12 no erythromycin resistance (*Table 182*).

TABLE 182 *Discontinued groups: mean inflamed lesion counts by baseline erythromycin resistance status*

	Week 12				Week 18			
Erythromycin resistance:	**Without (*n* = 53)**		**With (*n* = 59)**		**Without (*n* = 53)**		**With (*n* = 59)**	
Treatment group	**Mean**	**Rank**	**Mean**	**Rank**	**Mean**	**Rank**	**Mean**	**Rank**
Erythromycin	0.9	6	–6.9	6	–2.3	4	–11.4	6
Top. erythromycin	–10.0	2	–18.3	3	–8.1	3	–24.1	=2
Clindamycin	–1.5	4	–24.3	2	3.7	6	–23.7	4
Ery. + zinc acetate	–23.5	1	–8.1	5	–24.3	1	–17.0	5
Tetracycline + oxytet.	–1.5	5	–16.3	4	–1.7	5	–24.1	=2
BP + oxytet.	–7.6	3	–25.0	1	–8.8	2	–30.3	1

Lesion counts by baseline tetracycline resistance status

Baseline tetracycline resistance was not a statistically significant factor in the analysis of lesion counts (week 12 $p = 0.415$, week 18 $p = 0.482$). Baseline by treatment interaction was significant for week 18 both with and without tetracycline resistance (*Table 183*).

TABLE 183 *Discontinued groups: mean inflamed lesion counts by baseline tetracycline resistance status*

	Week 12				Week 18			
Tetracycline resistance:	**Without (*n* = 92)**		**With (*n* = 20)**		**Without (*n* = 92)**		**With (*n* = 20)**	
Treatment group	**Mean**	**Rank**	**Mean**	**Rank**	**Mean**	**Rank**	**Mean**	**Rank**
Erythromycin	–7.7	5	14.8	6	–12.5	4	15.1	4
Top. erythromycin	–18.3	1	–1.4	5	–22.6	1	–5.1	3
Clindamycin	–11.9	4	–35.5	1	–10.1	5	–9.6	2
Ery. + zinc acetate	–14.8	3	–28.8	3	–19.7	2	17.8	5
Tetracycline + oxytet.	–5.9	6	–15.2	4	–5.4	6	–30.8	1
BP + oxytet.	–17.1	2	–34.7	2	–18.8	3	[a]	

[a] Not estimable.

Lesion counts by baseline clindamycin resistance status

Baseline clindamycin resistance was not a statistically significant factor in the analysis of lesion counts (week 12 $p = 0.091$, week 18 $p = 0.583$). Baseline by treatment interaction was significant for week 12 no clindamycin resistance (*Table 184*).

TABLE 184 *Discontinued groups: mean inflamed lesion counts by baseline clindamycin resistance status*

	Week 12				Week 18			
Clindamycin resistance:	**Without (*n* = 53)**		**With (*n* = 59)**		**Without (*n* = 53)**		**With (*n* = 59)**	
Treatment group	**Mean**	**Rank**	**Mean**	**Rank**	**Mean**	**Rank**	**Mean**	**Rank**
Erythromycin	–10.1	4	–1.4	6	–8.0	5	–10.2	6
Top. erythromycin	–18.8	2	–14.4	3	–18.8	2	–19.0	4
Clindamycin	–13.4	3	–25.3	1	–14.3	3	–23.7	2
Ery. + zinc acetate	–22.6	1	–9.0	5	–24.3	1	–15.2	5
Tetracycline + oxytet.	–7.1	6	–10.7	4	–0.9	6	–22.2	3
BP + oxytet.	–8.7	5	–25.0	2	–12.4	4	–29.9	1

Time-related resistance patterns

The percentage of participants colonised by propionibacteria (total load) decreased slightly from baseline in all groups, the biggest sustained decrease (from 100% to 88%) occurring in the BP + oxytet. group.

The BP + oxytet. group was the only one with decreases in all three resistant bacteria over time. In the ery. + zinc acetate group, clindamycin and erythromycin resistance increased while tetracycline resistance decreased over time. In the clindamycin group erythromycin resistance decreased slightly. In the tetracycline + oxytet. group tetracycline resistance decreased slightly.

No participants were colonised with resistant minocycline bacteria in these treatment groups. No participants gained or increased tetracycline-resistant bacteria during the study.

Percentages of participants colonised and mean scores are given in *Tables 185–188*. Scores are on a scale of 0 to 5 (degree of colonisation).

TABLE 185 *Discontinued groups: changes over time in total viable propionibacterial load*

	Mean growth scores on non-selective medium				% of participants colonised			
Week:	**0**	**6**	**12**	**18**	**0**	**6**	**12**	**18**
Treatment								
Erythromycin	4.7	3.1	3.7	3.7	100.0	84.2	94.7	94.7
Top. erythromycin	4.7	4.1	3.7	3.8	100.0	95.0	85.0	95.0
Clindamycin	4.3	3.4	3.7	3.6	100.0	100.0	100.0	94.4
Ery. + zinc acetate	4.1	3.6	3.7	3.4	94.4	88.9	94.4	94.4
Tetracycline + oxytet.	4.9	4.3	4.4	3.7	100.0	100.0	100.0	95.0
BP + oxytet.	4.6	3.1	2.8	2.4	100.0	88.2	88.2	88.2

TABLE 186 *Discontinued groups: changes over time in population density and prevalence of clindamycin-resistant propionibacteria*

	Mean growth scores				% of participants colonised			
Week:	**0**	**6**	**12**	**18**	**0**	**6**	**12**	**18**
Treatment								
Erythromycin	1.5	1.4	1.8	2.2	52.6	47.4	47.4	63.2
Top. erythromycin	2.4	2.3	2.1	2.1	60.0	55.0	55.0	60.0
Clindamycin	1.4	1.1	1.3	1.3	50.0	38.9	38.9	44.4
Ery. + zinc acetate	1.4	1.7	1.7	1.9	44.4	50.0	55.6	72.2
Tetracycline + oxytet.	1.3	1.2	1.2	1.1	40.0	40.0	40.0	40.0
BP + oxytet.	1.4	0.8	0.5	0.7	41.2	29.4	23.5	23.5

TABLE 187 *Discontinued groups: changes over time in population density and prevalence of erythromycin-resistant propionibacteria*

	Mean growth scores				% of participants colonised			
Week:	**0**	**6**	**12**	**18**	**0**	**6**	**12**	**18**
Treatment								
Erythromycin	1.8	1.6	2.2	2.2	57.9	52.6	57.9	63.2
Top. erythromycin	2.5	2.5	2.4	2.3	60.0	60.0	60.0	65.0
Clindamycin	1.8	1.2	1.5	1.6	61.1	44.4	50.0	55.6
Ery. + zinc acetate	1.6	1.7	1.8	2.2	50.0	50.0	55.6	77.8
Tetracycline + oxytet.	1.6	1.5	1.5	1.4	45.0	45.0	45.0	45.0
BP + oxytet.	1.4	0.8	0.5	0.6	41.2	29.4	23.5	23.5

TABLE 188 *Discontinued groups: changes over time in population density and prevalence of tetracycline-resistant propionibacteria*

	Mean growth scores				% of participants colonised			
Week:	**0**	**6**	**12**	**18**	**0**	**6**	**12**	**18**
Treatment								
Erythromycin	0.7	0.7	0.7	0.7	15.8	21.1	15.8	15.8
Top. erythromycin	1.1	1.2	0.9	0.8	25.0	25.0	20.0	20.0
Clindamycin	0.6	0.4	0.5	0.0	16.7	11.1	11.1	0.0
Ery. + zinc acetate	0.3	0.3	0.3	0.2	16.7	16.7	11.1	5.6
Tetracycline + oxytet.	1.0	0.8	0.4	0.4	25.0	20.0	10.0	10.0
BP + oxytet.	0.2	0.1	0.0	0.0	5.9	5.9	0.0	0.0

Participants gaining and losing resistant propionibacteria

A number of participants who had resistant organisms at baseline had lost them by week 18, and others who had no resistance at baseline had gained them. These numbers are summarised in *Table 189*.

TABLE 189 *Discontinued groups: participants gaining and losing resistance during the study*

Resistant organism	Treatment group	Gained resistance	%	Lost resistance	%
Clindamycin	Erythromycin	3 (of 9)	33	1 (of 10)	10
	Top. erythromycin	2 (of 8)	25	2 (of 12)	17
	Clindamycin	2 (of 9)	22	3 (of 9)	33
	Ery. + zinc acetate	5 (of 10)	50	0 (of 8)	0
	Tetracycline + oxytet.	1 (of 12)	8	1 (of 8)	13
	BP + oxytet.	0 (of 10)	0	3 (of 7)	43
Erythromycin	Erythromycin	3 (of 8)	38	2 (of 11)	18
	Top. erythromycin	2 (of 8)	25	1 (of 12)	8
	Clindamycin	2 (of 7)	29	3 (of 11)	27
	Ery. + zinc acetate	5 (of 9)	56	0 (of 9)	0
	Tetracycline + oxytet.	1 (of 11)	9	1 (of 9)	11
	BP + oxytet.	0 (of 10)	0	3 (of 7)	43
Tetracycline	Erythromycin	0 (of 16)	0	0 (of 3)	0
	Top. erythromycin	0 (of 15)	0	1 (of 5)	20
	Clindamycin	0 (of 15)	0	3 (of 3)	100
	Ery. + zinc acetate	0 (of 15)	0	2 (of 3)	67
	Tetracycline + oxytet.	0 (of 15)	0	3 (of 5)	60
	BP + oxytet.	0 (of 16)	0	1 (of 1)	100

Participants whose resistance category increased

TABLE 190 *Discontinued groups: participants[a] who became colonised with increased numbers of resistant propionibacteria (higher growth score) during the active treatment phase*

Resistant organism	Treatment group	Increased growth score	%
Clindamycin	Erythromycin	6 (of 18)	33
	Top. erythromycin	4 (of 15)	27
	Clindamycin	4 (of 18)	22
	Ery. + zinc acetate	6 (of 17)	35
	Tetracycline + oxytet.	1 (of 19)	5
	BP + oxytet.	1 (of 14)	7
Erythromycin	Erythromycin	6 (of 18)	33
	Top. erythromycin	4 (of 13)	31
	Clindamycin	4 (of 18)	22
	Ery. + zinc acetate	8 (of 17)	47
	Tetracycline + oxytet.	1 (of 16)	6
	BP + oxytet.	1 (of 15)	7
Tetracycline	Erythromycin	0 (of 17)	0
	Top. erythromycin	0 (of 18)	0
	Clindamycin	0 (of 18)	0
	Ery. + zinc acetate	0 (of 18)	0
	Tetracycline + oxytet.	0 (of 19)	0
	BP + oxytet.	0 (of 17)	0

[a] Of those who did not already have confluent growth.

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The HTA Programme and the authors would like to know your views about this report.

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We look forward to hearing from you.

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