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British Association of Dermatologists (BAD)	Guideline	003	004	Standardising information and assessing the impact of different formats would be very helpful. The committee suggest there is little evidence to suggest what information people with acne would like to know about. A robust James Lind Alliance Acne Priority Setting Partnership conducted in 2015 provided significant data on what people with acne would like to know more about and this could inform future studies in this area. Raw data is available.	Thank you for your comment. The publication related to the James Lind Alliance Priority Setting Partnership was not included as evidence because the agreed review protocol was looking for data from qualitative studies. However, the committee noted that many of the 10 research priorities listed by the James Lind Alliance were consistent with the guideline recommendations or research recommendations, apart from prevention and lifestyle factors other than diet which are topics outside the scope of this guideline and so could not be commented on. The list of topics to discuss in recommendation 1.1.1 is not exhaustive and should be tailored to the individual and may therefore vary on a case by case basis.
British Association of Dermatologists (BAD)	Guideline	003	007	Giving patients information about why they have acne – please clarify this point. Would providing the BAD's PILs suffice? https://www.skinhealthinfo.org.uk/a-z-conditions-treatments/	Thank you for your comment. Providing information using a leaflet could be an important resource but this would need to align with the guideline content and the information accessed using the link currently does not. NICE guidance only cross references to other NICE or public health guidance or endorsed resources. If the advice in the leaflet is amended to be consistent with the guideline a leaflet could be endorsed using the endorsement programme which allows resources to be linked to guidance see https://www.nice.org.uk/about/what-we-do/into-practice/endorsement.
British Association of Dermatologists (BAD)	Guideline	004	001	There is limited evidence from clinical trials about skin care and as the committee have noted pH is an important factor. Syndet bars are not routinely recommended or used in current everyday practice but multiple OTC products bought by patients it would be useful to emphasise the important of optimising pH and helping to direct patients.	Thank you for your comment. There was one randomised controlled trial that showed acne improvement with a syndet bar compared to ordinary soap and the committee thought that advice could be given. Such syndet products are widely available. The committee amended the recommendation to emphasise the pH level. The recommendation related to 'oil-free' was also amended and now states 'to avoid oil-based and comedogenic preparations'.

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				The guideline group advises the use of oil-free products – it would be useful to be more specific about this as some essential oils are advocated in acne which causes some confusion. There is some evidence the benzoyl peroxide washes are helpful in reducing resistant and sensitive strains of *C. acnes*, so potentially may provide a useful adjuvant in a treatment regimen if people in longer term treatments that may drive antimicrobial resistance.	There was no consensus or evidence about any essential oils that could be recommended so the committee did not comment on this. Although there was some limited evidence on the use of acidic skin cleansers and benzoyl-peroxide-based face washes, the committee agreed that this was not sufficient to make a recommendation.
British Association of Dermatologists (BAD)	Guideline	004	002	We are concerned about the recommendations of "syndet" products. We cannot find any robust evidence for this and it seems that it will lead people to purchase expensive specialist products rather than soap.	Thank you for your comment. Even though there was limited evidence the committee decided that the non-alkaline (skin pH neutral or slightly acidic) properties of syndet cleansers would make them preferable to traditional soap. The recommendation was revised to emphasise this point: 1.2.1 Advise people with acne to use a non-alkaline (skin pH neutral or slightly acidic) synthetic detergent (syndet) cleansing product twice daily on acne-prone skin. The committee acknowledged that there are a wide range of syndet cleansers available and that they vary in price. To address this point, the following was added to the rationale section: 'Although the research was carried out using a syndet bar, many syndets are now available in different formulations such as liquid or foam. The committee agreed that different formulations are probably similarly effective, so the findings would still be applicable and it would be reasonable to try the cheapest syndet in the first instance'
British Association of Dermatologists (BAD)	Guideline	005	005	"Persistent pigmentary changes secondary to acne" should be referred to secondary care dermatology. We are not clear why these patients should be referred at all, as NHS England does not allow treatment of cosmetic problems in the NHS.	Thank you for your comment. This has been reworded to 'acne with persistent pigmentary changes'. The rationale was revised to emphasise that the objective of this referral is to provide optimal treatment and prevent progression of symptoms, such as further pigmentary changes. The cosmetic treatment of pigmentary changes is outside the scope of the guideline.

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British Association of Dermatologists (BAD)	Guideline	006	007 +	*Mild-to-moderate acne* A minor point, the report refers to antiseptics and includes benzoyl peroxide in this – in fact, benzoyl peroxide is a very effective antimicrobial and I would broaden this heading to "antiseptics/antimicrobials". The use of fixed combination products is recommended but there may be practical reasons why patients may not be able or want to use some products, e.g. benzoyl peroxide on the trunk due to bleaching. Fixed dose combinations that do not include benzoyl peroxide but include a topical antibiotic, e.g. tretinoin/clindamycin are likely to promote Antimicrobial resistance over time and therefore some caution about prolonged use would be helpful. Evidence would suggest AMR in *C. acnes* emerges by 12 weeks when using a topical antibiotic agent and the presence of resistant strains can correlate with reduced efficacy and resistant strains can be transferred to others. This should be considered in recommendations.	Thank you for your comment. The evidence specifically related to benzoyl peroxide rather than broader antiseptics or antimicrobials and therefore the committee used this in the recommendation. In the section on 'factors to take into account when choosing a treatment option' the committee recommended against antibiotic monotherapy or combinations of a topical antibiotic and an oral antibiotic. The committee also highlighted in the section 'factors to take into account at review' that the use of antibiotic treatments (topical or oral) for acne is associated with a risk of antimicrobial resistance and that the antibiotic should be discontinued as soon as possible and only in exceptional circumstances be continued beyond 6 months. Therefore, the committee felt that the guideline would promote good antimicrobial stewardship.
British Association of Dermatologists (BAD)	Guideline	006	007 +	*Moderate-to-severe acne* As above topical retinoid and clindamycin has potential to drive antimicrobial resistance may wish to discuss limiting the duration or adding in benzoyl peroxide. It would be useful to consider what oral antibiotics are appropriate in those not able to tolerate tetracyclines or in younger children. Erythromycin or trimethoprim may be alternatives to consider. It would be useful to discuss use of antibiotics and other treatments in pregnancy – note recent concerns about erythromycin use in pregnancy and foetal abnormalities. Regarding cumulative dose of isotretinoin – the early studies were all conducted using the parent drug Roaccutane - it has been suggested that there are some differences in absorption with generic formulations and the medication is very lipophilic meaning that absorption may be significantly affected by fat intake in the diet.	Thank you for your comment. In the section on 'factors to take into account when choosing a treatment option' the committee recommended against antibiotic monotherapy or combinations of a topical antibiotic and an oral antibiotic. The committee also highlighted in the section 'factors to take into account at review' that the antibiotic (topical or oral) should be discontinued as soon as possible and only in exceptional circumstances be continued beyond 6 months. Therefore the committee felt that the guideline would promote good antimicrobial stewardship. We conducted a Network Meta-Analysis of all randomised controlled trial evidence of all acne treatments that met the inclusion criteria of the systematic review protocol, which subsequently informed an economic model. There was evidence showing that combinations of a topical treatment together with an oral tetracycline were clinically

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				This has challenged the evidence around cumulative dosing regimens. It is also clear that some patients do require higher cumulative doses as has been reported in the literature. These facts would be useful to consider further in any discussion and to confirm that cumulative dosing provides a guide, but that clinical assessment is important, and some patients may need more, or less (as has been stated). Isotretinoin – would be useful to confirm this is not contraindicated in patients with mental health issues but clearly need to have appropriate support in place. There is no evidence that dose of isotretinoin relates to mental health issues it would be useful to clarify this.	and cost-effective for the treatment of moderate to severe acne. The evidence was insufficient to recommend trimethoprim or erythromycin as a first line treatment option. Nevertheless, the committee acknowledged that treatment options would be limited for people with moderate to severe acne for whom tetracyclines are contraindicated or not tolerated, and have now decided, based on experience and expertise, to add a recommendation that for these people, oral lymecycline or doxycycline could be replaced by trimethoprim or an oral macrolide, for example erythromycin. However, they did not comment on its use in pregnancy. The committee had already recommended benzoyl peroxide which can be used during pregnancy as well as topical benzoyl peroxide with clindamycin which can be used with caution during pregnancy. With regards to absorption of isotretinoin which may be affected by diet the we follow MHRA advice regarding isotretinoin dose and accept that there may be circumstances where a higher dose may be required but this would be a clinician based decision and potentially off-label use. The committee therefore did not comment on this. With regard to dosing of isotretinoin, there was very little evidence related to different dosages. Therefore, a standard dosage was recommended and the committee revised the recommendation to say that a reduced dose should only be considered for people at increased risk of, or experiencing significant adverse effects. The bullets with examples were removed to allow this to be decided according to individual circumstances using clinical expertise. The bullet point suggesting that dose of isotretinoin relates to mental health issues was removed because there is no evidence to support this. A research recommendation was also made to assess the efficacy of reduced dose isotretinoin treatment.

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					Support for people with mental health conditions has been emphasised throughout (see for example recommendations 1.5.19 and 1.5.24).
British Association of Dermatologists (BAD)	Guideline	006	015	The guideline suggests fixed combinations, which may be more effective as first line, but there is no statement about those that may not tolerate being able to use monotherapy of, e.g. adapalene rather than adapalene and benzoyl peroxide fixed combination.	Thank you for your comment. We conducted a Network Meta-Analysis of all randomised controlled trial evidence of all acne treatments that met the inclusion criteria of the systematic review protocol, which subsequently informed an economic model. Monotherapies were found to be less clinically and cost-effective than combination therapies. The committee therefore recommended these combination treatments and only recommended monotherapy with benzoyl peroxide to those who cannot tolerate other treatment or to those people where other treatments are contraindicated. Adapalene monotherapy was not recommended as first-line treatment option because it was less clinically and cost-effective than combination therapies and, for people with moderate-to-severe acne, it was also less clinically and cost-effective than other monotherapies as well. However, the committee did not recommend against its use either, and therefore this does not preclude it being used by clinicians in the management of acne based on individual circumstances and clinical expertise. We have emphasised this in the rationale section and have also extended the discussion in the evidence review to clarify the reasons why these options were not included as first-line treatments.
British Association of Dermatologists (BAD)	Guideline	007	Table 1	The guideline does not mention macrolides or trimethoprim as options which are used occasionally as second line. Is trimethoprim not mentioned in view of a higher risk of SCARS and best not prescribed in the community?	Thank you for your comment. We conducted a Network Meta-Analysis of all randomised controlled trial evidence of all acne treatments that met the inclusion criteria of the systematic review protocol, which subsequently informed an economic model. There was evidence showing that combinations of a topical treatment together with an oral tetracycline were clinically and cost-effective for the treatment of moderate to severe acne. The evidence was insufficient to recommend trimethoprim or erythromycin as a first line treatment option. The committee acknowledged that treatment options would be limited for people with moderate to severe acne for

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					whom tetracyclines are contraindicated or not tolerated, and have decided to add, based on experience and expertise, a recommendation that for these people, oral lymecycline or doxycycline could be replaced by trimethoprim or an oral macrolide, for example erythromycin.
British Association of Dermatologists (BAD)	Guideline	007	Table 1	There is a higher risk of developing bacterial resistance with macrolides, but it can be beneficial in patients not tolerating tetracyclines or when tetracyclines are contraindicated. We fear GPs will refer more without using an oral antibiotic if only oral tetracyclines are advised prior to referral.	Thank you for your comment. The committee, based on experience and expertise, have amended the guideline to recommend to consider trimethoprim or oral macrolides if oral lymecycline or doxycycline are contraindicated or not tolerated.
British Association of Dermatologists (BAD)	Guideline	008	001	We feel that azelaic acid should be another alternative as well as benzoyl peroxide.	Thank you for your comment. We conducted a Network Meta-Analysis of all RCT evidence that met the inclusion criteria, which subsequently informed an economic model. Monotherapies were found to be less clinically and cost-effective than combination therapies. The committee therefore recommended these combination treatments and only recommended monotherapy with benzoyl peroxide to those who cannot tolerate other treatment or to those people where other treatments are contraindicated. Monotherapy with azelaic acid was not recommended as a fist-line treatment option because it was found to be ineffective in people with mild-to-moderate acne, and no evidence was found for people with moderate-to-severe acne. However, the committee did not recommend against its use either, and therefore this does not preclude it being used by clinicians in the management of acne based on individual circumstances and clinical expertise. We have emphasised this in the rationale section and have also extended the discussion in the evidence review to clarify the reasons why these options were not included.
British Association of Dermatologists (BAD)	Guideline	008 & 041	Table & 005	In the tables some colleagues would also add in use of topical retinoids on alternate days initially as clinicians may just look at the tables as a short cut. Also in the tables, we would suggest mentioning that azelaic acid is less irritating than topical retinoids.	Thank you for your comment. Whist we understand that it is good to have everything in one place, we have an entire section entitled 'factors to take into account when choosing a first line treatment option' and 'alternate day application' is one of them. Not all of these factors can be added to the table and therefore we believe that

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					clinicians using the table should not do so out of context. We have therefor left this as it is.
British Association of Dermatologists (BAD)	Guideline	010	018	We disagree with the recommendation that prohibits use of oral antibiotics for more than 6 months. The scenario would be a patient who is responding well but is not appropriate for or does not wish to take isotretinoin? There is no evidence that resistance is more likely to arise between 6-12 months than for the first 6 months of treatment. A "do not" recommendation usually arises when the evidence indicate the harms outweighing the benefits. This recommendation will result in more patients being treated with isotretinoin.	Thank you for your comment. The committee discussed this recommendation and decided that the wording was too strong and that there should be some level of clinical judgment related to stopping a treatment option that includes a topical antibiotic or an oral antibiotic. They decided to amend the recommendation to allow for this but only in exceptional circumstances. If it is decided to continue it should then be reviewed at 3 monthly intervals, and the antibiotic should be stopped as soon as possible.
British Association of Dermatologists (BAD)	Guideline	011	017	The list should also include those who have failed other treatments.	Thank you for your comment. In the committee's experience failing treatment would not necessarily result in oral isotretinoin treatment but would also depend on the severity of acne in the first instance. The related recommendation is in the 'factors to take into account at review' section (in the consultant dermatologist-led team it can then be decided whether oral isotretinoin would be the next treatment option): 1.5.16 If acne fails to respond adequately to a 12-week course of a first-line treatment option and at review the severity is: • mild to moderate: offer another option from the table of treatment choices (see table 1) • moderate to severe, and the treatment did not include an oral antibiotic: offer another option that includes an oral antibiotic from the table of treatment choices (see table 1) • moderate to severe, and the treatment included an oral antibiotic: consider referral to a consultant dermatologist-led team.
British Association of Dermatologists (BAD)	Guideline	011	017	We disagree with the recommendation that for management of severest forms of acne, e.g. nodulo-cystic acne/acne fulminans, two 12-week courses of antibiotics and topical therapy need to have tried first prior to isotretinoin. In cases of severe acne, it may sometimes be appropriate, using clinical judgment, to give isotretinoin as a first option alongside other treatments.	Thank you for your comment. The committee drafted their recommendations according to regulatory guidance from the Medicines & Healthcare products Regulatory Agency (MHRA) which stipulates to only use isotretinoin for severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) that are resistant to adequate courses of standard therapy with systemic antibacterials and topical therapies. The committee noted

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					that the MHRA is conducting a review of oral isotretinoin and any changes that would impact on the current wording of the guideline will be updated.
British Association of Dermatologists (BAD)	Guideline	012	013	Very clearly written regarding the PPP for isotretinoin, i.e. it will be for *everyone* with potential to become pregnant – this may impact some of our colleagues' practices and needs to be highlighted when the guideline is finalised.	Thank you for your comment. Due to the teratogenic effects of oral isotretinoin the committee worded it this way but did not think that this would be a major change to clinical practice.
British Association of Dermatologists (BAD)	Guideline	012	013	There is also an opportunity here to provide absolute clarity regarding the PPP for isotretinoin: a. Regarding the requirement that all with 'potential to become pregnant' on isotretinoin follow the Pregnancy Prevention Programme. There is no definition in the guideline of 'potential to become pregnant', e.g. is it biological potential, or behavioural potential. b. What is meant by 'inform them that they will need to follow the Pregnancy Prevention Programme', i.e. is the recommendation 'to inform' them of this or 'to make sure that they follow' it? c. Has the matter of exceptions to the PPP been considered by the guideline group, e.g. if patients decline it, or if they are abstinent, or if they are on highly effective contraception. **Ref:** https://assets.publishing.service.gov.uk/media/5c936a4840f0b633f5bfd895/pregnancy_testing_and_contraception_table_for_medicines_with_teratogenic_potential_final.pdf.	Thank you for your comment. Due to the teratogenic effects of oral isotretinoin the committee worded it in this way to capture anyone with the potential to become pregnant be it biological or behavioural. Further information is provided on the pregnancy prevention website and therefore the recommendation directly links to this so that the healthcare professional can follow the details of this guidance. Providing a link rather than quoting details also ensures that in case future guidance on the pregnancy prevention programme changes, the most up-to-date guidance can still be accessed. Once the guideline is published in digital format it will be straightforward to navigate from the guideline to the pregnancy prevention programme website. The committee felt unable to comment on matters of exceptions to the pregnancy prevention programme because this was outside the scope of this guideline.
British Association of Dermatologists (BAD)	Guideline	012	020	The statement to give a dose adjustment/reduced dosage for patients with a previous/current mental health disorder is unclear. The 2010 BAD isotretinoin guideline emphasises that mental health disorder is unlikely to be dose-dependent and not reliably related to pre-existing mood disorders.	Thank you for your comment. The committee decided to reword this recommendation and remove the bullets. It now states: '1.5.21 Consider a reduced daily dose of isotretinoin (less than 0.5 mg/kg) for people at increased risk of, or experiencing significant adverse effects'. This can then be decided on a case by case basis based on clinical expertise.
British Association of Dermatologists (BAD)	Guideline	013	012	We are concerned about the PDT recommendation and the fact that having it on the NICE guideline would force us to provide this service. This would be a particular problem post-COVID, where PDT services might get priority over more urgent backlogs. It is also	Thank you for your comment. Recommendations are formulated based on evidence of clinical and cost-effectiveness. The guideline economic analysis that informed this recommendation took into account the heavier resource use associated with PDT. According to

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				heavy on resource, rooms, nursing times and budgets as the photosensitisers are expensive.	this analysis, PDT was less cost-effective than other options recommended in the guideline, but more cost-effective than a number of other treatments assessed, despite its heavier resource use. Some recommendations are made with more certainty than others. NICE word recommendations to reflect this. For example, 'offer' is used to reflect a strong recommendation, usually where there is clear evidence of benefit. 'Consider' is used to reflect a recommendation for which the evidence of benefit is less certain (this is described in 'Making decisions using NICE guidelines' to which a hyperlink is provided in the document). The recommendation on PDT is not strong and asks healthcare professionals to 'consider' this option for a small population for whom all else has failed or other options are contraindicated. The recommendation does not force trusts to provide PDT as a routine treatment option.
British Association of Dermatologists (BAD)	Guideline	014	004	The dosage of triamcinolone at 0.6 mg/ml is unusual – what literature evidence is available?	Thank you for your comment. This dosage is closest to the dosage used in the evidence that was identified for this and the committee therefore decided to recommend this.
British Association of Dermatologists (BAD)	Guideline	014	009	There are guidelines for management of PCOS and it would be useful to align these to recommendations so consistent for community practitioners. Regulatory authorities currently suggest hormonal treatments for acne should be used in adult women who also require a contraceptive and the current suggestions may be at odds with this. The likelihood of relapse is higher in patients with PCOS and it would be useful to consider use of maintenance in this group. If basing recommendations on experience rather than evidence which is not available, it would be worth discussing use of spironolactone.	Thank you for your comment. Given that there was little evidence for first-line treatment options for people with PCOS, the committee was more confident recommending first-line options available to everyone. If these first-line treatment options do not work, adding a hormonal treatment could be effective because of hyperandrogenism in people with polycystic ovary syndrome. The committee decided based on experience and expertise that either the combined oral contraceptive pill (which is an established and widely available hormonal treatment for the symptoms of polycystic ovary syndrome) or ethinylestradiol with cyproterone acetate (co-cyprindiol) could be used, as they have different mechanisms of action from one another. They also made a research recommendation to encourage studies to investigate acne

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					treatments for people with polycystic ovary syndrome including the use of spironolactone.
British Association of Dermatologists (BAD)	Guideline	016	004	Some colleagues would question the recommendation that maintenance therapy is not needed. We suggest rewording this phrase in a less contradictory way, i.e. maintenance therapy with a topical agent is often required long-term to maintain clear skin.	Thank you for your comment. The committee discussed that there would be people who receive first line treatment and their acne may respond well to this. They therefore decided that it is not inevitable that a person has to have maintenance treatment and that this should be explained to the person.
British Association of Dermatologists (BAD)	Guideline	016	008	This is also mentioned in the maintenance section, but this should be an option for patients with a high risk of irritancy first-line.	Thank you for your comment. Recommendations in the maintenance section are based on a separate evidence base. The evidence came from studies with participants who already had significant improvements with prior treatment of their acne. There was some evidence that these could be effective to maintain this improvement. For first-line treatments we conducted a Network Meta-Analysis of all randomised controlled trial evidence of all acne treatments that met the inclusion criteria of the systematic review protocol, which subsequently informed an economic model. Monotherapies were found to be less clinically and cost-effective than combination therapies. The committee therefore recommended these combination treatments and only recommended monotherapy with benzoyl peroxide to those who cannot tolerate other treatment or to those people where other treatments are contraindicated. Monotherapy with azelaic acid was not recommended as a fist-line treatment option because it was found to be ineffective in people with mild-to-moderate acne, and no evidence was found for people with moderate-to-severe acne. However, the committee did not recommend against its use either, and therefore this does not preclude it being used by clinicians in the management of acne based on individual circumstances and clinical expertise. We have emphasised this in the rationale section and have also extended the discussion in the evidence review to clarify the reasons why these options were not included.
British Association of	Guideline	016	012	Consider removing this point as some people will need the topicals long-term and it does not need regular questioning.	Thank you for your comment. The committee based their decision on the available evidence as the majority of studies included in this

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Dermatologists (BAD)					review reviewed participants at 12 weeks and discussed based on their experience that 6 to 8 weeks was the minimum time required to see a response to a treatment. They discussed that maintenance treatment is not always needed or does not always need to continue and therefore decided that a review should take place at 12 weeks to assess whether further maintenance treatment is needed and wanted.
British Association of Dermatologists (BAD)	Guideline	016	014	There is some recent evidence to suggest early intervention can reduce the likelihood of scarring but as the committee suggest there is probably an innate susceptibility as it has been shown patients who scar mount a different innate immune reaction that those that do not. As such the severity of the acne may not be the main contributory factor and it would be useful to emphasise the important of recognising scarring early and managing accordingly as resultant scarring is so challenging to treat.	Thank you for your comment. As noted in the rationale and impact section of the guideline, the committee acknowledged that there is substantial uncertainty around the results of studies that examined the risk factors of acne-related scarring as they did not control for the influence of other factors. Innate susceptibility was not a factor that featured in the evidence. The committee noted that acne severity but also duration of acne may lead to scarring and recommended that awareness is raised about this. They revised the guideline by adding a recommendation related to referral for people with acne likely to lead to scarring to ensure optimal treatment of their acne to prevent further scarring. They also recognised the insufficient evidence regarding possible risk factors for acne-related scarring and made a research recommendation.
British Association of Dermatologists (BAD)	Guideline	017	005	Treatment options for acne-related scarring including "glycolic acid 5 peel or CO_2 laser treatment (alone or after a session of punch elevation)" but these are not routinely commissioned by any CCG. Inclusion may clash with commissioning practices and change patient expectations. Some colleagues feel very strongly about treatments not available on the NHS listed in the guideline. If they remain it should be clear this *currently* is only available privately. There is also some concern that those in the beauty industry may start to offer such treatment privately and without the necessary qualification and experience.	Thank you for your comment. As noted in the rationale and impact section of the guideline, there was some evidence to suggest that glycolic acid peels and CO2 laser treatment either alone or after a session of punch elevation were efficacious in improving the appearance of acne-related scars, and therefore the committee agreed to recommend these treatments but stressed that only people fulfilling certain criteria would be eligible for the recommended treatments that can be considered (if a person's acne-related scarring is severe and persists a year after their acne has cleared). They also agreed that the recommendation is expected to result in a change in current clinical practice but they did not expect the impact to be substantive as only a small number of those affected would be eligible. This should also not result in

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					significant resource impact since it is intentionally stating that this is a treatment option that can be considered, rather than an option that should routinely be provided. NHS commissioners should take the guideline into account when commissioning services for people with acne.
British Association of Dermatologists (BAD)	Guideline	026	001	The guideline should be phrased in a more permissive way, emphasising that so long as patients with previous/existing mild/moderate depression with no history of suicidality/self-harm are followed up regularly (and this could be in primary care/with the dermatology team/with the help of the patient's support network if they have a good one), isotretinoin is not contraindicated, and patients do not necessarily need to be seen by a mental health specialist beforehand.	Thank you for your comment. The committee drafted the recommendations in accordance with MHRA safety advice on oral isotretinoin and recommended its use only in situations when they agreed the benefits outweighed the risks such as in severe forms of acne that is resistant to adequate courses of standard therapy with systemic antibiotics and topical therapy. The committee noted that the MHRA is in the process of reviewing this topic. New MHRA advice would lead to an update of this part of the guideline to reflect any possible changes.
British Association of Dermatologists (BAD)	Guideline	028	006	There should be discussion of using erythromycin in pregnancy if severe acne/psychological distress after careful discussion with patients and avoiding the first trimester.	Thank you for your comment. We conducted a Network Meta-Analysis of all randomised controlled trial evidence of all acne treatments that met the inclusion criteria of the systematic review protocol, which subsequently informed an economic model. There was evidence showing that combinations of a topical treatment together with an oral tetracycline were clinically and cost-effective for the treatment of moderate to severe acne. The evidence was insufficient to recommend erythromycin as a first line treatment option. The committee acknowledged that treatment options would be limited for people with moderate to severe acne for whom tetracyclines are contraindicated (for example during pregnancy) or not tolerated, and have decided, based on experience and expertise to add a recommendation that, for these people, oral lymecycline or doxycycline could be replaced by trimethoprim or an oral macrolide (for example erythromycin). The committee recommended against the use of topical or oral antibiotics as monotherapies or in combination because of lower clinical and cost effectiveness of oral antibiotics when used as monotherapy compared with the

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					recommended treatment options in moderate to severe acne, and no clinical effectiveness in mild to moderate acne, as well as due to considerations of antibiotic stewardship.
British Association of Dermatologists (BAD)	Guideline	030	018	Some colleagues feel that isotretinoin can sometimes be an appropriate first-line treatment for patients with very severe acne who, in the professional opinion and clinical experience of a dermatologist, would be unlikely to respond adequately to other therapies. Yet the guideline and MHRA guidance specify it should never be used unless adequate courses of standard therapies have been tried first.	Thank you for your comment. The committee drafted the recommendations in accordance with MHRA safety advice on oral isotretinoin and recommended its use only in situations when they agreed the benefits outweighed the risks such as in severe forms of acne that is resistant to adequate courses of standard therapy with systemic antibiotics and topical therapy. The committee noted that the MHRA is in the process of reviewing this topic. New MHRA advice would lead to an update of this part of the guideline to reflect any possible changes.
British Association of Dermatologists (BAD)	Guideline	033	013	The guideline specifies that isotretinoin should be prescribed for patients with 'severe' forms of acne who have failed to respond to standard therapies (in line with the guidance on the MHRA drug safety update on isotretinoin). However, many patients would be classified as having 'moderate-to-severe acne' rather than 'moderate' acne, and the current guideline limits patients and dermatologists who wish to use isotretinoin for those with truly moderate acne which has failed to respond to other therapies and causes distress. Perhaps section 1.5.15 should be rephrased to read 'Consider oral isotretinoin for people who have a moderate-to-severe form of…'	Thank you for your comment. The committee drafted the recommendations in accordance with MHRA safety advice on oral isotretinoin and recommended its use only in situations when they agreed the benefits outweighed the risks such as in severe forms of acne that is resistant to adequate courses of standard therapy with systemic antibiotics and topical therapy. The committee noted that the MHRA is in the process of reviewing this topic. New MHRA advice would lead to an update of this part of the guideline to reflect any possible changes.
British Association of Dermatologists (BAD)	Guideline	039	027	There is evidence that some patients, under certain circumstances, benefit from cumulative dosages of isotretinoin >150 mg/kg in a course of treatment (e.g. reduced rates of relapse in those who have previously relapsed following a previous course, without increasing adverse effects). The guideline mentions that patients who have relapsed following two separate courses of isotretinoin might benefit from a tailored approach, including changes in dose or duration of isotretinoin. There is scope for the guideline to be far more specific than this. Many dermatologists use higher cumulative dosages at an earlier stage.	Thank you for your comment. The committee decided that cumulative dosages >150mg/kg would be considered off license use and that there was insufficient data to justify this. We cross-checked the provided reference and the Blasiak 2013 study is a non-randomised which, according to the protocol, is not a study design that would be included.

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				Ref: Blasiak RC, Stamey CR, Burkhart CN, Lugo-Somolinos A, Morrell DS. High-dose isotretinoin treatment and the rate of retrial, relapse, and adverse effects in patients with acne vulgaris. JAMA Dermatol. 2013 Dec;149(12):1392-8	
British Association of Dermatologists (BAD)	Guideline	General	General	This is a very comprehensive overview of the evidence and the team should be congratulated.	Thank you for your comment.
British Association of Dermatologists (BAD)	Guideline	General	General	It would be useful to discuss the challenges of comparing studies in more detail given the lack of standardisation of outcome measures in acne and the failure to always capture the impact of acne and what is important to the patient.	Thank you for your comment. Challenges related to the data and analysis are discussed in evidence reports E1 and F1.
British Association of Dermatologists (BAD)	Guideline	General	General	Many guidelines have failed to secure a robust patient perspective and it would be good to see these guidelines seizing the opportunity to do this through broad stakeholder engagement and to acknowledge this in the final publication as this has been noted as lacking in other guidelines.	Thank you for your comment. We looked for qualitative evidence of the views of people with acne and their families in the 'information and support' evidence review. Without published peer reviewed evidence the committee felt unable to comment on this in detail. However, there was a lack of evidence and the committee therefore made a research recommendation to encourage further studies of this topic. All NICE committees include at least 2 lay members (people with personal experience of using health or care services, including carers, or from a community affected by the guideline) and the guideline consultation was open to all stakeholders, representing professional or lay people.
British Association of Dermatologists (BAD)	Guideline	General	General	It would be useful to distinguish management approaches for truncal rather than facial acne – there has been significant interest in the literature recently about this.	Thank you for your comment. The committee decided that the current criteria provided in the 'terms used in this guideline' section apply to acne anywhere on the body. The committee decided in the protocol not to divide evidence into facial and truncal acne to optimise the overall evidence base for the Network Meta-Analysis of randomised controlled trials so the committee could not directly comment on this but decided that the first-line treatment options would apply to all people with acne.
British Association of	Guideline	General	General	There is no mention of spironolactone in managing acne. It can be extremely helpful in women.	Thank you for your comment. There was insufficient evidence to recommend spironolactone. We cross checked the provided

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Dermatologists (BAD)				**Ref:** Spironolactone in dermatology: uses in acne and beyond. T.N Searle F. Al-Niaimi F. R. Ali Clinical and Experimental Dermatology.2020 Dec vol 45 (8) p986-993. See also comment no. 26.	reference against our protocol's inclusion criteria and Searle 2020 is not a randomised study; the study design that does not match our inclusion criteria and was therefore not included in the guideline systematic review. The committee discussed this issue and decided that further evidence is needed and added a research recommendation to address this.
British Dermatological Nursing Group (BDNG)	Evidence review B	General	General	The patient needed to be washing 5 times a day with a syndet skin cleansing product, also 3 times a day with no soap – this needs to be clearer as this is impractical. It needs to be mentioned that the products patients need to use is not only oil free but the word non – comedogenic must come into this.	Thank you for your comment. The committee based their recommendation on a study which compared Sebamed compact (a syndet soap) to Lux soap (traditional type of soap), where the participants were asked to use these products twice daily. There was no evidence identified relating to washing with no soap. We do not recognise the reference to washing 5 times a day which the committee did not recommend. The committee decided that as well as oil-free it is also advisable that the products are also non-comedogenic. We have therefore added this to the recommendations (see also the 'terms used' section for a brief definition, and the rationale sections, which were updated accordingly).
British Dermatological Nursing Group (BDNG)	Evidence review E1	General	General	There has been a comprehensive look at all the evidence, but it is very confusing on treatments this needs to be simplified. The economic analysis is ok, but unless you had more than one area that has acne you would only ever get 1 tube of topical treatments. The standard dose of isotretinoin is 0.5-1mg/kg and am not sure why its in the mild acne section Never use topical antibiotics as monotherapy despite them being cost effective needs to be highlighted a lot more. Need to add in adapalene 0.3% with 2.5% BPO as a treatment Also, little mention of systemic antibiotics if a patient has more inflammatory lesions, also alternative antibiotics if intolerant or resistant to tetracyclines. Statement 1.5.11 – Do not use topical OR oral antibiotics for longer than 6 months, could this be made clearer	Thank you for your comment. We have reviewed evidence reports E1 and F1 and made some changes to make them easier to follow and more reader friendly. Regarding the economic analysis, the number of tubes assumed for each topical treatment was determined by the committee's expert advice: 1g/day was assumed for topical treatments for people with mild-to-moderate acne and 1.5g/day was assumed for topical treatments for people with moderate-to-severe acne; in making these estimates, the committee also took into account the fact that people may have acne lesions in different parts of face/body, so that they may need a larger amount of topical treatment per day. Depending on the amount of cream/gel contained in each tube, the number of tubes needed for a full course of each topical treatment was estimated (please note that separate estimates were made if people discontinued treatment early – 1 tube was mostly assumed

					in this case). In any case, the change in treatment cost if 1 tube was assumed instead of 2 would be small, and the cost difference between two different topical treatments would be even smaller, so the assumptions comprise a rather conservative estimate. The recommendations refer to a course of treatment which would be determined by what type and severity of acne the person has and do not specify number of tubes needed. The lower total cumulative dose of oral isotretinoin in the evidence review for mild to moderate acne was included because there was evidence on it, and therefore it was included in the NMA conducted for this population. However, no recommendation was made for people with mild-to-moderate acne. In the guideline it is only recommended for severe forms of acne in accordance with regulatory guidance from the Medicines and Healthcare products Regulatory Agency (MHRA). The guideline includes a recommendation against use of topical antibiotics as a monotherapy; the rationale for this recommendation is discussed in the respective rationale and impact section of the guideline. Moreover, the evidence review report includes the committee's discussion and justification of this recommendation under 'The Committee's Discussion – benefits and harms' section. The Network Meta-Analysis was conducted by drug class, but adapalene 0.3% and 2.5% BPO is noted in the guideline (see 'terms used in the guideline' section). The cost of adapalene and BPO fixed combination is the same whether the gel includes adapalene 0.1% or 0.3%, so the total cost of the intervention is the same; nevertheless, we have now added the cost information for the fixed combination of adapalene 0.3% and BPO 2.5% at the bottom of the table with intervention costs. Having more inflammatory lesions would be classed in the guideline as moderate to severe acne (which is covered by evidence report F1) and in the guideline the committee recommended combination treatments that include oral tetracyclines for people with moderate to severe acne. A recommendation related to alternative oral antibiotic if a person is intolerant to tetracyclines has been added (trimethoprim or macrolides).

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					The recommendation about not using oral or topical antibiotics beyond 6 months has now been modified and further clarification is given.
British Dermatological Nursing Group (BDNG)	Evidence review E2	General	General	Figure 1 study selection flow chart is missing. An awful lot of work gone in with the forest graphs and grade tables, inclusion, and exclusion studies but it needs a final summary page that is much clearer to follow.	Thank you for your comment. The study selection flow chart has been added. A summary discussion of the pairwise and network meta-analysis evidence that supported the recommendations of mild-to-moderate acne is presented in evidence report E1, in section "The committee's discussion of the evidence", sub-section "Interpreting the evidence".
British Dermatological Nursing Group (BDNG)	Evidence review F1	General	General	The review questions set out in each chapter are good, with a list of all the oral and topical treatments listed in no 24 – 41, then it becomes really confusing adding in the Pico table?	Thank you for your comment. We have reviewed evidence reports E1 and F1 and made some changes to make them easier to follow and more reader friendly. The PICO table is lengthy because there are many interventions listed (further details are in appendix A). We have listed the classes and subclasses of treatments because these detail how treatments were grouped in the network meta-analysis. So the PICO table is an important part to set the scene for what follows. It would be difficult to understand the rest of the sections without this context.
British Dermatological Nursing Group (BDNG)	Evidence review G	General	General	Like what is outlined in appendix L - even though it is research recommendations it is clear for practitioners to use or not to use in PCOS and acne	Thank you for your comment. For clarification this is not a recommendation for practitioners but a recommendation for further research. We have reviewed this appendix and are satisfied that it is describing a research question rather than making a recommendation for healthcare professionals to use.
British Dermatological Nursing Group (BDNG)	Evidence review H	General	General	No 32 – 38 regarding low dose isotretinoin saying there a no studies published – this is not the case as there are many studies published in the UK, America and Poland on low dose and its usefulness in certain patients and those with refractory acne The Pregnancy Prevention Programme is mandatory but thinking about certain patients who wish to sign the disclaimer, would it be useful to have a standard form?	Thank you for your comment. We looked at the issue of isotretinoin dose in the network meta-analysis (see evidence report F1), which compared different dosing regimens. Our literature searches did not identify any randomised trials of long term low dose isotretinoin to prevent relapse of acne, although there may be observational studies (which did not meet our inclusion criteria). The Pregnancy Prevention Programme uses a standardised form which has to be signed by the prescriber and the person.

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British Dermatological Nursing Group (BDNG)	Evidence review I	General	General	Maintenance treatment – could it be added in the practicalities of how to use the topical therapies and how to stop patients getting erythema, dryness etc also introducing the topical therapies slowly and gradually build up – the idea of topicals is to dry the skin, reduce comedones but you need to apply and wait 10 mins then use a non-comedogenic moisturiser to help combat the dryness. Glad topical therapies were given a weak recommendation as they are an important part of any maintenance regime for acne patients.	Thank you for your comment. In the general section on 'factors to take into account when choosing a treatment option' we have a recommendation addressing this point: 1.5.7 To reduce the risk of skin irritation associated with topical treatments, such as benzoyl peroxide or retinoids, start with alternate-day or short-contact application (for example washing off after an hour). If tolerated, progress to using a standard application. We have added a cross-reference to this recommendation to recommendation 1.7.4 to address this point.
British Dermatological Nursing Group (BDNG)	Evidence review J	General	General	No comments except glad to see you leave this to the consultant led team as patients are individuals and need different regimes	Thank you for your comment.
British Dermatological Nursing Group (BDNG)	Evidence review K	General	General	Glad to see again it is left to the consultant led team to decide. This is a good treatment option for patients with very painful lesions and it does make a difference to have this as a treatment option – even though there is little evidence	Thank you for your comment.
British Dermatological Nursing Group (BDNG)	Evidence review L & M	General	General	Patients pick and squeeze their spots they don't tend to scratch them "choose the risk of scarring as a critical outcome and how it substantially affects a person's physical and overall psychological wellbeing" – statement from NICE and prioritise this as a topic for research recommendations. We can't get NHS treatments for patients with scarring and we need to be careful with this comment to refer patients who are scarred to the NHS 1.4.5 this needs to be clearer. Also wonder which areas offer acne scarring as an NHS treatment, and do they fill out an IFR? Hardly any get approved and if they do it is only for the face. Needs to be worded better this section but hopefully this is a service NICE could recommend as its certainly a needed service	Thank you for your comment. The committee discussed the various actions that people with acne vulgaris can subject their acne lesions to such as picking, scratching, squeezing and scooping, which may lead to scarring. However, the committee noted the absence of evidence for these actions, and the lack of certainty about whether or not squeezing or scooping a lesion to release pus could be beneficial or harmful with regard to scarring. They therefore referred to picking and scratching only. Since there was very limited data on the risk factors leading to scarring the committee decided to suggest further research on this topic. The committee were aware that treatment for acne associated scarring is rarely provided in the NHS. The evidence was not strong and the committee was aware that there were resource implications. However, they did not want to completely rule this option out for people whose acne-related scarring is severe and persists a year after their acne has cleared.

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					They therefore made a recommendation in favour of this but asked healthcare professionals to 'consider' this as an option rather than providing it to all people meeting these criteria. This can then be adopted on a case by case basis. Whether or not this should be done using an individual funding request is outside the scope of this guideline.
British Dermatological Nursing Group (BDNG)	General	General	General	Little information on trimethoprim and spironolactone and their uses, also metformin. Be helpful for clinical practise	Thank you for your comment. We conducted a Network Meta-Analysis of all randomised controlled trial evidence of all acne treatments that met the inclusion criteria of the systematic review protocol, which subsequently informed an economic model. There was evidence showing that combinations of a topical treatment together with an oral tetracycline were clinically and cost-effective for the treatment of moderate to severe acne. The evidence was insufficient to recommend trimethoprim as a first line treatment option. The committee acknowledged that treatment options would be limited for people with moderate to severe acne for whom oral tetracyclines are contraindicated or not tolerated, and have decided, based on experience and expertise, to add a recommendation that for these people oral lymecycline or doxycycline could be replaced by trimethoprim or an oral macrolide, for example erythromycin. There was insufficient evidence to recommend spironolactone or metformin so the committee added a research recommendation to encourage further studies to investigate how effective these options are.
British Dermatological Nursing Group (BDNG)	Guideline	005	General	Mental Health referral - It clear on who to refer to MH services for severe cases– however the patients that have mild to moderate anxiety or depression when and where to refer? Often, they do not need MH service as not severe and do not want to overwhelm a MH service. However before prescribing isotretinoin, often asking primary care to carry out a MH assessment and report back. Should this be part of NICE recommendations? If so a recommended MH assessment tool for primary care to use? Or should it be the	Thank you for your comment. Mental health assessment was outside the scope of this guideline and assessment and referral related to anxiety and depression is the topic of other relevant NICE guidance that we cross refer to. In that way any updates to the depression guideline (which is currently in the process of being updated - see https://www.nice.org.uk/guidance/proposed/gid-qs10057) will be available to the healthcare professional and the

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				specialist care to complete? It would be great for more guidance on the mild to moderate MH health patients.	person with acne. In the final published web version of the guideline it will be easy navigation from one to the other guideline.
British Dermatological Nursing Group (BDNG)	Guideline	015	General	Relapse section - As this is NICE guidance for both primary and specialist care, it would be beneficial for clinicians to have more guidance if fails second course of isotretinoin? suggestions for further treatment? Third courses? or alternative treatments.	Thank you for your comment. No relevant evidence was identified for this review question, therefore the recommendations were based on the committee's experience and expertise. They decided that they could not be prescriptive about any further steps since they would have to be based on each individual circumstance and condition and that there are too many different scenarios to have a general recommendation for acne that fails to respond to two courses of oral isotretinoin. As is highlighted in the rationale and impact section of the guideline, the committee noted that in case of repeated acne relapse people should be referred or re-referred to a consultant dermatologist-led team where a tailored approach to their acne treatment could be offered. This would then be based on clinical judgment.
British Society for Medical Dermatology (BSMD)	Guideline	009	015	The committee question why the hormonal therapy, including spironolactone, is not to be considered in females outside of the circumstances stated.	Thank you for your comment. There was insufficient evidence to recommend antiandrogens such as spironolactone in the management of acne, therefore the committee made a recommendation for further research.
British Society for Medical Dermatology (BSMD)	Guideline	011	017	The committee disagree with this position. What is the rational for delaying treatment with isotretinoin in inflammatory forms of acne that are recognised to cause significant long term scarring? What is the evidence for the use of oral and topical therapies before the use of isotretinoin in these cases?	Thank you for your comment. The committee drafted their recommendations according to regulatory guidance from the Medicines & Healthcare products Regulatory Agency (MHRA) which stipulates to only use isotretinoin for severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) that are resistant to adequate courses of standard therapy with systemic antibacterials and topical therapies. The committee noted that the MHRA is conducting a review of oral isotretinoin and any changes that would impact on the current wording of the guideline will be updated.
British Society for Medical Dermatology (BSMD)	Guideline	012	007	The committee feel more guidance is required on the pregnancy prevention programme.	Thank you for your comment. Details of the pregnancy prevention programme and how advice should be given about contraception (in general or specifically in the context of oral isotretinoin) are outside the scope of this guideline. This is why the recommendation directly

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				What is the guidance for clinicians of women not wishing to follow the pregnancy prevention programme? Furthermore, the committee feel that there are circumstances in which it maybe appropriate to proceed with isotretinoin without the need to follow the pregnancy prevention programme and that these should be considered within the guideline e.g. women in a single sex relationship, women not sexually active for religious or other reasons, most girls under the age of 16	links to the website so that the healthcare professional can follow the details of this guidance. Providing a link rather than quoting details also ensures that in case future guidance on the pregnancy prevention programme changes, the most up-to-date guidance can still be accessed. Once the guideline is published in digital format it will be straightforward to navigate from the guideline to the pregnancy prevention programme website. Due to the teratogenic effects of oral isotretinoin the committee worded it in this way to capture anyone with the potential to become pregnant be it biological or behavioural. Making exceptions may lead to assumptions being made, for example about same sex relationship or transgender people.
British Society for Medical Dermatology (BSMD)	Guideline	012	023	The committee feel further information needs to be provided on the approach to be taken when an incomplete but ongoing response is achieved by the cumulative dose of 150mg/kg. There recognised problems and evidence against the use of fixed total dose approach to management of severe acne.	Thank you for your comment. The committee decided that there was insufficient evidence to make a specific recommendation in relation to this situation. Continuing above the cumulative dose to achieve further improvement or maintain ongoing response is not recommended and would be off-license use. Low dose isotretinoin was discussed in this context as maintenance treatment but due to a lack of evidence could not be recommended. The committee has made a research recommendation to encourage studies to investigate this further.
British Society for Medical Dermatology (BSMD)	Guideline	014	010	The committee question why the hormonal therapy, including spironolactone, is not to be considered in females outside of the circumstances stated.	Thank you for your comment. We conducted a Network Meta-Analysis of all randomised controlled trial evidence of all acne treatments that met the inclusion criteria of the systematic review protocol. There was insufficient evidence to recommend spironolactone so the committee added a research recommendation to encourage further studies to investigate how effective these options are.
Faculty of Sexual and Reproductive Healthcare Clinical	Guideline	009	012 - 014	We would suggest that recommendation 1.5.6 should be more strongly worded eg "Advise individuals with childbearing potential that they **must** use **highly** effective contraception." This is current FSRH and MHRA guidance during use of any teratogen or potential teratogen. We realise that topical retinoids are considered to be	Thank you for your comment. This sentence is in the context of a discussion with the person and 'will need to' refers to what they would 'need' to do if they were to choose this option. Using 'must' seems to suggest that they have already made the decision to take a tetracycline. We have therefore kept the wording as is.

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Effectiveness Unit				associated with low systemic absorption, but teratogenicity is not excluded.	
Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit	Guideline	009	015	Recommendation 1.5.7 The correct term is progestogen-only pill, rather than progesterone. We are concerned that the wording of this recommendation "For people receiving treatment for acne who wish to use hormonal contraception, consider using the combined oral contraceptive pill in preference to the progesterone-only pill." could be misleading and suggest (particularly if taken out of the context of this section of the guideline) that the combined pill is the best contraceptive option for everyone receiving any treatment for acne. We agree that combined hormonal contraception can be beneficial for management of acne. However, for individuals with childbearing potential who are using potentially teratogenic treatments, we would recommend use of a more effective method of contraception; the typical use first year contraceptive failure rate for any oral contraceptive is estimated at 9%, which is not acceptable in the presence of a teratogen or potential teratogen – condoms would have to be used absolutely reliably in addition. Highly effective contraceptive methods have failure rates lower than 1% and are the FSRH and MHRA-recommended contraceptive options during use of a teratogen. We note that the advice given here for topical retinoids is different to that given later for oral retinoids, and we assume that that is because risk of teratogenicity is assumed to be low with topical treatments. Regardless, we would advocate use of highly effective contraception.	Thank you for your comment. We have corrected the terminology to progestogen-only pill. Best contraceptive methods for women with acne was outside the scope of this guideline. There was insufficient evidence that the combined oral contraceptive pill is effective as a first line treatment option for acne. However, the committee noted that the progestogen only pill is known to be associated with acne. They therefore intentionally worded it like this to highlight that the combined oral contraceptive pill may be preferable the progestogen-only pill. It is also in the context of when this choice has already been made by the women rather than in discussions about contraception in general. This is explained in the rationale and impact section. We have highlighted elsewhere that a number of treatments should not be used in pregnancy and that people taking oral isotretinoin need to follow the pregnancy prevention programme. We have added to the recommendation a link to the recommendation in the oral isotretinoin section that references the pregnancy prevention programme to highlight this point.
Faculty of Sexual and Reproductive	Guideline	012	013 - 014	Recommendation 1.5.17	Thank you for your comment. Details of the pregnancy prevention programme and how advice should be given about contraception (in general or specifically in the context of oral isotretinoin) are outside

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Healthcare Clinical Effectiveness Unit				We suggest that it is inadequate to recommend that users of isotretinoin with childbearing potential are "inform[ed] that they need to follow the pregnancy prevention programme". We consider that the onus should be on the person initiating treatment with the teratogen to discuss the requirements of the PPP with the user and provide information as to how they can access highly effective contraception (ideally they would have a direct referral). You might consider revising the bullets here to include one that says that the user should be informed that they **must** use **highly effective** contraception during use of oral isotretinoin and one that says that the prescriber must ensure that highly effective contraception is in place. The current work on implementation of the PPP for valproate medications is highlighting the importance of facilitating access to appropriate contraception.	the scope of this guideline. This is why the recommendation directly links to the website so that the healthcare professional can follow the details of this guidance. Providing a link rather than quoting details also ensures that in case future guidance on the pregnancy prevention programme changes, the most up-to-date guidance can still be accessed. Once the guideline is published in digital format it will be straightforward to navigate from the guideline to the pregnancy prevention programme website.
Galderma (UK) Ltd	Evidence review E1	057	030	Could you please check that the sentence should read 'topical retinoid or an oral …', not as stated.	Thank you for your comment. This has been corrected.
Galderma (UK) Ltd	Evidence review E1	132	General	Could you please check for a typo, we think it should read ...'is affected' and not ...'is afaffected' as stated.	Thank you for your comment. This has been corrected.
Galderma (UK) Ltd	Evidence review E2	030	General	The text currently included under 'Stein Gold 2016' makes reference to the following intervention arms of the study: Stein Gold, L. F., Jarratt, M. T., Bucko, A. D., Grekin, S. K., Berlin, J. M., Bukhalo, M., Weiss, 2 J. S., Berk, D. R., Chang-Lin, J. E., Lin, V., et al. Efficacy and Safety of Once-Daily Dapsone Gel, 7.5% for Treatment of Adolescents and Adults With Acne Vulgaris: first of Two Identically Designed, Large, Multicenter, Randomized, Vehicle-controlled Trials. Journal of Drugs in Dermatology, 2016, 15(5):553-61: Intervention arm 1: Dapsone gel 7.5%. ADAP 0.3%/BPO 2.5% gel	Thank you for your comment. This has been corrected to dapsone gel 7.5% versus vehicle. This mistake did not affect the network or pairwise meta-analysis, where the interventions were correctly classified.

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				Intervention: arm 2: Vehicle. ADAP 0.1%/BPO 2.5% gel However, in view of the study focusing on dapsone gel 7.5% vs vehicle, we feel that ADAP 0.3%/BPO 2.5% gel and ADAP 0.1%/BPO 2.5% gel have been erroneously mentioned in this section, and the two study descriptions have been amalgamated into one. The following study evaluates ADAP 0.3%/BPO 2.5% gel, ADAP 0.1%/BPO 2.5% gel, and vehicle in 3 intervention arms, as per Evidence Review F1 page 28: Stein Gold, L., Weiss, J., Rueda, M.J., Liu, H. and Tanghetti, E., 2016. Moderate and severe inflammatory acne vulgaris effectively treated with single-agent therapy by a new fixed-dose combination adapalene 0.3%/benzoyl peroxide 2.5% gel: a randomized, double-blind, parallel-group, controlled study. American journal of clinical dermatology, 17(3), pp.293-303.	
Galderma (UK) Ltd	Evidence review E2	143 - 145	General	The text currently included under 'Stein Gold 2016' makes reference to the following intervention arms of the study: Stein Gold, L. F., Jarratt, M. T., Bucko, A. D., Grekin, S. K., Berlin, J. M., Bukhalo, M., Weiss, 2 J. S., Berk, D. R., Chang-Lin, J. E., Lin, V., et al. Efficacy and Safety of Once-Daily Dapsone Gel, 7.5% for Treatment of Adolescents and Adults With Acne Vulgaris: first of Two Identically Designed, Large, Multicenter, Randomized, Vehicle-controlled Trials. Journal of Drugs in Dermatology, 2016, 15(5):553-61: Intervention arm 1: Dapsone gel 7.5%. ADAP 0.3%/BPO 2.5% gel Intervention: arm 2: Vehicle. ADAP 0.1%/BPO 2.5% gel However, in view of the study focusing on dapsone gel 7.5% vs vehicle, we feel that ADAP 0.3%/BPO 2.5% gel and ADAP	Thank you for your comment. This has been corrected to dapsone gel 7.5% versus vehicle. This mistake did not affect the network or pairwise meta-analysis, where the interventions were correctly classified.

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				0.1%/BPO 2.5% gel have been erroneously mentioned in this section, and the two study descriptions have been amalgamated into one. The following study evaluates ADAP 0.3%/BPO 2.5% gel, ADAP 0.1%/BPO 2.5% gel, and vehicle in 3 intervention arms, as per Evidence Review F1 page 28: Stein Gold, L., Weiss, J., Rueda, M.J., Liu, H. and Tanghetti, E., 2016. Moderate and severe inflammatory acne vulgaris effectively treated with single-agent therapy by a new fixed-dose combination adapalene 0.3%/benzoyl peroxide 2.5% gel: a randomized, double-blind, parallel-group, controlled study. American journal of clinical dermatology, 17(3), pp.293-303.	
Galderma (UK) Ltd	Evidence review F1	009	General	Please consider adding to the 'Retinoid or retinoid like' options box – **for completeness we request that you include trifarotene to the existing list**.	Thank you for your comment. We have added trifarotene to the PICO summary tables and full protocols of evidence reviews E1, E2, F1 and F2.
Galderma (UK) Ltd	Evidence review F1	060	001	The reference currently included under 'Stein Gold 2016' is stated as: Stein Gold, L. F., Jarratt, M. T., Bucko, A. D., Grekin, S. K., Berlin, J. M., Bukhalo, M., Weiss, 2 J. S., Berk, D. R., Chang-Lin, J. E., Lin, V., et al. Efficacy and Safety of Once-Daily Dapsone Gel, 7.5% for Treatment of Adolescents and Adults With Acne Vulgaris: first of Two Identically Designed, Large, Multicenter, Randomized, Vehicle-controlled Trials. Journal of Drugs in Dermatology, 2016, 15(5):553-61 However, the document makes reference to the following study evaluating ADAP 0.3%/BPO 2.5% gel, ADAP 0.1%/BPO 2.5% gel, and vehicle in 3 intervention arms instead:	Thank you for your comment. The correct reference has now been added. This mistake did not affect the network or pairwise meta-analysis, where the interventions were correctly classified.

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Galderma (UK) Ltd	Evidence review F1	161 - 163	General	The reference currently included under this study is stated as: Stein Gold, L. F., Jarratt, M. T., Bucko, A. D., Grekin, S. K., Berlin, J. M., Bukhalo, M., Weiss, 2 J. S., Berk, D. R., Chang-Lin, J. E., Lin, V., et al. Efficacy and Safety of Once-Daily Dapsone Gel, 7.5% for Treatment of Adolescents and Adults With Acne Vulgaris: first of Two Identically Designed, Large, Multicenter, Randomized, Vehicle-controlled Trials. Journal of Drugs in Dermatology, 2016, 15(5):553-61 However, the document makes reference to the following study evaluating ADAP 0.3%/BPO 2.5% gel, ADAP 0.1%/BPO 2.5% gel, and vehicle in 3 intervention arms instead: Stein Gold, L., Weiss, J., Rueda, M.J., Liu, H. and Tanghetti, E., 2016. Moderate and severe inflammatory acne vulgaris effectively treated with single-agent therapy by a new fixed-dose combination adapalene 0.3%/benzoyl peroxide 2.5% gel: a randomized, double-blind, parallel-group, controlled study. American journal of clinical dermatology, 17(3), pp.293-303. We feel this may be an error in referencing.	Thank you for your comment. The correct reference has now been added. This mistake did not affect the network or pairwise meta-analysis, where the interventions were correctly classified.
Galderma (UK) Ltd	Evidence review F2	040	014	The reference currently included under 'Stein Gold 2016' is stated as:	Thank you for your comment. The correct reference has now been added. This mistake did not affect the network or pairwise meta-analysis, where the interventions were correctly classified.

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Galderma (UK) Ltd	Evidence review F2	126 - 127	General	The reference currently included under 'Stein Gold 2016' is stated as: Stein Gold, L. F., Jarratt, M. T., Bucko, A. D., Grekin, S. K., Berlin, J. M., Bukhalo, M., Weiss, 2 J. S., Berk, D. R., Chang-Lin, J. E., Lin, V., et al. Efficacy and Safety of Once-Daily Dapsone Gel, 7.5% for Treatment of Adolescents and Adults With Acne Vulgaris: first of Two Identically Designed, Large, Multicenter, Randomized, Vehicle-controlled Trials. Journal of Drugs in Dermatology, 2016, 15(5):553-61	Thank you for your comment. The correct reference has now been added. This mistake did not affect the network or pairwise meta-analysis, where the interventions were correctly classified.

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				However, the document makes reference to the following study evaluating ADAP 0.3%/BPO 2.5% gel, ADAP 0.1%/BPO 2.5% gel, and vehicle in 3 intervention arms instead: Stein Gold, L., Weiss, J., Rueda, M.J., Liu, H. and Tanghetti, E., 2016. Moderate and severe inflammatory acne vulgaris effectively treated with single-agent therapy by a new fixed-dose combination adapalene 0.3%/benzoyl peroxide 2.5% gel: a randomized, double-blind, parallel-group, controlled study. American journal of clinical dermatology, 17(3), pp.293-303. The interior text also makes reference to 'DAPS-topical', which was not included in the trial. We feel this may be an error in referencing and interior text.	
Galderma (UK) Ltd	Guideline	004	001 - 009	The document makes reference to avoidance of 'oil-based skin products' for patients with acne, as well as use of 'oil-free products'. Some cosmetics may contain oils as part of their formulation to ensure hydration of the skin. **As such, we would like to recommend the consideration of inclusion of 'non-comedogenic' criteria instead. Cosmetic product directed studies often test for 'non-comedogenicity', which may be a better indicator of effect of the cosmetic on the skin of an acne patient.**	Thank you for your comment. The committee decided that as well as oil-based it is also advisable that comedogenic products should be avoided. The term 'oil-free' has been removed for consistency in wording.. We have therefore added this to the recommendations (see also the terms used section for a brief definition and the rationale sections which was updated accordingly). If cosmetics contain oils as part of their formulation but are not 'oil-based' or 'comedogenic' then they could be used.
Galderma (UK) Ltd	Guideline	004	004 - 005	Section 1.2.2 states 'advise people with acne to avoid oil-based skin products'. **In view of the broad definition of 'oil-based skin products, we feel that additional clarification is needed with regards to the percentage of oil content that falls under this definition.**	Thank you for your comment. The committee felt that the term 'oil based' is readily understood but it was noted that there is no clear definition for an exact percentage of oil that this can contain. They also decided that as well as avoiding oil based it is also advisable to avoid comedogenic skin care products. We have therefore added this to the recommendations (see also the terms used section for a brief definition and the rationale sections which was updated accordingly).

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Galderma (UK) Ltd	Guideline	004	017 - 018	Section 1.4.2 makes reference to referral to 'consultant dermatologist-led' team. In clinical practice, General Practitioners with Extended Role in Dermatology are a valuable resource, who may also be able to assist in diagnosis and treatment of patients who fall under the categories listed. Such primary care led services are already in place in many parts of the country, and are a valuable resource in terms of the currently restricted access of patients to hospital-led services. **We would like to suggest a consideration of the addition of this healthcare professional type to the Guideline, such as 'Consultant Dermatologist/GP Dermatology Specialist led team'.**	Thank you for your comment. We have now acknowledged in the 'terms used in the guideline' that 'this team may include associate specialists and healthcare professionals accredited for extended roles for dermatology under consultant supervision'. We reviewed all recommendations using 'consultant-dermatologist-led team' and for recommendations that mention this team it is possible that oral isotretinoin might be or may become a treatment option. In line with MHRA advice regarding oral isotretinoin prescribing (that is the prescriptions for oral isotretinoin should be issued under the consultant's name from a hospital-based pharmacy), then the team may include GPwERs
Galderma (UK) Ltd	Guideline	016	014	Section 1.8 explored the management of acne-related scarring. We note that several physical interventions have been recommended for severe acne-related scarring persistent a year after acne has cleared. Evidence for adapalene 0.3%/benzoyl peroxide 2.5% and its effect on the reduction of acne scars has been appraised by the MHRA and subsequently, as of 27th August 2020, has been included in the Summary of Product Characteristics, Section 5.1. The core study shows that patients with moderate or severe facial acne with mild or moderate scars treated with adapalene 0.3%/benzoyl peroxide 2.5% (Study reference: Dréno *et al*., Prevention and Reduction of Atrophic Acne Scars with Adapalene 0.3%/Benzoyl Peroxide 26 2.5% Gel in Subjects with Moderate or Severe Facial Acne: Results of a 6-Month 27 Randomized, Vehicle-Controlled Trial Using Intra-Individual Comparison. American Journal 28 of Clinical Dermatology, 2018, 19(2):275-286) vs. vehicle had a decreased scar count after 24 weeks of -15.5% ($p<0.0005$). The difference between total acne scars between the treatment vs.	Thank you for your comment. There was some evidence to suggest that glycolic acid peels and CO2 laser treatment either alone or after a session of punch elevation were efficacious in improving the appearance of acne-related scars, and therefore the committee agreed to recommend these treatments. We have checked the quoted references against our included and excluded studies lists. Dreno 2018 study was included in the pairwise meta-analysis related to the management of moderate to severe acne, but the outcome of scarring was not often enough reported across studies to be analysed in the Network Meta-Analysis. The study was not included in the scarring management review as this focussed on scarring management and the topic of the Dreno 2018 is a combination of prevention and management. Therefore it did not meet the criteria of the protocol. Loss 2018 is not relevant as it is a phase II, single-center, open-label, exploratory study.

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				vehicle sides of the face was -3.7 ± 4.4. Adapalene 0.3%/benzoyl peroxide 2.5% gel primarily reduced scars of 2-4mm size. Further evidence, based on the following study: 'Loss *et al*, 2018. Adapalene 0.3% gel shows efficacy for the treatment of atrophic acne scars. Dermatology and therapy, 8(2), pp.245-257', showed that "treatment with adapalene 0.3% gel led to modifications in the expression of serine proteases and serine protease inhibitors. The expression of several serine proteases, including KLK6, KLK9 and KLK13, was upregulated along with that of members of the SERPIN family, suggesting an activation of the desquamation process. In terms of dermal matrix macromolecules, both type I collagen alpha 1 (COL1A1) and type III collagen alpha 1 (COL3A1) showed higher expression levels after 24 weeks of adapalene treatment compared to baseline … the mRNA levels of COL1A1 and COL3A1 were slightly increased after 24 weeks of therapy with adapalene 0.3% gel. The clinical improvement of atrophic scars after adapalene 0.3% gel treatment could be concomitantly related to an increase in epidermal thickness and activation of collagen production". **In view of the evidence included above, we would like the group to consider the addition in the Guideline on the potential effect of adapalene 0.3%/benzoyl peroxide 2.5% on the reduction of acne scars in patients with current active moderate to severe acne vulgaris with mild or moderate scars.**	
Galderma (UK) Ltd	Guideline	017 - 018	019 – 021 001 - 008	The guideline makes reference to treatments that apply to the management of acne on the face, chest and back. Given the high prevalence of truncal lesions of around 50% in patients with acne vulgaris (Reference: Del Rosso *et al*., 2019. Truncal Acne: A Neglected Entity. Journal of drugs in dermatology: JDD, 18(12), pp.205-1208.), special reference to this phenomenon should be made.	Thank you for your comment. The committee decided that the current criteria provided in the 'terms used in this guideline' section apply to acne anywhere on the body. The committee decided in the protocol not to divide evidence into facial and truncal acne to optimise the overall evidence base for the Network Meta-Analysis of randomised controlled trials so the committee could not directly

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				We suggest specifically including recommendation in the Guideline that patient assessment is not restricted solely to the face, with a reminder to check the trunk for acne lesions when reviewing the patient, to encourage good clinical practice. Under 'Terms used in this guideline', there is a defined criterion of lesions which delineates between 'mild to moderate acne' and 'moderate to severe acne'. It would be useful to clarify if the guideline implies whether the criteria listed (inflammatory, non-inflammatory, nodules) apply to the face only, or the entire area affected by acne (face, chest and back). **It would be useful for Healthcare Professionals to have further clarification on this in the Guideline to help categorise patients (such as patients with acne lesions on the face only, or patients with both face and truncal lesions), and improve overall assessment, thus allowing appropriate treatment.**	comment on this but decided that the first-line treatment options would apply to all people with acne. Please note that assessment of acne was beyond the scope of this guideline.
Galderma (UK) Ltd	Guideline	General	General	The Guideline is very clear on the position of antimicrobial resistance, and the importance of antibiotic stewardship. We feel that avoidance of overuse of antibiotics is crucial in acne and offer full support of the recommendation.	Thank you for your comment.
Galderma (UK) Ltd	Guideline	General	General	The Guideline recommends the use of retinoid monotherapy solely as a second-line maintenance treatment. Shared clinician experience has highlighted that dermatologists are likely to apply a step-wise approach to treatment for patients who are on the milder spectrum of acne. We have received reports that certain cohorts of patients (such as teenagers) are more likely to be compliant with a simple regimen, thus starting with monotherapy initially, before moving to dual/combination therapies if it does not improve. Evidence from: 'Tan *et al*., 2019. Randomized phase 3 evaluation of trifarotene 50 µg/g cream treatment of moderate facial and truncal acne. Journal of the American Academy of Dermatology, 80(6),	Thank you for your comment. We conducted a Network Meta-Analysis of all randomised controlled trial evidence of all acne treatments that met the inclusion criteria of the systematic review protocol, which subsequently informed an economic model. Monotherapies were found to be less clinically and cost-effective than combination therapies. The committee therefore recommended these combination treatments and only recommended monotherapy with benzoyl peroxide to those who cannot tolerate other treatment or to those people where other treatments are contraindicated. Due to the findings of the network meta-analysis and economic analysis (no evidence, evidence of no efficacy, or lower clinical and cost-effectiveness) for other options, for example azelaic acid or

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				pp.1691-1699', to date the largest clinical study evaluating outcomes not only in facial acne, but also in truncal acne as two separate, defined endpoints, involved a total of 2,420 randomised patients, of which 1,214 received trifarotene cream and 1206 received vehicle. The results showed that in the treatment arm of patients with moderate facial and truncal acne, trifarotene led to a statistically significant reduction in inflammatory and non-inflammatory lesions at week 12 versus vehicle. This demonstrated efficacy of retinoid monotherapy in not only the primary endpoints of facial acne but also in the defined secondary endpoints of acne on large body surface areas (on the chest and back). Furthermore, retinoid monotherapy may be of additional benefit for patients with acne on both face and trunk in that the absence of benzoyl peroxide will prevent bleaching of fabrics during the treatment of these large surface areas. **In view of the above evidence on the use of retinoid monotherapy, we would suggest adding into the Guideline this management option for patients who may be on the milder end of the 'mild to moderate' acne spectrum, for those who may have a sensitivity to antibiotics or benzoyl peroxide, as well as those with facial acne who also require treatment of acne on large body surface areas (such as the trunk).**	adapalene monotherapy, the committee did not recommend those as first line treatments. Neither did they recommend against their use and therefore this does not preclude them being used by clinicians in the management of acne based on individual circumstances and clinical expertise. We have emphasised this in the rationale section and have also extended the discussion in the evidence review to clarify the reasons why these options were not included. The reference by Tan (2019) is included in the evidence review F1 on moderate to severe acne and therefore contributed to the overall Network Meta-Analysis results which overall as described above showed favourable results for combination treatments over monotherapies.
Healthcare Improvement Scotland - Scottish Antimicrobial Prescribing Group	Guideline	006	007	Section 1.5 • The use of Azelaic Acid for darker skin to reduce the risk of hyperpigmentation associated with other topical treatments has not been highlighted • The use of Dianette, for patients with mild-moderate and even severe acne, (along with topical treatment if needed) who wish contraception as well as acne treatment, seems to be suggested as second line, behind first line combined contraceptive pill and any acne treatment, whereas in general	Thank you for your comment. The committee is not ruling out the use of azelaic acid but did not feel that they could explicitly comment on this since the evidence did not support this to be an effective treatment strategy (there was also no specific evidence for its use in people with darker skin). Dianette (co-cyprindiol) was not recommended as a first line treatment because, according to the results of the guideline network meta-analysis, there was no evidence that it was effective in either mild-to-moderate or moderate-to-severe acne.

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				practice it would probably be used first line, to improve compliance. • There does not seem to be a warning on not using tetracyclines in the under 12s? It would be helpful to give recommended first line tetracycline. To preserve activity of doxycycline for use in respiratory infections and limit resistance it may be useful to suggest lymecycline as first line. • Erythromycin use as first line in pregnancy does not seem to be mentioned. • The issue of photosensitivity is a very real issue with the tetracyclines and should be highlighted more.	Table 1 of the guideline, which lists all recommended first-line treatment options together with advantages and disadvantages, does have a warning against use of treatments containing oral tetracycline for aged under 12. The committee recommended either oral lymecycline or oral doxycycline after consideration of practicalities in use and side effects of oral tetracyclines. The recommendations now include use of an oral macrolide (for example erythromycin)as an alternative for people who cannot tolerate or have contraindications to oral lymecycline or oral doxycycline. The fact that oral tetracyclines can cause photosensitivity is included in Table 1, under disadvantages of therapies that include oral tetraclyclines.
Healthcare Improvement Scotland - Scottish Antimicrobial Prescribing Group	Guideline	General	General	Supportive of clear advice included on duration of use for oral antibiotics to limit inadvertent long term use.	Thank you for your comment.
Healthcare Improvement Scotland - Scottish Antimicrobial Prescribing Group	Questions on comments form	General	General	No particular issues identified with implementation and largely reflects current practice. Impact of COVID-19 – changes in face-to-face vs virtual consultations may require consideration for assessing symptoms and response to treatment.	Thank you for your comment. The use of virtual consultations is outside the scope of the guideline. However, the committee were aware of resources that are available addressing this issue. In 2020 the British Association of Dermatologists issued publicly available guidance for managing patients on isotretinoin during the Coronavirus pandemic (https://www.bad.org.uk/shared/get-file.ashx?itemtype=document&id=6661) and also on teledermatology including video consultation and remote working (https://www.bad.org.uk/healthcare-professionals/covid-19/remote-dermatology-guidance).

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Mylan UK	Guideline	006 – 007	017 Table 1	We are in agreement with the first-line treatment outlined in Table 1 highlighting the use of topical tretinoin with topical clindamycin for any severity of acne ranging from mild to severe as defined in the current NICE draft guideline version. This recommendation fully reflects the currently available data on this topical fixed dose combination including a pooled analysis of efficacy data from three pivotal studies of topical tretinoin with topical clindamycin in which data from the three studies were combined. It showed that this topical fixed dose combination was significantly more effective than clindamycin, tretinoin and vehicle in terms of the median percentage change from baseline to week 12 in inflammatory, non-inflammatory and total lesions in the overall population. The same result was obtained for adolescent subgroup (patients aged 11–17 years), and subgroup of patients with mild/moderate and severe acne.[1] Additionally, another study showed a significant improvement in acne severity in the group using topical tretinoin with topical clindamycin, indicated by the patient-assessed VAS score decreasing continuously from baseline to Week 12. QoL also improved after treatment with this topical fixed dose combination.[2] In alignment with the antimicrobial resistance agenda, topical tretinoin with topical clindamycin is not associated with the development of antibiotic resistance. Data from a 16-week study of 54 acne patients showed that topical tretinoin with topical clindamycin was not associated with the development of clindamycin-resistant C. acnes, in contrast to a 16-week study of 79 patients treated with clindamycin monotherapy in which clindamycin-resistant C. acnes (formerly P. acnes) increased by approximately 1600% versus baseline.[1,3-5]	Thank you for your comment. It is good that the recommendations reflect your knowledge from the current evidence. For your information we cross checked the quoted references with our included and excluded studies: The Cunliffe 2002 and Jackson 2010 studies were included in the mild-to-moderate and moderate-to-severe acne Network Meta-Analysis (NMA), respectively. Dréno 2014 was excluded because it did not report data in the way that allowed it to be extracted for the NMA – (pooled analysis of 3 studies combined, 2 of which include people with mild to severe acne which did not fit the population protocol characteristics). Ohlson 2019 was also excluded as it is a non-randomised study but it does not appear in the excluded studies list because it was excluded early on in the study identification process because it clearly did not meet study design criteria. Dreno 2016 was a published letter rather than a research study and was therefore not included.

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				References: 1. Dréno B, Bettoli V, Ochsendorf F, Layton AM, Perez M, Dakovic R, Gollnick H. Efficacy and safety of clindamycin phosphate 1.2%/tretinoin 0.025% formulation for the treatment of acne vulgaris: pooled analysis of data from three randomised, double-blind, parallel-group, phase III studies. Eur J Dermatol. 2014 Mar-Apr;24(2):201-9. 2. Ohlson J, Dakovic R, Berg M. Observational Study of Clindamycin Phosphate and Tretinoin Gel for the Treatment of Acne. J Drugs Dermatol. 2019 Apr 1;18(4):328-334. 3. Cunliffe WJ, Holland KT, Bojar R, Levy SF. A randomized, double-blind comparison of a clindamycin phosphate/benzoyl peroxide gel formulation and a matching clindamycin gel with respect to microbiologic activity and clinical efficacy in the topical treatment of acne vulgaris. Clin Ther. 2002 Jul;24(7):1117-33. 4. Jackson JM, Fu JJ, Almekinder JL. A randomized, investigator-blinded trial to assess the antimicrobial efficacy of a benzoyl peroxide 5%/ clindamycin phosphate 1% gel compared with a clindamycin phosphate 1.2%/tretinoin 0.025% gel in the topical treatment of acne vulgaris. J Drugs Dermatol. 2010 Feb;9(2):131-6. 5. Dréno B, Lambert J, Bettoli V. Are retinoid/antibiotic fixed-dose combination acne treatments associated with antibiotic resistance? Eur J Dermatol. 2016 Jan-Feb;26(1):90-1.	
Mylan UK	Guideline	007	Table 1	In column 3 row 2 we suggest adding tolerability/suitable for sensitive skin as an advantage of topical tretinoin with topical clindamycin as a study by Goreshi et al. found that topical tretinoin	Thank you for your comment. The committee recommended these options because they had similar effectiveness and cost effectiveness. No clear difference in overall discontinuation and

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				with topical clindamycin was less irritating than adapalene and benzoyl peroxide when used daily over a period of 3 weeks' application. The authors suggested that topical tretinoin with topical clindamycin may be a better first choice combination topical acne medication for patients with sensitive skin if choosing a treatment based solely on short-term irritancy potential.[6] This is further supported by an article recently published on the Journal of Drugs in Dermatology, while we accept that this isn't included in the remit of the method generation of this guideline, the findings suggest that topical tretinoin with topical clindamycin and adapalene and benzoyl peroxide have similar efficacy in the treatment of mild to moderate papulopustular acne. However, topical tretinoin with topical clindamycin was better tolerated than adapalene and benzoyl peroxide by both medical and subject evaluation. The authors conclude that topical tretinoin with topical clindamycin is an effective and tolerated treatment option.[7] We suggest that it is important to stress the need for patient adherence. Having a good tolerability profile, the combination topical tretinoin with topical clindamycin can improve patient adherence thanks also to its ease of use as stated by Yentzer BA, et al.[8] References 6. Goreshi R et al. A Double-Blind, Randomized, Bilateral Comparison of Skin Irritancy Following Application of the Combination Acne Products Clindamycin/Tretinoin and Benzoyl Peroxide/Adapalene. Journal of Drugs in Dermatology. 2012 11(12):1422-6 7. Aschoff R, Möller S, Haase R, Kuske M. Tolerability and Efficacy of Clindamycin/Tretinoin versus Adapalene/Benzoyl Peroxide in the Treatment of Acne	discontinuation due to side effects was shown. However, the table highlights that tretinoin with clindamycin is not associated with bleaching of hair and fabric which implies that it may be better tolerated. There are pros and cons associated with any of the options and they have to be discussed with the person to agree a shared treatment plan. We have also cross checked the provided references against our included and excluded studies according to our protocol. The Yentzer 2010 study was included in the mild-to-moderate NMA. Goreshi 2012 was excluded because it did not report the outcomes specified in the protocol and Achoff 2021 was published after the search date, so was not included. Since the Achoff study reported on two recommended options it may not have had a substantial effect on the results of the Network Meta-Analysis and tolerability would be an issue to discuss in the shared decision making process. The need for patient adherence has been stressed in recommendation 1.1. We agree that good tolerability is likely to improve patient adherence and several recommendations were made aiming at improving adherence, for example 1.5.5 and 1.5.7. The committee also added a cross reference to the NICE guideline on medicine adherence to recommendations 1.1.1 and 1.5.5 to emphasises the importance of this.

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				Vulgaris. J Drugs Dermatol. 2021;20(3): doi:10.36849/JDD.2021.5641 8. Yentzer BA, et al. Simplifying regimens promotes greater adherence and outcomes with topical acne medications: a randomized controlled trial. Cutis. 2010 Aug;86(2):103-8.	
Mylan UK	Guideline	General	General	We feel that in the guideline there is a lack of focus on product tolerability. We suggest this could be an important factor in treatment choice and for improving patient adherence.	Thank you for your comment. Table 1 includes information about tolerability and the Network Meta-Analysis included outcomes related to discontinuation for any reason and discontinuation due to side effects. The committee took these into account when making their recommendations and selected those which they considered to have the best balance between benefits and risks.
NHS England and NHS Improvement	General	General	General	Consideration needs to be given in this guidance to supporting individuals who may need extra support because of their ability, to ensure they are not marginalised. For example reasonable adjustments, use of a range of media and mediums to support understanding, support with medication compliance where a person may have a cognitive impairment or social situation which may impact this. A clear outline of working towards the persons goals is also needed to be emphasised to ensure this isn't just seen as a medical approach to a complex condition. Also what are the implications for commissioners and although the guidance is directed to them there isn't reference to their role in this in the guidance itself. (NP)	Thank you for your comment. The committee reviewed the document and decided that they made their recommendations to apply to all age groups equally, which would therefore advance equality of access. The use of a range of ways of providing information is described in the NICE guideline on patient experience of adults in NHS services to which we cross-reference (this includes sections on shared decision making and tailoring information to the individual). In relation to people with cognitive impairments, a new recommendation was added: 1.1.2 Include parents and carers in discussions if the person with acne would like them to be involved, or when support is required (for example, for a person with cognitive impairment). This will ensure that people with cognitive impairment will get support. The impact on practice is described in the guideline's 'rationale and impact' section which would also be relevant to commissioners particularly in relation to management of scarring.

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NHS England and NHS Improvement	Guideline	003	005 - 013	We welcome the guidance on the topics to cover in the formation given to the patients.	Thank you for your comment.
NHS England and NHS Improvement	Guideline	004	006	1.2.3 - Suggest consideration as to including what products to be used to remove make-up as this may have a significant impact. (NP)	Thank you for your comment. Recommendations 1.2.1 and 1.2.2 refer to syndet-based skin cleansers or oil-free products. We have clarified in that rationale that the committee noted that make-up should be removed at the end of the day. This could be part of skin cleansing advice (see recommendation 1.2.1) or in addition to it if it is a specific area of the face or a specific type of make-up. Given the lack of evidence, the committee decided that they could not be prescriptive about the products that should be used for make-up removal.
NHS England and NHS Improvement	Guideline	004	008	1.2.4 - Suggest further detail/content including advice on how to stop this behaviour (NP)	Thank you for your comment. The committee was not aware what the best approach would be to stopping such behaviour that can be generalised to everyone with acne. They thought that this would depend on the individual as well as the type of acne they have (i.e. if the lesions are infected they may be more itchy) and this would therefore be discussed on a case by case basis when the advice is given. Therefore they felt that they could not comment on that in the guideline.
NHS England and NHS Improvement	Guideline	004	011	1.3.1 - Recommend addition of general healthy eating and exercise be included as a health promotion message and ensure the impact of diet and exercise are clear here. (NP)	Thank you for your comment. There was insufficient evidence for any particular diet. However, we have now added a link to general NHS information about a healthy balanced diet to the guideline. So that a healthy dietary lifestyle can be promoted. Exercise was not a topic addressed in the guideline because it was beyond the guideline scope.
NHS England and NHS Improvement	Guideline	004	017	1.4.2 - Will this include Consultant Dermatologists and GPs with a special interest working in Primary Care? (NP)	Thank you for your comment. We have now acknowledged in the 'terms used in the guideline that 'this team may include associate specialists and healthcare professionals accredited for extended roles for dermatology under consultant supervision'. We reviewed all recommendations using 'consultant-dermatologist-led team' and for recommendations that mention this team it is

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					possible that oral isotretinoin might be or may become a treatment option. In line with MHRA advice regarding oral isotretinoin prescribing (that is the prescriptions for oral isotretinoin should be issued under the consultant's name from a hospital-based pharmacy), then the team may include GPwERs
NHS England and NHS Improvement	Guideline	006	027	First Line treatment options – what about Area Prescribing Committee Formulary's - have the recommendations been checked against these and local antibacterial guidelines? (NP)	Thank you for your comment. The committee took into account the principles of antimicrobial stewardship on an overall rather than regional level because guideline apply to all of England and are influential elsewhere. The committee decided that treatment that is supported by the evidence would lead to skin improvement that may mean no antibiotic is used or a shorter duration of an antibiotic is used. They also recommended against monotherapy with antibiotics. The committee believed that this would promote a cautious use of antibiotics in line with antibiotic guidance.
NHS England and NHS Improvement	Guideline	011	004	1.5.13 - Is there a definition of 'adequate response' and how clinicians and individuals are to measure this i.e. reduction in certain numbers of lesions or is it a joint decision with patient? Also applicable to the term 'relapse', what is the definition here? (NP)	Thank you for your comment. We have clarified in the rationale section that both of these ('adequate response' and 'relapse') would be based on a joint decision made by the healthcare professional and the person.
NHS England and NHS Improvement	Guideline	011	016	Clarification whether oral isotretinoin can be started in primary care without referral to secondary care.	Thank you for your comment. We have directly linked the oral isotretinoin recommendation to the MHRA advice which states that it can only be prescribed by a consultant dermatologist-led team. In the referral section we have also ensured that any person who would potentially benefit from oral isotretinoin would be referred to such a team.
NHS England and NHS Improvement	Guideline	012	007	1.5.17 - Will the Expert Working Group advising the MHRA on Isotretinoin outcomes be included when available? (NP)	Thank you for your comment. The MHRA is conducting a review of oral isotretinoin and any changes that would impact on the current wording of the guideline will be updated. However, the NICE guideline committee is not involved in the MHRA review.
NHS England and NHS Improvement	Guideline	013	005	Again clarification whether use of oral corticosteroids with oral isotretinoin can occur in primary care or should be under secondary care	Thank you for your comment. Since oral isotretinoin according to the MHRA safety advice can only be prescribed by a consultant dermatologist-led team this would be done under secondary care.

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NHS West Essex CCG	Guideline	004	013	Concerned referral to specialist care does not include acne scarring	Thank you for your comment. The committee decided that it is not feasible to refer everyone with acne associated scarring to specialist care. In the committee's experience prompt treatment may prevent acne associated scarring and therefore the guideline aims to prevent significant scarring. However, people with acne-related scarring which is severe and persists a year after their acne has cleared should be referred as noted in recommendation 1.8.2.
NHS West Essex CCG	Guideline	006	007	For mild acne - primary care could/should suggest OTC products if not tried prior to consultation e.g Benzoyl peroxide 5% gel and 4% cream.	Thank you for your suggestions. Recommendations were based on evidence on clinical and cost-effectiveness. Benzoyl peroxide was shown to be clinically effective but somewhat less effective than combined topical treatments. The committee expressed the view that service users should have access to the most effective treatments, if these are also shown to be cost-effective from the NHS perspective, rather than to be advised to take less effective treatments OTC. Therefore the committee made a strong ('offer') recommendation for combined topical treatments, which were shown to be the most clinically and cost-effective options for mild-to-moderate acne, and not for BPO, whether the latter is paid OTC or by the NHS. Considering its somewhat lower clinical and cost-effectiveness (the latter from a NHS perspective), the committee decided to make a weaker ('consider') recommendation for BPO only when other recommended treatments are not tolerated or are contraindicated.
NHS West Essex CCG	Guideline	006	General	Azelaic acid is less irritant than the fixed combination topical products so could be added, consider as monotherapy for mild - moderate acne when one of the single ingredients from the fixed combination topical products is not suitable because of CI, not tolerated, prefer by patient	Thank you for your comment. We conducted a Network Meta-Analysis of all RCT evidence that met the inclusion criteria, which subsequently informed an economic model. Monotherapies were found to be less clinically and cost-effective than combination therapies. The committee therefore recommended these combination treatments and only recommended monotherapy with benzoyl peroxide to those who cannot tolerate other treatment or to those people where other treatments are contraindicated. Monotherapy with azelaic acid was not recommended as a fist-line treatment option because it was found to be ineffective in people

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					with mild-to-moderate acne, and no evidence was found for people with moderate-to-severe acne. However, the committee did not recommend against its use either, and therefore this does not preclude it being used by clinicians in the management of acne based on individual circumstances and clinical expertise. We have emphasised this in the rationale section and have also extended the discussion in the evidence review to clarify the reasons why these options were not included as first-line treatments.
NHS West Essex CCG	Guideline	006	General	The draft guidance does not include the topical antibiotic products e.g Erythromycin/zinc, clindamycin 1%. Do you think there is an argument for Erythromycin/ zinc for pregnant and benzoyl peroxide not tolerated. Also for neonatal acne	Thank you for your comment. We conducted a Network Meta-Analysis of all RCT evidence that met the inclusion criteria, which subsequently informed an economic model. The recommended treatment options were shown to be the most clinically and cost-effective options. The committee decided that there was insufficient evidence to recommend erythromycin/zinc for use during pregnancy. Neonatal acne was outside the guideline scope.
NHS West Essex CCG	Guideline	017	005 - 006	Treatment of scars by Glycolic acid peels, CO2 laser etc is not generally available under NHS. The NICE guidance proposes inclusion for NHS referral to dermatologist. Concerned the evidence of clinical and cost effectiveness is not robust enough to be a consider option in NICE clinical guidelines	Thank you for your comment. As noted in the rationale and impact section of the guideline, there was some evidence to suggest that glycolic acid peels, CO2 laser treatment either alone or after a session of punch elevation were efficacious in improving the appearance of acne-related scars, and therefore the committee agreed to recommend these treatments but stressed that only a small number of those affected by it and fulfilling certain criteria would be eligible for the recommended treatments that can be considered (if a person's acne-related scarring is severe and persists a year after their acne has cleared). They also agreed that the recommendations are expected to result in a change in current clinical practice but they did not expect the impact to be substantive as only a small number of those affected would be eligible. This should also not result in significant resource impact since it is intentionally stating that this is a treatment option that can be considered rather than an option that should routinely be provided.

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					NHS commissioners should take the guideline into account when commissioning services for people with acne.
Ollys Friendship Foundation	Evidence review C	010	001 - 010	Whilst I understand the need for caution over diet, but dermatologists generally know very little about diet advice. May I suggest a suitable clause for training in this area is added. The importance is mainly to avoid the risk of ADRs from oral Isotretinoin intervention but also not to close off an effective treatment and cost effective one too	Thank you for your comment. There was insufficient evidence for any particular diet so the committee made a recommendation for further research. The committee decided that they could not comment about training in this area because evidence was unclear which would make it difficult to know what the content of such training would be. However, we have added a link to general NHS information about a healthy balanced diet to the guideline so that a healthy dietary lifestyle can be promoted.
Ollys Friendship Foundation	Guideline	004	011	Add There is good evidence that Paleo diets do help to clear acne. My own son did it, but all the dermatologist could say, when his skin had greatly improved was that he wouldn't get rid of the scarring, so he gave up the diet. Attitudes need to change as this is also a very cost effective method of treatment and avoids the risks of ADRs with Isotretinoin.	Thank you for your comment. There was insufficient evidence for any particular diet, including paleo diets. However, we have now added a link to general public health information about a healthy balanced diet to the guideline, so that a healthy dietary lifestyle can be promoted.
Ollys Friendship Foundation	Guideline	005	018	It needs to be stated that a person with no previous mental health issues before suffering with acne may only need to clear their acne to regain good mental health.	Thank you for your comment. This recommendation is specifically related to people experiencing 'significant psychological distress or a mental health disorder'. Whether or not people would regain good mental health if they had clear skin is not certain and the committee believed that referral to mental health services should be considered to ensure patient safety.
Ollys Friendship Foundation	Guideline	008	004	1.5.1 Table under Advantages 1.5.8 and the MHRA alert on Isotretinoin for severe acne:….. neither link works	Thank you for your comment. This has been corrected.
Ollys Friendship Foundation	Guideline	012	018	Explain how is a dermatologist able to assess this risk – it is just a gamble. Our research has shown that many dermatologists and doctors have never even heard of Akathisia, which is a restless mind and body caused by an adverse drug reaction (ADR) to Isotreinoin, so they don't recognise this serious indication of an (ADR) to a drug they have prescribed – incredible.	Thank you for your comment. The committee decided to reword this recommendation. It now states: '1.5.21 Consider a reduced daily dose of isotretinoin (less than 0.5 mg/kg) for people at increased risk of, or experiencing significant adverse effects'. The committee discussed that the risk of adverse events is multifactorial and that its assessment would be dependent on individual circumstances and therefore could not be quantified as

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				Many psychiatrists have never even heard of Isotreinoin. These facts show the desperate need for better training and diagnosis.	part of the recommendation. We have added this to the rationale to clarify this point.
Ollys Friendship Foundation	Guideline	012	023	A course should state 12 weeks or less. Line 24 It should state ' per course' otherwise it is not clear whether it is per course or in total, and 'to 150' should be deleted (See E1 Page 78)	Thank you for your comment. Rather than measured by weeks a course of oral isotretinoin is determined by when a total cumulative dose of 120 to 150 mg/kg is reached (see recommendation 1.5.22).
Ollys Friendship Foundation	Guideline	013	001 - 004	The reality of spontaneous suicide will not be picked up by a dermatologist nor will sexual dysfunction as young people will often not mention the latter as they think it is something wrong with them and not caused by an acne drug. **EVIDENCE – DERMATOLOGIST CANNOT DETERMINE RISK** I understand that NICE are currently conducting an investigation into the use of Roaccutane/ Isotretinoin for Acne. I would like my experience to be included in as part of this. I lost my 15 year old daughter, Miss A, in May 2019 to this drug. She had been prescribed it for Acne, which in her case, was relatively mild. Unbeknown to me, one of the side effects of this drug is that it can cause sudden suicidal impulses, which come out of the blue and can be overwhelming. Sadly, we are not the only family to have lost a child to this drug. There have been several other suicides linked to this drug in this country, and I am in contact with another family in France who lost their 15 year old son in April 2020, and a family in the USA who also lost their 15 year old daughter in May 2020. Our story featured in a Channel 4 news article last year and can be watched on https://youtu.be/kmiAXmvfLV8. Isotretinoin comes with a warning that it can cause suicide ideation, along with many other psychiatric disorders and can only be prescribed by a dermatologist. However, my experience is that the	Thank you for your comment and for sharing your experience with us. The committee has been aware of this serious concern and have therefore particularly highlighted mental health impact, referral, as well as mental health monitoring and review in this guideline (see recommendations 1.4.4, 1.4.5, 1.5.4, 1.5.19 and 1.5.24). The committee noted that the MHRA is conducting a review of oral isotretinoin and any changes that would impact on the current wording of the guideline will be updated. However, the NICE guideline committee is not involved in the MHRA review.

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				medical health professionals downplay the dangers of this drug, going so far as to reassure patients as to it's safety. In our case, when this drug was suggested for Miss A, I told the dermatologist that I had read about people who had taken their lives on it. She reassured me by saying " the people who do that do it because they are depressed about their skin." I believed her because it made sense and she was an expert and so should know. Had she admitted that what I had read was in fact correct, there is no way I would have allowed my daughter to take such a drug. No mother would. My daughter would still be alive. We were warned about minor things such as dry lips, nose bleeds, headaches and we were told to watch out for low mood or depression. Because Miss A was always an upbeat, positive, happy girl we were sure we would recognise if she became depressed. She never did. We were never told that a sudden impulse may overwhelm her. On the afternoon she died we had been to her monthly monitoring session at the hospital where the sum total of her psychiatric assessment was 1 question "How's your mood, Miss A?" to which she answered "Fine" because it was. She was dead 5 hours later. Had she been probed further perhaps her answer may have been different. On the evening of her death, Miss A had been chatting with her friend who was coming on holiday with us later in the year. She had just booked her flight and the girls were excitedly making plans. At dinner time Miss A cuddled her dog, who had licked her face and woken her up that morning and she said to him "Are you going to wake me up like that every morning?" She didn't know that she would never wake up again. She berated me for washing her school trousers, which were covered in paint saying " they're just going to	

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				get paint on them at school tomorrow". They were her last words to me. She didn't know she would never go to school again. She had a perfectly normal conversation with her father about her day 20 minutes before she came downstairs, walked past him without showing any signs of anxiety or distress, grabbed what she needed and went straight back upstairs and took her own life. The police said that there were no signs that she intended to take her own life. There was no note or evidence that it was planned. There was no secrecy around it, like most intended suicides. She had been alone for 2 hours before her father came home and chatted to her. The police said that if it had been planned the obvious time to do it would be when she had been alone. The only clue was she sent 1 text to a friend just before she did it to say "I feel down". Miss A was hit by a huge suicidal impulse caused by the effect this drug was having on her brain, and she acted on it before it had time to pass. I know she did not want to die. She had so many plans. She was happy. Since she died, I have heard from so many others who have experienced similar. One person described it as " an overwhelming feeling of wanting to die." Another described it as "a sudden flash of absolute despair, this indescribable rush of energy that made me want to smash my head against a brick wall". I can not describe the devastation Miss A's death has brought to our family. We will never get over it. Whilst I can accept that sadly not all children make it until adulthood, I cannot accept that my daughter died because she took a pill, prescribed by a health professional, even though that health professional knew it could cause her death. And it did. I cannot believe that as a society we rightfully place so much emphasis on safeguarding children, and yet my daughter died, needlessly, due to a drug for, in her case, a minor skin	

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				condition. The ethics of modern medicine are "First do no harm", and yet a perfectly healthy child is now dead because of a drug prescribed to her, a drug which has knowingly harmed so many others too. Miss A did not have bad acne. She had oily skin. The dermatologist did not offer anything else but this drug, and went so far as to scare us into agreeing to it stating that she would rather Miss A took it now, before she got any scarring. Thus she ensured a willing patient- what 14 year old girl wants a scarred face? After her death, my husband and I went to see the MHRA and had a meeting with June Raine, the Director of Vigilance and Risk Management for Medicines. We told our horrific story and were accompanied by a mother of a child with severe ongoing psychiatric issues due to this drug, and a young man, who very bravely spoke about the side effect of sexual dysfunction he suffers from since using this drug. I never received any further communication from the MHRA. Around the time of our meeting there were 25 reported suicides in 2019 linked to this drug according to the MHRA website. After our meeting, this number was reduced to 10. I was told that this was due to "duplicates" but no one has been able to substantiate this. In my opinion the actual number is likely to be far higher due to the fact that most people are not aware of the Yellow Card Scheme, whereby the side effects of drug are recorded. I certainly wasn't aware. Moreover, the suicidal dangers of this drug can persist for months after treatment is ceased leading many people to not make the connection to this drug. The MHRA are due to hold an investigation into this drug, however my experience with the MHRA does not inspire me with much hope that things will change.	

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				For your information, the current Yellow Card data shows that in 2020 there were 12 recorded deaths, including 11 suicides on this drug (7 of which were teenagers). In total, 97 people have died using this drug, of which 79 of them were suicides. 32 of those deaths were teenagers. Whilst these figures are shocking, it must be borne in mind that most people do not report and therefore these figures will be much greater in reality. I am aware that for some people the use of Isotretinoin has been beneficial in terms of treating their acne, however, this drug is being prescribed too readily (6,522 prescriptions a year in 2006 rising to 48,997 in 2016), despite the terms of its license being "for use only when all other options have failed." The dermatologist in our case, did not offer any other treatments at all. The medical health professionals are not alerting people to its true dangers. I believe that Isotretinoin should not be prescribed to anyone under the age of 18. Children are taking their lives on this drug, not because they are depressed about the state of their skin. This drug works to clear acne in most cases. Those who are taking their lives are doing it whilst their skin is improved. Furthermore, it is not possible to accurately monitor the mental state of a teenager who's hormonal fluctuations mean that their moods are not stable. In addition, the dermatologists monitoring of patients is largely ineffective. Dermatologists are not qualified to assess mental health. We have lost our beautiful daughter. She had her whole life ahead of her and she died for nothing. I owe it to her to try to fight so that others are spared the devastation our family is going through. Try to imagine if this happened to your child, and please take the action needed to stop this happening again. Please ban this toxic drug as a treatment for Acne in children under the age of 18.	

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Ollys Friendship Foundation	Guideline	019	008	Add There is good evidence that Paleo diets do help to clear acne. The benefits of a non invasive diet far outweigh the risks of anorexia and a dangerous drug. Attitudes need to change and dermatologists need to be trained in the use of diets as this is also a very cost effective method of treatment and avoids the risks of ADRs with Isotretinoin	Thank you for your comment. There was insufficient evidence for any particular diet so the committee made a recommendation for further research. Some evidence suggested that a low glycaemic load diet may lead to some improvement but the committee was concerned about the possibility of weight loss or eating disorders, especially as most people with acne vulgaris are young and the onset of eating disorders is most common in adolescence. Further details of the committee's discussion of the evidence can be found in evidence review C. There is general NHS advice about a balanced diet so the committee added this to promote a healthy lifestyle.
Ollys Friendship Foundation	Guideline	024	009 - 010	Link does not work	Thank you for your comment. We have corrected this.
Ollys Friendship Foundation	Guideline	033	018	Isotretinoin is not licenced for mild to moderate acne and should not be being prescribed. Your clauses and advice needs reviewing.	Thank you for your comment. Oral isotretinoin is not being recommended for mild or moderate acne in this guideline. The sentence relates to the evidence which was classified according to mild to moderate or moderate to severe acne. Therefore, the rationale and Impact section of the guideline refers to moderate to severe acne and summarises the committee's discussion of the evidence and why recommendations were made or not made. Although in case of oral isotretinoin there was relevant evidence for moderate to severe acne, the committee drafted the recommendations in accordance with MHRA safety advice on oral isotretinoin recommended its use only in situations when they agreed the benefits outweighed the risks such as in severe form of acne that is resistant to adequate courses of standard therapy with systemic antibiotics and topical therapy.
Ollys Friendship Foundation	Guideline	035	001 - 006	I am not sure where to add this suggestion but much of your research data comes from the USA as the Yellow Card system in the UK severely under-reports (confirmed in MHRA report November 2014). In the USA they have an 'Informed Consent Form' where the patient signs accepting that Isotretinoin could	Thank you for your comment. The impact section states the recommendations would not change current practice since they align with current MHRA guidance. The committee were aware of the updated GMC guidance on 'Decision Making and consent' and there is a section in every NICE guideline entitled 'Making decisions

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				cause them to take their own life. This form is desperately needed in the UK so that patients and parents understand the risks that they are being asked to take. In addition the GMC have issued new guidelines to doctors dated 9th November 2020 'Decision Making and Consent' which states the 'Must Do' clauses doctors must follow in discharging their 'Duty of Care' and to 'Do no harm' – these are clauses 11, 16, 18, 21, 23, 25, 30 and 31. Your draft makes no mention of the GMC guidelines at all. If it was received too late for your draft then after 39 years of Isotretinoin without any NICE guidelines ,you must delay publication and prepare a fresh draft for consultation. At present lived experience by patients and parents will mean that the obligations imposed by the GMC will mean Duty of Care is not fulfilled and that will leave you vulnerable to Negligence. It should be noted that the suicide rate stated by the MHRA and stated in the Patient Information Leaflet is 1 in 10,000 whereas in the last 8 years it has been consistently between 1 in 2,000 and 1 in 4,000 and that is based on the inadequate Yellow Card reporting. This is a breach of Duty of Care on information that is relied on by patients. Will you please look into this and add appropriate clauses. Final Comment – there is a desperate need for a SAFE treatment for acne to replace Isotretinoin. Remember the Thalidomide tragedy when we were promised safer prescribing and that was in 1962! In order to improve data all prescriptions for Isotretinoin should be issued with a compulsory Yellow Card to report all ADRs.	using NICE guidelines' which directly links to relevant professional guidelines, standards and laws that should be taken into consideration. This contains a link to the GMC website where this updated information on decision making and consent can be found. The committee are aware that the MHRA is conducting a review of oral isotretinoin and any changes that would impact on the current wording of the guideline will be updated.. The committee are aware of safety concerns about the use of oral isotretinoin and have therefore particularly highlighted mental health impact, referral, as well as mental health monitoring and review in this guideline (see recommendations 1.4.5, 1.4.6, 1.5.3, 1.5.16 and 1.5.21). In Appendix J, under 'Discussion – conclusions, strengths and limitations of economic analysis' it is stated: "relevant data on side-effect rates for each treatment considered in the economic model, from large observational studies, were not readily available. Therefore, the impact of side effects on HRQoL and their associated management costs were not considered in the economic model. On the other hand, the analysis incorporated the impact of intolerable side effects on HRQoL and costs; however, the costs associated with management of intolerable side effects may have been underestimated, as they were limited to the cost of one healthcare professional contact. Antimicrobial resistance resulting from use of topical or oral antibiotics and associated costs were also not considered in the analysis. These omissions in the model structure are acknowledged as limitations of the analysis. In any case, isotretinoin was neither the cheapest treatment nor the most cost-effective one, either in the mild-to-moderate or in the moderate-to-severe acne.

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				Page 283 E1 It should be noted that Isotretinoin may be the cheapest treatment initially but that takes no account of additional services to deal with ADRs and restrictions and costs to a patients' lifestyle so the true cost is very different.	
Primary Care Dermatology Society (PCDS)	Guideline	004	010	Although evidence is not entirely convincing for diets with low glycaemic index or low dairy intake, a general approach towards opportunistic health promotion and smoking cessation is advisable at any encounter including a consultation for a skin related condition such as acne	Thank you for your comment. There was insufficient evidence for any particular diet. However, we have now added a link to general NHS information about a healthy balanced diet to the guideline. So that a healthy dietary lifestyle can be promoted. Smoking cessation is outside the scope of this guideline. We have also reviewed and revised the rationale section to clarify why a low glycaemic load diet, for which there was evidence, was not recommended.
Primary Care Dermatology Society (PCDS)	Guideline	005	005	…pigmentary change has already happened: in line with the recent BAD SOC course advice it is better to refer early those that are 'at risk of prolonged/permanent pigmentary change such as in people with skin of colour e.g. Fitzpatrick 5/6	Thank you for your comment. The purpose of the referral for acne with pigmentary changes is to treat the acne to prevent further changes. The committee decided that 'risk of pigmentary changes' would be difficult to define or assess. This bullet point was therefore reworded to 'acne with persistent pigmentary changes'.
Primary Care Dermatology Society (PCDS)	Guideline	005	006	There are very established community dermatology GPwER services in England that initiate and monitor isotretinoin prescribing in the community. Such services work in an integrated fashion with secondary care, with agreed pathways for acne. Access for patients is improved due to shorter waiting times and with such less risk of scarring and the potential for improved psychological outcomes. GPwERs have the additional experience of being generalists which enables them to comfortably manage any contraceptive and psychological needs of patients requiring isotretinoin. We need to move away from isotretinoin being only accessible for patients in Secondary Care (which has not been the case in some areas for a number of years) given the strain on the system not just during Covid times. Please add the position of nationally accredited GPWERs working in community dermatology services into the document wherever there is a reference to 'refer to a consultant dermatologist led service' especially given that the accreditation	Thank you for your comment. We have now acknowledged in the 'terms used in the guideline' that 'this team may include associate specialists and healthcare professionals accredited for extended roles for dermatology under consultant supervision'. We reviewed all recommendations using 'consultant-dermatologist-led team' and for recommendations that mention this team it is possible that oral isotretinoin might be or may become a treatment option. In line with MHRA advice regarding oral isotretinoin prescribing (that is the prescriptions for oral isotretinoin should be issued under the consultant's name from a hospital-based pharmacy), then the team may include GPwERs

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				framework has been agreed between the RCGP, BAD and PCDS to ensure delivery of high standard care within these services.	
Primary Care Dermatology Society (PCDS)	Guideline	006	011	Not enough consideration is given to single component treatments such as adapalene, only azelaic acid is mentioned. Especially at the onset of treatment the tolerability of single active treatments might be higher and in that adherence to treatment plans. Monotherapy with benzoyl peroxide is only considered if the patient does not wish to use retinoid or can not tolerate or is contraindicated. On page 16 line 8 you make reference to intolerance to combined products and switching to monotherapy, This should feature earlier.	Thank you for your comment. We conducted a Network Meta-Analysis of all randomised controlled trial evidence of all acne treatments that met the inclusion criteria of the systematic review protocol, which subsequently informed an economic model. Monotherapies were found to be overall less effective and cost-effective than combination therapies. The committee therefore recommended these combination treatments and only recommended monotherapy with benzoyl peroxide to those who cannot tolerate other treatment or to those people where other treatments are contraindicated. Due to the limited evidence around azelaic acid monotherapy as first-line treatment option the committee did not recommend this. Neither did they recommend against its use and therefore, this does not preclude it being used by clinicians in the management of acne based on individual circumstances and clinical expertise. We have emphasised this in the rationale section and have also extended the discussion in the evidence review to clarify the reasons why these options were not included. Switching to monotherapy is recommended as an option regarding maintenance therapy, based on available evidence in this population (that is, people with acne who have received and responded to initial treatment).
Primary Care Dermatology Society (PCDS)	Guideline	007	Before table 1	There is no mentioning of the role of anti-androgens such as spironolactone in the management of acne in females. It is often referred to by consultants in presentations and suggested as alternative treatment before referring. This is easily initiated in Primary Care and would make an ideal additional treatment option to add to the existing list to defer or even avoid referral.	Thank you for your comment. There was insufficient evidence to recommend antiandrogens such as spironolactone in the management of acne, therefore the committee made a recommendation for further research.
Primary Care Dermatology Society (PCDS)	Guideline	014	014	There is evidence that a useful alternative to co-cyprindiol may be the newer COCPs containing the anti-androgen Drosperinone whether combined with low-dose oestradiol (20mcg) or with 30cmg oestradiol. Tricycling these ie using continuously for 63 days then	Thank you for your comment. We conducted a Network Meta-Analysis of all randomised controlled trial evidence of all acne treatments that met the inclusion criteria of the systematic review protocol. There was insufficient evidence to recommend anti-

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				breaking for up to seven days may also reduce the possible pre-menstrual flares as well as improving contraceptive efficacy. Most acne is managed in primary care which is where also most contraception is prescribed hence the guideline might want to reference the above.	androgens as first-line treatment options so the committee added a research recommendation to encourage further studies to investigate how effective these options are.
Primary Care Dermatology Society (PCDS)	Guideline	016	014	In reality acne scarring treatment is not funded under the NHS and requires exceptional treatment funding application. There is also a variation in service provision across England hence resulting in health inequalities. It is better to emphasise prevention and not to raise expectations that scars can be managed within an already stretched health economy. Most CCGs will advise on seeking treatment privately. Alternatively, as per experience by some dermatologists consider using adapalene post isotretionoin treatment as a it has shown to have positive impact on scarring and as such is a low cost option.	Thank you for your comment. As noted in the rationale and impact section of the guideline, there was some evidence to suggest that glycolic acid peels and CO2 laser treatment either alone or after a session of punch elevation were efficacious in improving the appearance of acne-related scars, and therefore the committee agreed to recommend these treatments but stressed that only people fulfilling certain criteria would be eligible for the recommended treatments that can be considered (if a person's acne-related scarring is severe and persists a year after their acne has cleared). They also agreed that the recommendation is expected to result in a change in current clinical practice but they did not expect the impact to be substantive as only a small number of those affected would be eligible. This should also not result in significant resource impact since it is intentionally stating that this is a treatment option that can be considered, rather than an option that should routinely be provided. We did not identify evidence that adapalene used after isotretinoin treatment would reduce scarring. The committee therefore did not comment on this in this section. However, they have recommended adapalene as a potential maintenance option which would mean that it could be used if acne has cleared after isotretinoin use.
Primary Care Dermatology Society (PCDS)	Guideline	018	022	Various strengths of benzoyl peroxide are available yet not all are available on local formularies. There is no evidence that one strength is superior to another hence all strengths should be mentioned here and an addendum made in the section of monotherapy with benzoyl peroxide on page 16 line 8	Thank you for your comment. The committee were aware that there are various strengths of benzoyl peroxide available. However, according to the British National Formulary the strength of a standard formulation is 5% which is therefore what was specified in the guideline.
RCGP - GPs with Extended	Guideline	004 005	017	Only 'Consultant Dermatology-led teams' can manage acne services and prescribe isotretinoin. This has **not been the case for**	Thank you for your comment. We have now acknowledged in the 'terms used in the guideline' that 'this team may include associate

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Roles in Dermatology (GPwERs)		011 015 024	006/014 011-012 013/014 026	**many years.** This wording needs to be amended in points 1.4.2, 1.4.3, 1.4.5, and 1.5.13 (and all other relevant parts of the document) such that there can be: **Referral to any of the following:** • **Consultant dermatologist** • **Nationally accredited Group 1 and 3 Dermatology GPwERs** • **Arguably you may think about including associate specialists, as in some areas of the UK there are no consultants** You may wish to put in an additional note along the lines of existing GPwSI in Dermatology who have not been through the GPwER national accreditation program are not included on the list as standards of training, mentorship and integration cannot be verified. **Notes:** All accredited Dermatology GPwERs have been through a national program of accreditation - this is for new candidates in addition to existing GPwSIs, thus moving away from the previous issue of not knowing which GPwSIs had received the appropriate training in dermatology, in addition to ongoing mentorship and integration with Secondary Care services. There are now almost 140 nationally accredited GPwERs. Moving on to our response to the guidelines, I am sure we all agree that the focus has to be on providing the best outcomes for the patient, which for the most part means a reduction in the number of patients ending up with significant scarring. Even with laser therapy we know that the skin will not return to normal, and in many places laser therapy is either not locally available and/or cannot be provided in the NHS, therefore meaning a postcode lottery. As such	specialists and healthcare professionals accredited for extended roles for dermatology under consultant supervision'. We reviewed all recommendations using 'consultant-dermatologist-led team' and for recommendations that mention this team it is possible that oral isotretinoin might be or may become a treatment option. In line with MHRA advice regarding oral isotretinoin prescribing (that is the prescriptions for oral isotretinoin should be issued under the consultant's name from a hospital-based pharmacy), then the team may include GPwERs.

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				getting patients with scarring acne seen in the shortest possible time is paramount, and this is where nationally accredited GPwERs have come into the fold. Details on GPwERs including frameworks and supporting documents can be found at: https://www.rcgp.org.uk/training-exams/practice/general-practitioners-with-extended-roles.aspx https://www.rcgp.org.uk/training-exams/practice/guidance-and-competences-for-gps-with-extended-roles-in-dermatology-and-skin-surgery.aspx Essentially, Group 1 and 3 nationally accredited Dermatology GPwERs are able to deliver GPwER-led acne clinics, which include for many the use of isotretinoin. While these are not consultant led, one of the key features of the national accreditation program is that Dermatology GPwERs must work in an integrated fashion with secondary care colleagues with agreed care pathways, which include the use isotretinoin where appropriate. There are now a significant number of Dermatology GPwERs (40 or more) who prescribe isotretinoin in the community. All submissions for national GPwER accreditation go through the framework signed off by the RCGP, BAD and PCDS, and all candidates going through the assessment process are assessed by both generalists and consultant dermatologists. In many areas, the provision of GPwER acne clinics has meant that patients with scarring acne are seen sooner, which can only be a good thing for the patient. Indeed, the GPwER is ideally placed to manage acne with isotretinoin because not only have they had the necessary dermatology training, but their generalist training makes them ideally placed to deal with relevant potential issues such as contraception, depression and monitoring lipids/LFTs.	

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RCGP - GPs with Extended Roles in Dermatology (GPwERs)	Guideline	009 014	015 013	1. References are made to the combined oral contraceptive pill and then Dianette. The evidence from Professor John Guillebaud is that alternative combined oral contraceptive pills (COCPs) with a lower oestrogen content are equally effective for acne with a better safety profile. The COCPs referred to have an oestrogen content of 20mcg and include Eloine and Mecilon. The Faculty of Sexual and Reproductive Healthcare also promote tricycling of combined oral contraceptive pills taking 9 consecutive weeks before having a 4-7 day break 2. Guidelines for isotretinoin refer to the Progesterone only pill (POP) not being a suitable contraceptive for isotretinoin, however, there are many women who cannot take oestrogen, do not tolerate progesterone only injections and are not suited for IUDs. Further, the specific POP Cerazette is equally effective as COCP from a contraceptive perspective, as it is taken daily and has a 12 hour window in which to take the pill each day (most POPs have a 3 hour window, and so if taken unreliably then there effectiveness as a contraceptive may be less). As such POPs should not be excluded from the list of contraceptives suitable for use with isotretinoin, especially given that the requirement in any case is for 2 forms of contraceptives. Perhaps the committee could refer to COCPs and the POP Cerazette as being suitable for isotretinoin along with a second method of contraception. Other POPs could be considered if there are no suitable alternatives and patient is deemed as reliable in terms of taking the pill at the same time each day?	Thank you for your comment. The evidence came from trials about effective treatments for acne rather than contraception to prevent pregnancy. There was evidence for the combined oral contraceptive pill for acne treatment but it was insufficient to recommend it as a first line treatment option. The best method of contraception to prevent pregnancy is outside the scope of the guideline.
RCGP - GPs with Extended Roles in	Guideline	012	024	Error – the document states 'continue until a total cumulative dose of **120 to 150 mg/kg is reached'** … need to take out /kg	Thank you for your comment. It is correct as it is and should be mg/kg. See relevant BNF guidance ("maximum 150 mg/kg per course").

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RCGP - GPs with Extended Roles in Dermatology (GPwERs)	Guideline	General	General	There should be an emphasis that patients with severe acne (which should be quantified) need to be commenced on relevant treatment and referred at the same time. It may also be appropriate to specify a timeframe within which patients with severe acne are seen. In some parts of England patients are waiting longer than 12 months to be seen	Thank you for your comment. Moderate to severe acne is defined in the 'Terms used in this guideline' of the guideline. There was no evidence identified on referral criteria including timings. The committee therefore only specified a timeframe for the most severe form of acne (acne fulminans). Setting other referral targets would have resource implications which the committee would be unable to justify without evidence to support that. However, the committee noted that effective first-line treatments would most likely reduce the need for specialist referral.
RCGP - GPs with Extended Roles in Dermatology (GPwERs)	Guideline	General	General	Follow-up of acne in primary, intermediate and secondary care: what measures are we looking at to monitor improvement? Grading scales can be used, but perhaps the gold standard to consider is serial photography (although cost implications in Secondary Care, and so not always possible, this is not so for Primary or Intermediate care if take images in clinic and then use Pando App to send to NHS email and upload into patient notes)	Thank you for your comment. Diagnosing and assessing acne were outside the scope of this guideline.
RCGP - GPs with Extended Roles in Dermatology (GPwERs)	Guideline	General	General	I cannot see a specific mention of acne with multiple macrocomedones – such lesions require gentle hyfirecation under topical anaesthetic prior to isotretinoin, otherwise the acne can flare badly. I recommend adding in a note along these lines on this type of acne	Thank you for your comment. Management of macrocomedones by using hyfrecation is outside the scope of the guideline, therefore the committee could not comment on this.
Royal College of Nursing (RCN)	Guideline	003	005	"Give people with acne clear information tailored to their needs". Need to consider how this may best be achieved, giving people a handful of leaflets is rarely helpful	Thank you for your comment. The principles of tailoring information and how to best provide it are described in the NICE guideline on 'Patient experience in adult NHS services'. We have revised the wording related to the cross reference to this guideline to make this clearer.
Royal College of Nursing (RCN)	Guideline	010	009	"Review first-line treatment at 12 weeks": This is a departure from normal practice, is there any new incentive to review?	Thank you for your comment. There are two reasons for a 12 week review. In the committee's experience it is not uncommon that people stay on suboptimal treatments for too long. The committee also wanted to encourage healthcare professionals not to use antimicrobials for too long. So if effective at the 12 week review they

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					could be discontinued. We have added the first reason to the rationale section and the other reason was already described. Further points highlighted by the committee in their discussion of the evidence are described in the relevant sections of evidence reports E1 and F1 (sections entitled 'the committee's discussion of the evidence').
Royal College of Nursing (RCN)	Guideline	018	025	"The guideline committee has made the following recommendations for research": Need to reference the Acne Priority Setting Partnership Top Ten https://www.jla.nihr.ac.uk/priority-setting-partnerships/acne/	Thank you for your comment. Research recommendations, like practice recommendations, originate from the evidence to address topics where gaps in the evidence were identified. It therefore does not reference a specific other resource. However, the committee noted that many of the 10 research priorities listed by the James Lind Alliance were consistent with the guideline recommendations or research recommendations, apart from prevention and lifestyle factors other than diet which are topics outside the scope of this guideline and so could not be commented on.
Royal College of Nursing (RCN)	Guideline	General	General	Psychological distress is mentioned many times in the document, this is positive, but little attention has been paid to preventative / self-management interventions which if implemented early enough may reduce escalation of suffering. Use standard self-completed measures of psychological health.	Thank you for your comment. Psychological management of acne and prevention of psychological distress was outside the scope of this guideline. Evidence reviews were therefore not conducted and the committee could not comment on this. However, they linked relevant recommendations to other NICE guidance such as for example the depression guideline which covers aspects such as self-management.
Royal College of Nursing (RCN)	Guideline	General	General	Community pharmacists (and pharmacy counter assistants) are often first line in advising on acne, this should be acknowledged.	Thank you for your comment. This guideline can be informative to many healthcare professionals as well as people with acne, their families or carers. Apart from 'consultant dermatologist-led teams' the committee intentionally did not name any specific roles so that advice can be given by any specialist with appropriate expertise (including pharmacists).
Royal College of Paediatrics and Child Health (RCPCH)	Guideline	007	Table 1	The reviewer was unsure as to why some of the medications are described as not suitable for pregnant/breast feeding or **under 12 years**, the reviewer noted that most have known patients who have been pregnant at or just around 12 years of age and questioned why the guidance is specific about this age group?	Thank you for your comment. NICE guidelines align with the Summary of product characteristics and the British National Formulary. The details in Table 1 are consistent with these.

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Royal College of Paediatrics and Child Health (RCPCH)	Guideline	General	General	The reviewer was happy with this guidance.	Thank you for your comment.
Society for Academic Primary Care - Special Interest Group in Dermatology	Guideline	003	005	Thank you for including a section on 'information for people with acne'. For most people with acne the first line treatment will be topical, and a frequent reason for early discontinuation of these is experience of side effects. It would therefore be useful if core information includes advice on avoiding side effects. This appears in 1.5.5 but could be emphasised by inclusion in 1.1.1.	Thank you for your comment. The committee decided that this is covered under 'the benefits and drawbacks of treatment' which would include the different treatment regimens. We have added text to the rationale section to make this point clearer.
Society for Academic Primary Care - Special Interest Group in Dermatology	Guideline	003	005	In the section 'information for people with acne relapses during or after treatment' it would be very helpful to add a bullet point, "the importance of maintenance treatment to prevent relapse," as it would be better to avoid relapse through continued use of topical therapy than wait for relapse to occur	Thank you for your comment. The committee did not agree that maintenance treatment is always necessary and stated this as a recommendation in the maintenance section. We can therefore not add this to the 'information for people with acne' section because it would be internally inconsistent.
Society for Academic Primary Care - Special Interest Group in Dermatology	Guideline	General	General	We are concerned that this guideline does not go far enough in addressing the issue of antimicrobial resistance associated with the use of prolonged courses of oral antibiotics in acne. • Unlike other guidelines (e.g. US, Netherlands), there is no differentiation between known pregnancy risks of oral tetracyclines and low risk from topical adapalene or fixed combination topical adapalene with topical benzoyl peroxide. This may deter prescribers from using effective non-antibiotic topical treatments as first choice in women. • Other guidelines offer clarity around a 3 month course for oral antibiotics. This draft guideline states that courses of oral antibiotics "should last no longer than 6 months."	Thank you for your comment. With regards to pregnancy risks we followed the Summary of Product Characteristics and British National Formulary descriptions of known risks. We conducted a Network Meta-Analysis of all randomised controlled trial evidence, which subsequently informed an economic model. For moderate to severe acne some combinations which also included an oral antibiotic were shown to be among the most clinically and cost-effective as first-line treatment options. However, the committee added recommendations about reviews of antibiotic treatments so that they are not continued indefinitely and discontinued as soon as possible. There was another recommendation that highlighted not to use antibiotic monotherapy as well as a combination of a topical antibiotic and an oral antibiotic.

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				• While the need for topical treatment alongside and after oral antibiotics is mentioned in parentheses, there should be greater emphasis on this to reduce antimicrobial resistance and prevent relapse. Furthermore, it could be clearer that non-antibiotic topical treatments are preferred to antibiotic topical treatments for the avoidance of antimicrobial resistance.	The committee believed that this would improve current practice with regards to antibiotic use for acne. Their thinking around this is described in the rationale and impact section particularly for related to 'factors to take into account when choosing a treatment option' and 'factors to take into account at review'.. There was no evidence related to an optimal duration of antibiotic treatment and the committee were trying to emphasise that the antibiotic treatment should be discontinued as soon as possible. However, they did not want to prohibit longer use but this should happen if clinical judgement was that this would be beneficial, based on a person's individual circumstances. There should then be a review at 3 monthly intervals, and the antibiotic should be stopped as soon as possible. With regards to favouring topical treatment without an oral antibiotic over those including an oral antibiotic, the antibiotic option is only recommended as first-line treatment for people with moderate to severe to make it less likely that it is given routinely to all people with acne. It is therefore restricting its use. Moreover, the committee had to take into account MHRA guidance regarding use of isotretinoin, which can be prescribed only when severe acne is resistant to adequate courses of standard therapy with systemic antibiotics and topical therapy, so oral antibiotics should have been tried first.
Society for Academic Primary Care - Special Interest Group in Dermatology	Guideline	General	General	The need for referral to a consultant dermatologist-led team where isotretinoin is needed can lead to barriers and delay to effective treatment. Prescription of isotretinoin, including Pregnancy Prevention Programmes, are carried out by GPs in several other countries, and reflected in guidelines in the Netherlands and New Zealand[1, 2]. Indeed, GPs in the UK are familiar with pregnancy prevention programmes for other teratogenic treatments such as sodium valproate. Widening access to isotretinoin and reducing waiting times through community provision could prevent scarring, reduce mental health impact and decrease inequalities in access[3, 4] to effective treatment.	Thank you for your comment. The committee drafted the guidance in accordance with the MHRA safety advice on oral isotretinoin which currently states that oral isotretinoin should be prescribed by a consultant dermatologist led team. The committee noted that the MHRA is in the process of reviewing this topic. New MHRA advice would lead to an update of this part of the guideline to reflect any possible changes. We cross-checked the provided reference against the inclusion criteria of the review protocol. Reference no.1 is not in English and is not a randomised study which means it does not meet the inclusion criteria of the protocol. References no.2 and no.3, and Barbieri 2020 are not randomised studies which is a study

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				1. https://richtlijnen.nhg.org/standaarden/acne#volledige-tekst-medicamenteuze-behandeling 2. Managing acne in primary care. BPJ 2013; 51: 16–27. https://bpac.org.nz/ BPJ/2013/March/docs/BPJ51-pages-16-27.pdf 3. Moodie P, Jaine R, Arnold J, Bignall M, Metcalfe S, Arroll B. Usage and equity of access to isotretinoin in New Zealand by deprivation and ethnicity. The New Zealand Medical Journal (Online). 2011 Nov 25;124(1346). Barbieri JS, Shin DB, Wang S, Margolis DJ, Takeshita J. Association of Race/Ethnicity and Sex With Differences in Health Care Use and Treatment for Acne. JAMA Dermatol. 2020 Mar 1;156(3):312-319. doi: 10.1001/jamadermatol.2019.4818. PMID: 32022834; PMCID: PMC7042795	design that does not match inclusion criteria.
Society for Academic Primary Care - Special Interest Group in Dermatology	Guideline	General	General	'Referral to specialist care' document suggests referral for the management of polycystic ovary disease, although the draft guideline does not suggest this. This would have substantial cost implications and would not appear to be consistent with the NICE CKS guideline on PCOS.	Thank you for your comment. We have reviewed the section in the rationale and impact section and given that there was a lack of evidence related to the referral of people with polycystic ovary syndrome the committee decided that the rationale sounded more certain than the recommendation where referral could be considered rather than should routinely take place. We have therefore softened the wording from 'would benefit from referral' to 'may benefit from referral' to indicate that there are treatment options for acne for people with polycystic ovary syndrome that ought to be tried first.
University of Southampton NGHS Foundation Trust	Guideline	010	018	1.5.11 We disagree with the recommendation that prohibits use of oral antibiotics for more than 6 months. What happens if the patient is responding well but is not appropriate for or does not want isotretinoin? There is no evidence that resistance is more likely to arise between 6-12 months than for the first 6 months of treatment. This rule will result in more patients being treated with isotretinoin.	Thank you for your comment. The committee discussed this recommendation and decided that the wording was too strong and that there should be some level of clinical judgment related to stopping a treatment option that includes a topical antibiotic or an oral antibiotic. They decided to amend the recommendation to allow for this but only in exceptional circumstances. If it is decided to continue it should then be reviewed at 3 monthly intervals, and the antibiotic should be stopped as soon as possible.
University of Southampton	Guideline	011	017	1.5.15 We disagree with the recommendation that for management of severest forms of acne eg nodulo-cystic acne/ acne fulminans,	Thank you for your comment. The committee made the recommendations following regulatory guidance from the Medicines

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NGHS Foundation Trust				the guideline recommends two 12 week courses of antibiotics and topical therapy before isotretinoin. What is the evidence to support this change in practice?	& Healthcare products Regulatory Agency (MHRA) which should be standard practice and stipulates to only use isotretinoin for severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) that are resistant to adequate courses of standard therapy with systemic antibacterials and topical therapies. The committee noted that the MHRA is conducting a review of oral isotretinoin and any changes that would impact on the current wording of the guideline will be updated.
University of Southampton NGHS Foundation Trust	Guideline	012	007	1.5.17 There is lack of clarity regarding the pregnancy prevention programme for isotretinoin. a. Regarding the requirement that all with 'potential to become pregnant' on isotretinoin follow the Pregnancy Prevention Programme. There is no definition in the guideline of 'potential to become pregnant'. E.g. is it biological potential, or behavioural potential. b. What is meant by 'inform them that they will need to follow the pregnancy prevention programme'. Ie is the recommendation 'to inform' them of this or 'to make sure that they follow' it? c. Have any exceptions to the PPP been considered by the guideline? EG if patients decline it.	Thank you for your comment. Due to the teratogenic effects of oral isotretinoin the committee worded it in this way to capture anyone with the potential to become pregnant be it biological or behavioural. Details of the pregnancy prevention programme and how advice should be given about contraception (in general or specifically in the context of oral isotretinoin) are outside the scope of this guideline. This is why the recommendation directly links to the website so that the healthcare professional can follow the details of this guidance. Providing a link rather than quoting details also ensures that in case future guidance on the pregnancy prevention programme changes, the most up-to-date guidance can still be accessed. Once the guideline is published in digital format it will be straightforward to navigate from the guideline to the pregnancy prevention programme website.
University of Southampton NGHS Foundation Trust	Guideline	014	018	1.5.26 We think anti-androgens should be included as options for females even if they don't have PCOS. Spironolactone is not mentioned.	Thank you for your comment. We conducted a Network Meta-Analysis of all randomised controlled trial evidence of all acne treatments that met the inclusion criteria of the systematic review protocol. There was insufficient evidence to recommend anti-androgens as first-line treatment options so the committee added a research recommendation to encourage further studies to investigate how effective these options are.

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*