COMMENTS RECEIVED FROM EXTERNAL REFEREES AND OTHERS

***British guideline on the management of asthma***

*All reviewers submitted declarations of interests which were viewed prior to the addressing of comments.*

| Open Consultation | | | Type of response and declared interests |
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| **Ai** | Airsonett UK Ltd | Patrik Karrberg, Business Development Manager commenting on behalf of Airsonett UK Ltd | *Group response.*<br><br>*Nature and purpose of your group or organisation:*<br><br>Pharmaceutical equipment manufacturer<br><br>*How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?*<br><br>Our organisation would be strengthened following a recommendation in favour of using Airsonett Air4 Temperature-controlled Laminar Airflow technology (TLA). It would increase the treatment options for patients suffering from severe asthma. |
| **ALUK** | Allergy UK | Amena Warner, Head of Clinical Services commenting on behalf of Allergy UK | *Group response.* |
| **AM** | Dr Anna Murphy | Consultant Respiratory Pharmacist, University Hospitals of Leicester NHS Trust, Leicester | *Individual response.*<br><br>*Remuneration from consultancy or other other fee paid work:*<br><br>Participation in advisory boards and lecturing for various pharmaceutical companies |
| **ARNS** | Association of Respiratory Nurse Specialists | Natalie Harper, Respiratory Consultant Nurse commenting on behalf of Association of Respiratory Nurse Specialists | *Group response.*<br><br>*Nature and purpose of your group or organisation:*<br><br>A group of nurses and allied HCPs who promote excellence in practice, and influence respiratory health policy. ARNS also works to influence the direction of |

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| | | | respiratory nursing care.<br><br>*How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?*<br><br>As per the latter statement above. |
| **AUK** | Asthma UK | Samantha Walker, Deputy Chief Executive and Director of Research and Policy commenting on behalf of Asthma UK | *Group response.*<br><br>*Nature and purpose of your group or organisation:*<br><br>Asthma UK is a UK charity which works to stop asthma attacks, and, ultimately, cure asthma by funding world leading research and scientists, campaigning for change and supporting people with asthma to reduce their risk of a potentially life-threatening asthma attack.<br><br>*How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?*<br><br>Asthma UK believes that the recommendations around using the most up-to-date diagnostic testing are particularly important for people with asthma and therefore the guidelines promoted around different forms of diagnostic testing will directly affect the people our charity represents. For the same reason we believe that the respiratory community needs to be responsive to the adoption of new technologies to transform the diagnosis and treatment of asthma, for the benefit of patients.<br><br>The only impact on our work is therefore around ensuring the best possible outcomes for people with asthma. |
| **AZ** | AstraZeneca UK Limited | Gina Bariah, Medical Affairs Lead commenting on behalf of AstraZeneca UK Limited | *Group response.*<br><br>*Nature and purpose of your group or organisation:*<br><br>Pharmaceutical Manufacturer. |

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| | | | *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?*<br><br>AstraZeneca would like to ensure the guideline is up to date, forward facing and provides guidance for best-practice patient care for asthma patients of all severities. The draft SIGN/BTS guidance may impact prescribing patterns in therapy areas in which AstraZeneca currently promotes medicines. |
| **BFS** | Bedfont Scientific Ltd | Louise Bateman, QA & RA Manager commenting on behalf of Bedfont Scientific Ltd | *Group response.* |
| **BSACI** | British Society for Allergy and Clinical Immunology | Nicola Braithwaite, Honorary Secretary BSACI commenting on behalf of British Society for Allergy and Clinical Immunology (BSACI) | *Group response.*<br><br>*Nature and purpose of your group or organisation:*<br><br>The BSACI is the national, professional and academic society which represents the specialty of allergy at all levels.<br><br>*How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?*<br><br>The draft SIGN recommendation is welcomed by our organisation. Our comments relate to section 6.2.1 - House dust mite avoidance where we have concerns about the methodology of the systematic reviews forming the basis of the recommendation that house dust mite avoidance measures should not be routinely recommended. The section would benefit from revision which acknowledges the limitations of the systematic reviews conducted. |
| **BTS** | British Thoracic Society | Sally Welham, Deputy Chief Executive, sommenting on behalf of The British Thoracic Society | *Group response.*<br><br>*Nature and purpose of your group or organisation:*<br><br>Professional organisation.<br><br>*How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?* |

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| | | | This is an important guideline for BTS. |
| **Ch** | Chiesi Ltd | Deaghlan O'Hagan, Medical Manager commenting on behalf of Chiesi Ltd | *Group response.*<br><br>*Nature and purpose of your group or organisation:*<br><br>Pharmaceutical company<br><br>*How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?*<br><br>The SIGN recommendations will naturally influence our organisation's productivity and performance as a manufacturer of respiratory medications. It should be noted however that the comments that we have made with regard this document as an organisation are merely to ensure that any recommendations made are based on an appreciation of all the evidence that is available. And that where clinician guidance is provided it should be as clear as possible, thus ensuring the clinician can make the correct recommendation to their patient. |
| **Cl** | Cipla EU | Ian De'Ath, Head of Respiratory Marketing commenting on behalf of Cipla EU | *Group response.*<br><br>*Nature and purpose of your group or organisation:*<br><br>Pharmaceutical manufacturer.<br><br>*How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status/productivity?*<br><br>The draft recommendation could result in a safety issue for patients. |
| **Cir** | Circassia | Mr Alec Mushunje commenting on behalf Medical Director, Circassia, Oxford | *Group response.*<br><br>*Nature and purpose of your group or organisation:*<br><br>Pharmaceutical manufacturers of the NIOX VERO Device for FeNO measurements. |

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| | | | The device is a diagnostic for type 2 airway inflammation and recommendations will promote or reduce uptake in the UK. |
| **CS** | Mrs Catherine Sutton | Chartered Company Secretary, Lawnside Limited, London | *Individual response.*<br><br>*Non-financial interests:*<br><br>Director of Airborne Allergy Action CIC - applies directly. Airborne Allergy Action CIC has no conflicts of interest. |
| **ER** | Mr Euan Reid | Lead Pharmacist, Medicines Management Team, NHS Fife | *Individual response.*<br><br>*Remuneration from employment:*<br><br>Lead Pharmacist, NHS Fife |
| **GSK** | GlaxoSmithKline UK | Joanne Fletcher, Head of Medical Affairs, Respiratory, UK commenting on behalf of GlaxoSmithKline UK<br><br>Additional comments in separate attachment. | *Group response.*<br><br>*Nature and purpose of your group or organisation:*<br><br>Pharmaceutical manufacturer.<br><br>*How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?*<br><br>The draft SIGN recommendation will have an influence on the prescribing of GSK respiratory products. |
| **JK** | Dr Joanne Kavanagh | Research Fellow, Severe asthma, Guys & St Thomas' Hospitals, London | *Individual response.* |
| **NPRANG** | National Paediatric Respiratory and Allergy Nurses Group | Ann McMurray, Asthma Nurse Specialist and Chair of NPRANG, commenting on behalf of National Paediatric Respiratory and Allergy Nurses Group (NPRANG) | *Group response.*<br><br>*Nature and purpose of your group or organisation:*<br><br>Paediatric nurses group. We have received support from pharmaceutical companies |

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| | | | for our annual conference. In 2018 the following companies provided sponsorship however we have not endorsed their products. ALK Abello, Allergy Therapeutics, Aspire Pharma, Astra Zeneca, Bausch & Lomb, Bio-Diagnostics, Clement Clarke International, GSK, Intermedical, Novartis, Orion Pharma, PARI, Smart Respiratory Products, Thermo-Scientific, Trudell Medical.<br><br>*How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?*<br><br>This guideline is followed by clinical teams throughout the UK. The information contained within the guideline has a significant impact on the management of patients within our caseloads. Many of us are also responsible for education within primary care. |
| **PB** | Professor Peter Bradding | Clinical Professor of Respiratory Medicine, University of Leicester/ University Hospitals of Leicester NHS Trust, Leicester | *Individual response.*<br><br>*Remuneration from consultancy:*<br><br>Support for attendance at ERS Annual Congress - Napp Consultancy work on behalf of University of Leicester - Boehringer Ingelheim, GSK, Genetech-Roche Research funding - Genentech-Roche. |
| **PCRS** | Primary Care Respiratory Society | Duncan Keeley, Policy Lead on PCRS Executive Committee, Primary Care Respiratory Society | *Group response.*<br><br>*Nature and purpose of your group or organisation:*<br><br>Society for healthcare professionals working outside hospitals with an interest in lung disease.<br><br>*How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?*<br><br>The SIGN/BTS asthma guideline is key in guiding our healthcare professional members in evidence based optimal asthma management. We base communication about asthma care with members, and non-members through the Respiratory Academy, on guidelines from SIGN/BTS and NICE. We produce summaries of guidance for our members with a primary/community care emphasis. |

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| **SCRR** | Scottish Centre for Respiratory Research | Brian Lipworth, Professor of Pulmonology, Dundee commenting on behalf of Scottish Centre for Respiratory Research | *Group response.*<br><br>*Nature and purpose of your group or organisation:*<br><br>University based group - Research into airways disease<br><br>*How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?*<br><br>We use SIGN as guidance for clinical care of research patients. |
| **SF** | Dr Stephen Fowler | Senior Lecturer & Honorary Consultant Respiratory Physician, University of Manchester & Manchester University Hospitals, Manchester | *Individual response.*<br><br>*Remuneration from consultancy:*<br><br>In the last year I have received funding to attend and speak at educational meetings (non-promotional) by AstraZeneca, for investigator initiated research (non-asthma) and to speak at educational meetings (non-promotional) from Boehringer Ingelheim, attend an advisory board by Chiesi, and speak at educational meetings (non-promotional) by Novartis and Teva. |
| **SHTG** | Scottish Health Technologies Group | Moray Nairn, Programme Manager commenting on behalf of the Scottish Health Technologies Group | *Group response.*<br><br>*Nature and purpose of your group or organisation:*<br><br>The Scottish Health Technologies Group (SHTG) is an advisory group set up to provide assistance to NHSScotland boards when considering selected health technologies, excluding medicines which will be reviewed by the Scottish Medicines Consortium (SMC).<br><br>The remit of the SHTG is to provide advice on the evidence about the clinical and cost effectiveness of existing and new technologies likely to have significant implications for patient care in Scotland. This advice should support the planning and decision making processes in NHS boards. |

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| | | | *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?*<br><br>SIGN publications are taken into consideration by SHTG in the formulation of advice to NHSScotland. |
| **SMC** | Scottish Medicines Consortium | Christine Hepburn, Principal Pharmaceutical Analyst commenting on behalf of Scottish Medicines Consortium | *Group Response.* |
| **TeUK** | Teva UK Limited | John Holmes, Director of Medical Services UK and IRL commenting on behalf of Teva UK Limited | *Group response.*<br><br>*Nature and purpose of your group or organisation:*<br><br>Pharmaceutical manufacturer<br><br>*How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?*<br><br>"The draft SIGN recommendation in favour of Relvar which would promote uptake in NHS Scotland which may increase their company performance and affect patient safety." |
| **WS** | Dr William Sellers | Locum Consultant Anaethetist, University Hospital Coventry and Warwickshire, Coventry | *Individual response.*<br><br>*Non-financial interests:*<br><br>I suffer from asthma! |
| **Invited peer reviewers** | | | |
| **BH** | Dr Bernard Higgins | Consultant Respiratory Physician, Newcastle Upon Tyne Hospitals NHS Trust | *Individual response.*<br><br>*Remuneration as holder of paid office:*<br><br>I work on some NICE Guidelines as a Clinical Director of the National Guidelines |

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| | | | Centre, RCP London |
| **RB** | Professor Richard Beasley | Medical Research of New Zealand | *Individual response*.<br><br>Remuneration from employment:<br>Medical research, Institute of NZ (MRINZ) – Independent Research Organisation.<br>Capital and Coast District Health Board – Government Hospital<br>University of Otago – University<br><br>*Remuneration as a director:*<br>Medical Research – Institute of NZ (MRINZ) – Independent research organisation<br><br>*Remuneration from consultancy:*<br>Fees from AZ, GSK – lectures to advisory boards and presentations at meetings.<br><br>*Non-financial:*<br>Chair – Asthma and Respiratory Foundation – Adult asthma guidelines group<br><br>*Non-personal*:<br>MRINZ has received research funding from AZ, GSK and Fisher and Boehringer healthcare. |

| Section | | Comments received | Development group response | Editorial response |
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| **General** | | | | |
| | AUK | Thank you for extending the deadline for Asthma UK to submit comments on your draft BTS/SIGN consultation. That was very helpful. Please find our submission below.<br><br>**Aligning with NICE Guidance**<br><br>We hope that, over time, the BTS/SIGN British guideline on the management of asthma will align more closely with the NICE Guideline and Quality Standard on Asthma; Asthma UK has now endorsed both the NICE Asthma: diagnosis, monitoring and chronic asthma management guideline (November 2017) and the new NICE Quality Standard QS25 (September 2018). We believe that aligning the BTS/SIGN guideline with the NICE guideline will reduce confusion and provide greater clarity for everyone who manages people with asthma. | The SIGN/BTS guideline has been in existence since 2003, with annual and more recently biennial updates; there is only one edition of the NICE guideline, published in 2017. As the SIGN/BTS guideline is more comprehensive and is updated continuously, it may be that the NICE guideline needs to be more closely aligned with the SIGN/BTS guideline in order that the former remains up-to-date.<br><br>The NICE guideline and Quality Standards do not apply in Scotland.<br><br>Discussions between SIGN, BTS and NICE are taking place. | |
| | BTS | A very comprehensive and tightly written guideline | Thank you | |
| | GSK | GSK would like to thank BTS/SIGN for the opportunity to comment on the draft British Guideline on the Management of Asthma. We recognise the volume and complexity of the task which BTS and SIGN have undertaken and its desire to assess the full body of clinical evidence. We would like to congratulate BTS/SIGN on producing a leading guideline on asthma care in the UK. | Thank you. | |
| | PB | I like the style and presentation.<br><br>Sections 7.4.4 and 7.7.3 need revising although you say that you will not alter these unless factually incorrect. Please consider my comments as the world has moved on from the days of oral beta agonists, ciclosporin, gold and methotrexate! | Thank you.<br><br>See responses in individual sections. | |

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| | PCRS | We have had major challenges with this consultation from a process perspective.<br><br>Your feedback form is online, but you kindly provided a word version so that we could collate the views of members from a word version. Your form is very long - covering the whole guideline and I had to produce an edited version only highlighting the areas where you were inviting comments.<br><br>The draft guideline was not marked up with the changes - so in order to comment, people had to have the current guideline open, the draft guideline open, and the summary of key changes, AND the word doc. This has been a very unwieldy process from our perspective and combined with consulting over Christmas and New Year, means that we have not had the volume of comment that we would have expected/hoped for. Please consider your process carefully for the future. | The draft guideline contained a table in section 1.2.4 detailing which sections and sub-sections had been updated and the type/scale of the change, ie 'new', 'update' or 'minor update'.<br><br>These comments will be considered by SIGN so as to inform future consultations. | |
| | WS | It would be useful to have Anaesthetists and Intensivists on your Committee. | In order to maintain a manageable group size it is not possible to include representatives from all possible specialties for adults and children. Specialist input is welcomed at peer review and open consultation. | |
| | RB | The 2019 BTS/SIGN Asthma Guidelines is an impressive document presenting practical evidence-based recommendations in a clear easy to follow format. As with earlier editions, the guidelines will be widely read and followed globally. The incorporation of new evidence is apparent, although there are a number of key areas where further review of recent evidence may be warranted, and a paradigm shift in the recommended approach considered.<br><br>The key areas can be considered within the framework of Figure 2, the summary of asthma management in adults on page 76, in which it is recommended that a short acting beta agonist is required at all levels of severity, yet there is substantive evidence that ICS/formoterol reliever therapy is superior to SABAs as reliever therapy across the spectrum of severity. This evidence has recently been extended from ICS/formoterol reliever therapy markedly reducing the risk of severe exacerbations compared with SABA reliever therapy in adults with moderate and severe asthma taking ICS/LABA maintenance therapy,[1] to ICS/formoterol reliever | Thank you.<br><br>The use of reliever therapy including SABA was not covered by this update, but has been identified as a priority for the next update. | |

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| | | monotherapy markedly reducing the risk of severe exacerbations compared with SABA reliever monotherapy in adults with mild asthma.[2] It could be argued that there is now sufficient evidence to recommend ICS/formoterol reliever therapy as an alternative to SABA reliever therapy across the spectrum of asthma severity.[3,4] The statement made in section 7.1, that adults ( and children) with a diagnosis of asthma should be prescribed a short acting bronchodilator to relieve symptoms needs to be modified to be consistent with the substantive evidence that ICS/formoterol has superior efficacy than short acting bronchodilators in adults.<br><br>The implications of this evidence are that the entire guidelines would need to be revised accordingly. For example, in response to this evidence it could be argued that a strong recommendation can now be made that ICS/formoterol used as maintenance and reliever therapy is the preferred ICS/LABA regimen as recommended in the NZ Adult Asthma Quick reference guide.[5]<br><br>The next key issue is the level of control at which to increase treatment, in an attempt to achieve the 'unachievable' goal of total asthma control with absolutely to symptoms at all (page 63). While this goal is aspirational, it could be argued it is not realistic, and attempts to achieve total control may lead to over treatment. For example, in Figure 2 it is recommended to consider moving up a step in treatment if using SABA more than 3 doses a week. What is the evidence for this recommendation? There is evidence to suggest that neither total control nor well-controlled asthma cannot be achieved in a substantive proportion of patients even with the highest doses of ICS/LABA therapy,[6] and that this approach may result in overtreatment. The issue of potential overtreatment also relates to the terminology of ICS doses as low, moderate and high, as recently reviewed.[7] I note the revision that has been made in the Table to discourage high ICS does, but wonder whether it is now time to refer to standard and higher doses.[5]<br><br>In terms of acute asthma treatment I have a few comments. The first it is a relief to note that the previous recommendation for patients to take 10 actuations of SABA, repeated as necessary prior to obtaining medical review has been removed, (unless I missed it!). I was concerned by the statement that 'it is not known if ICS provide further benefit in addition to systemic steroids', when the updated 2012 Cochrane reference states that in patients treated with systemic steroids, repeat doses of ICS reduce the risk of hospital admission (odds ratio 0.54 95% CI 0.36 to 0.81).[8] As a | .<br><br>This is covered in section 7.3.1<br><br>SABA use was not covered by this update.<br><br>Management of acute asthma was not covered by this update.<br><br>Increasing inhaled steroids at the onset of an attack is | |

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| | | result, high repeated doses of ICS may warrant inclusion as a therapeutic option in acute severe asthma. I was also concerned that the recommendation re the doses of systemic steroids in acute severe asthma does not include the landmark RCT which investigated lower than standard doses.[9]<br><br>*Sobieraj DM, Weeda ER, Nguyen E, et al. Association of inhaled corticosteroids and long-acting beta-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. JAMA 2018; doi:10.1001/jama.2018.2769.*<br><br>*O'Byrne P, FitzGerald M, Bateman ED, et al. A7655/P918 – Efficacy and safety of as-needed budesonide/formoterol in mild asthma. N Engl J Med 2018; 378: 1865-76.*<br><br>*O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: time for a new approach? Eur Respir J 2017; 50: 1701103.*<br><br>*Beasley R, Bird G, Harper J, Weatherall M. The further paradoxes of asthma management: time for a new approach across the spectrum of asthma severity. Eur Respir J 2018; 52: 1800694.*<br><br>*Beasley R, Hancox R, Harwood M, Perrin K, Poot B, Pilcher J, Reid J, Talemaitoga A, Thayabaran D. Asthma and Respiratory Foundation NZ Adult Asthma Guidelines: a Quick Reference Guide. NZ Med J 2016; 129: 83-102.*<br><br>*Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med 2004; 170: 836-44.*<br><br>*Beasley R, Harper J, Bird G, Maijers I, Weatherall M, Pavord ID. Inhaled corticosteroid therapy in adult asthma: time for a new therapeutic dose terminology. Am J Respir Crit Care Med 2019; https://www.ncbi.nlm.nih.gov/pubmed/30645143*<br><br>*Edmonds ML, Milan SJ, Camargo Jr CA, Pollack CV, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute* | addressed in the self-management chapter in the context of PAAPs (section 5.2.3). This includes a review of recently published studies about increasing (quadrupling or quintupling) the dose of ICS at the start of an attack. | |

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| | | *asthma. The Cochrane Library 2012, Issue 12, CD002308.*<br><br>*Bowler SD, Mitchell CA, Armstrong JG. Corticosteroids in acute severe asthma: effectiveness of low doses. Thorax 1992; 47: 584-7.* | | |
| **Section 1** | | | | |
| **General** | PCRS | We welcome this further update of the long established, comprehensive and highly respected BTS SIGN guideline for asthma.<br><br>We note the continuing major differences between BTS/SIGN and NICE recommendations – including in areas covered by NICE that have been reviewed in this update. We have editorialised in the BMJ about the confusion that results in primary care from conflicting UK guidelines and the desirability of consensus. We are hopeful that any future UK guideline for asthma will combine the best of SIGN/BTS and NICE methodologies into a single consensus.<br><br>You do not refer to these issues at any point, and might consider referencing a companion article briefly discussing the reasons for the major differences in diagnosis and treatment recommendations between yourselves and NICE.<br><br>There are a number of issues where recommendations at a government policy level might be made, for example in respect of smoking cessation services (funding currently threatened) or air pollution.<br><br>The guideline does not contain any discussion of health inequalities which are important in asthma as in other areas.<br><br>We think that these issues should be considered for inclusion in future guidelines. | Thank you<br><br>The following article will be listed in the 'Supporting Information' section of the asthma homepage on the SIGN website*:* White J, Paton J, Niven R and Pinnock H. Guidelines for the diagnosis and management of asthma: a look at the key differences between BTS/SIGN and NICE. *Thorax,* 4 January 2018<br><br>The recommendation in section 6.2.3 covers the need for support to stop smoking.<br><br>This is covered briefly in section 4.1 Targeting care (previously included in section 4.2). | |
| **1.1.1** | AZ | There is a need to ensure the guideline is up to date and provides guidance for best-practice patient care for asthma patients of all severities. Recently there has been a lot of new data and publications looking at new treatment options specifically in the mild and severe asthma populations. Looking forwards there may be a paradigm shift in asthma management and this should be reflected in the new guidelines. | Future updates will take account of any new evidence that becomes available. | |

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| | BTS | "inpatient admissions" – suggest "inpatient services" | Agreed. Wording changed. | |
| **1.2.2** | ARNS | I think you should add "any other allied health care professionals with an interest in respiratory care after "pharmacists", as there are others such as physiotherapists, occupational therapist and so on who can have a great input into asthma patients management. | Agreed. Additional text added as suggested. | |
| | PCRS | Consider adding physiotherapists to the list of users. | Agreed. 'Allied health care professionals with an interest in respiratory care' added. | |
| **1.2.3** | PCRS | Helpful, but reviewing changes would be much easier if changes were highlighted in a different colour in the draft – any computer can do this! We believe the lack of clarity indicating where the changes are in the revised guideline for review has impacted people's ability to spend time commenting. | A detailed list of where changes have been made to this update is already included in section 1.2.4.<br><br>SIGN will consider options for future consultation drafts. | |
| **1.2.4** | ARNS | A useful section. | Thank you. | |
| | PCRS | See above!! | No response needed. | |
| | SF | "2.3 monitoring" – typo, should be "2.2" | Corrected. | |
| **1.3** | ARNS | At the end of this statement I would also suggest "and a rationale as to the decision made". | Disagree. This is standard text in all SIGN guidelines and the sentence already says that "…departures from the national guideline…should be fully documented…". | |
| **1.3.1** | ALUK | I am employed by the patient charity organisation Allergy UK, which was set up 26 years ago by Allergy clinicians to include a business arm which endorses products that may be of benefit to people living with allergic disease. All profits from this business arm are donated into the charity for it to enable its mission of helping people with allergy. I personally do not have any conflicts of interest, but a list of Allergy UK indirect financial interests are listed below for transparency.<br><br>Employers trading subsidiary (Allergy research limited) has product endorsements to signpost people affected by allergy to products which may be more suitable for them to help manage their exposure to allergens. | No response needed. | |

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| | | We currently endorse approximately 200 product ranges, comprising of vacuum cleaners, air purifiers, homecare products, bedding, and personal care products, all of which are assessed by independent laboratory or expert consultants.<br><br>We have two product approvals for different types of product:<br><br>• **Seal of Approval**; for products which can be/have been independently scientifically tested to prove they reduce the presence of allergens in the indoor environment or clinically tested on people and proven to be suitable for people affected by allergy.<br>• **Allergy Friendly Product Award**; for products which are 'unlikely or less likely to cause a reaction' and 'may be of benefit' when used by someone affected by allergy, these products are assessed based on their formulation and benefit. | | |
| **Section 2** | | | | |
| **General** | Cir | Please see comments on the key recommendation sections on the diagnosis (2.1) and Monitoring (2.2), as well as the relevant sections detailing the detailed recommendations for comments that may be considered to the conclusions. | See response in relevant sections. | |
| **2.1** | Cir | We propose a new evidence appraisal for this section, and an update as relevant.<br><br>In particular, we would like to highlight the discrepancy in the approach to the diagnosis of asthma between the main asthma guidelines in the UK; the BTS/SIGN guidelines, and NICE NG80 guidelines which may cause confusion for healthcare professionals, as well as for patients, with potential impact to patient care. Whereas NICE, with evidence backing, have proposed incorporation of objective/diagnostic tests to initial diagnosis and shown it to be cost effective, BTS/SIGN still proposes a diagnostic path with objective testing only for patients with intermediate probability of asthma diagnosis.<br><br>Asthma is both over- and under-diagnosed resulting in inappropriate or ineffective treatments for patients, and some have estimated that approximately one third of patients initially diagnosed with asthma cannot be confirmed to have asthma when objectively assessed. Of these | The diagnosis of asthma was not covered by this update. | |

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| | | misdiagnosed patients, more than 70% are receiving asthma treatments (Pakhale 2011, Looijmang-van-Akker 2016, Aaron 2017). Therefore, just like the approach taken to the diagnosis of any medical condition, it is relevant to incorporate objective testing in apny diagnostic pathway. The current BTS/SIGN approach of suggesting objective testing only to intermediate probability patients may therefore be restrictive, especially as there is already evidence and recommendations by NICE NG 80 that appropriate objective testing for all patients that qualify in the first instance is cost effective.<br><br>More specifically, incorporating biomarkers into the patient's clinical evaluation could uncover untreated airway inflammation and assists practitioners to properly classify the patient's asthma phenotype and therefore individualise drug therapy. There is therefore a need for an appraisal of the role of available objective tests in patients suspected to have asthma to support its diagnosis. This approach is in agreement with the NICE quality statement 1: People aged 5 years and over with suspected asthma have objective tests to support diagnosis as highlighted in the current draft BTS/SIGN guidelines.<br><br>Neither spirometry, nor the other diagnostic tools that are commonly used in clinical practice directly measure the amount of airway inflammation. Incorporating biomarkers into the patient's clinical evaluation uncovers untreated airway inflammation and assists practicing physicians to properly classify the patient's asthma phenotype and therefore individualize drug therapy.<br><br>FeNO (fractional exhaled nitric oxide) as an established, validated and specific biomarker for T2 driven airway inflammation in asthma that can aid in asthma diagnosis.<br><br>1. An evidence-based analysis that included 43 studies with a total of 13,747 patients concluded (depending on the FeNO level) that the likelihood of people ages 5 years and older having asthma increases by 2.8 to 7.0 times given a positive FeNO test result (based on evidence rated as moderate) (Wang et al 2017).<br><br>2. ATS Guideline strongly (Dweik et al 2011) recommends the use of FeNO in the diagnosis of eosinophilic airway inflammation based on a level of moderate evidence. In addition, the ATS Guideline recommends that cut | | |

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| | | points, rather than reference ranges, be used when interpreting FeNO values. Values of less than 25 ppb in adults (<20 ppb children) are considered low; intermediate values are 25 to 50 ppb in adults (20-35 ppb children), and high values are greater than 50 ppb in adults (>35 ppb children).<br><br>3. NICE guideline for the diagnosis, monitoring and treatment of asthma (NICE NG80, 2017) incorporates routine FeNO testing into their latest diagnostic algorithm based on evidence that demonstrated improved clinical accuracy and cost effectiveness. NICE recommends performing a FeNO test in adults (aged 17 and over) if a diagnosis of asthma is being considered, and to regard a FeNO level of 40 parts per billion (ppb) or more as positive. For paediatrics, NICE suggests to consider a FeNO test in children and young people (aged 5 to 16) if there is diagnostic uncertainty after initial assessment and they have either: normal spirometry or obstructive spirometry with a negative bronchodilator reversibility (BDR) test. A FeNO level of 35 ppb or more should be regarded as a positive test.<br><br>4. In a recent comparative meta-analysis of a variety of tests for diagnosing asthma (e.g. spirometry, bronchial challenge, and/or bronchial reversibility), FeNO was found to have good performance (Karrasch 2017), with a pooled sensitivity of 0.68 (0.53 to 0.79), and specificity 0.83 (0.74 to 0.89), and an area under the curve of 0.83 (0.75 to 0.92) for the 9 key studies. The authors conclude that in clinical practice, the diagnostic pathway could start with FeNO measurement as a first step. They also concluded that bronchial provocation would be superfluous when FeNO levels exceed a distinct cut-off value, which needs to provide a meaningful positive predictive value.<br>5. Other asthma guidelines recommend that asthma be diagnosed with a combination of a variety of clinical tools including patient and family history, physical examination, symptoms and objective lung function tests such as spirometry (NHLBI 2007, NICE 2017, GINA 2018), therefore there is a need to review the current BTS/SIGN diagnosis section that limits objective testing only to intermediate risk patients as this is not holistic.<br><br>References:<br><br>1. *Pakhale S, Sumner A, Coyle D, et al. (Correcting) misdiagnoses of asthma: a cost effectiveness analysis. BMC Pulmonary Medicine. 2011; 11:27* | | |

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| | | *2. Looijmang-van den Akker I, Luijn K, Verheij T. Overdiagnosis of asthma in children in primary care: a retrospective analysis. Br J Gen Pract 2016; 66 (644): e152-e157*<br><br>*3. Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P et al. Overdiagnosis of asthma in obese and nonobese adults. Canadian Medical Association Journal. 2008; 179(11):1121-1131.*<br><br>*4. Wang Z, Pianosi P, Keogh K, et al. The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management. Comparative Effectiveness Review No. 197 (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. 290-2015-00013-I).*<br><br>*5. Dweik RA, Boggs PB, Erzurum SC, et al. Interpretation of exhaled nitric oxide levels (FeNO) for clinical applications: an official ATS clinical practice guideline. Am J Respir Crit Care Med. 2011; 184: 602-615*<br><br>*6. NICE. National Institute for Health and Clinical Excellence. Asthma: diagnosis, monitoring and chronic asthma management NICE guideline [NG80]. November 2017. Available at: https://www.nice.org.uk/guidance/ng80 Accessed January 2019.*<br><br>*7. Karrasch S, Linde K, Rücker G, et al. Accuracy of FENO for diagnosing asthma: a systematic review. Thorax 2017; 72:109–116.*<br><br>*8. National Heart, Lung and Blood Institute Expert panel Report 2007: Accessed at https://www.nhlbi.nih.gov/sites/default/files/media/docs/asthgdln_1.pdf January 2019.*<br><br>*9. GINA-Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). 2018 Full text available online at: www.ginasthma.org (Accessed January 2019).* | | |
| **2.2** | ARNS | See Section 4 – General | | |
| | Cir | Comments in 4.2 | | |
| **2.8** | Cir | Comments in Section 12.1.2 | | |

| **Section 3** | | | | |
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| **General** | ARNS | Nothing to add to this whole section. | The diagnosis of asthma was not covered by this update. | |
| | PCRS | We are aware that this section has not been reviewed this time. Please consider these comments for any future revision of this section.<br><br>We think that the statement below is crucial and needs greater emphasis – clinical and physiological re-evaluation over time is key to accurate diagnosis - and to the detection of misdiagnosis (which should be specifically discussed). This is readily achievable in primary care.<br><br>P11<br>1. Time may, however, be used to advantage if objective signs and tests when a patient is symptomatic are compared to measurements when they are asymptomatic. In the event of diagnostic uncertainty it may be helpful to repeat investigations.<br><br>We also feel that spirometry, which is difficult in children, requires significant training for performance and interpretation, and is frequently negative in primary care populations with suspected asthma, and should not be mandatory for asthma diagnosis. In the NICE field testing pilot study, 70% of those eventually diagnosed with asthma had normal spirometry.<br><br>Peak flow monitoring should however be the recommended first line test in all patents old enough to perform it as the first line objective test to support asthma diagnosis.<br><br>We agree with the positioning of spirometry for patients with an intermediate probability of asthma after initial assessment.<br><br>Emphasis is needed that PEFR monitoring needs to be done when the patient is symptomatic.<br><br>P14<br><br>One limitation of these epidemiological studies is that it is not always clear whether the participants were symptomatic at the time of the monitoring. PEF charting when asthma is ‘inactive’ is unlikely to confirm variability; one study showed that significant PEF variability was associated with respiratory symptoms in the previous week. | Thank you. These comments will be considered for future updates of the guideline. | |

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| | | Reference 29 (p16) is about monitoring and is not relevant to diagnosis. Peak flow monitoring is valuable for diagnosis in children old enough to perform the test.<br><br>We remain in agreement with your conclusions over the role of FeNo in diagnosis which we believe that NICE have overemphasised.<br><br>Table 2 P 22<br><br>This sentence in the table:<br>• with symptomatic and objective improvement with time and/or treatment<br><br>Should be carried through into the bold bullet pointed recommendations – asking about previous episodes, and response to treatment is an important part of diagnostic assessment. | | |
| **3.1.1** | BTS | Agreed that this time the Diagnosis section is not being revised but would the authors consider a formal definition, e.g. Asthma is a syndrome of episodic respiratory symptoms (more than one of wheeze, breathlessness, chest tightness, cough) and of variable airflow obstruction. The section opens with "Central to all definitions..." but nowhere does it give a definition. Otherwise the paragraph and subsequent sections flow really well. | No. In the view of the GDG, the definition given in section 3.1.1 reflects the problems with defining asthma and evolving work in this area. | |
| **3.1.2** | SCRR | FeNO and blood Eos needs to put at the forefront of this section given that type 2 inflammation may be present in the absence of airflow obstruction on spirometry - ie the point needs to be made that markers of type 2 inflammation should be used in tandem with spirometry. This would be the case for example where spirometry is preserved.<br><br>Also nothing here is mentioned on small airways dysfunction (eg abnormal FeF25-75 or R5-20 or AX) which may be abnormal in patients with normal or equivocal spirometry. | The diagnosis of asthma was not covered by this update. The role of FeNO in diagnosis is covered in section 3.2.4.<br><br>There is no gold standard test for the diagnosis of asthma. | |
| **3.1.3** | BTS | Final para:<br><br>Add: ..... and look for previously performed tests.<br><br>Recommendation:<br><br>Ask about the existence of previous spirometry or peak flow recordings | The diagnosis of asthma was not covered by this update.<br><br>This point is covered by the existing recommendation. | |

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| | Cir | The publication by Schneider et al has been used to validate the performance of FeNO as an objective test for diagnosis of asthma. There has however been a larger metanalysis by Karrasch et al that may have a bearing on the performance of FeNO as a diagnostic test.<br><br>FeNO was found to have good performance, with a pooled sensitivity of 0.68 (0.53 to 0.79), and specificity 0.83 (0.74 to 0.89), and an area under the curve of 0.83 (0.75 to 0.92) for the 9 key studies. The authors conclude that in clinical practice, the diagnostic pathway could start with FeNO measurement as a first step.<br><br>Ref:<br>*Karrasch S, Linde K, Rücker G, et al. Accuracy of FENO for diagnosing asthma: a systematic review. Thorax 2017; 72:109–116* | The diagnosis of asthma was not covered by this update. | |
| **3.2.2** | SCRR | Again no mention here about *(sic)* | Incomplete comment. | |
| **3.2.3** | BTS | "high negative predictive value" Confusing? Favour "a low pre-test clinical probability"<br><br>Page 19 This page seems to be a repeat of page 18 | Sentence reworded to improve clarity.<br><br>Thank you. This duplication is an error and has been rectified. | |
| | NPRANG | In table 1 of challenge tests no value has been inserted under exercise test to determine positive result | Thresholds were not specified because all the papers were different (ranging from 8% to 20%). A statement to this effect has been added to Table 1. | |
| | SCRR | Again no mention here about small airways dysfunction eg using spirometry ( FEF25-75) and IOS ( R5-20 and AX) | The diagnosis of asthma was not covered by this update. | |
| **3.2.4** | AUK | **Using available diagnostic tests**<br><br>It is now understood that asthma is not a single condition, but a collection of symptoms caused by different mechanisms. Understanding the mechanisms that drive asthma symptoms in individuals is important because different types of asthma respond to different drugs. Assessing responses to treatment through measurement of biomarkers is increasingly possible, as is using biomarkers to measure adherence to treatment. Although there is a reluctance to adopt the newer diagnostic tests (e.g. FeNO) until there is stronger evidence of their utility, if people with asthma | The diagnosis of asthma was not covered by this update.<br><br>The use of FeNO in the diagnosis of asthma is covered in section 3.2.4. | |

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| | | are to see the benefits from these tests, they need to be trialled in practice now, with data collected to assess their impact. It is our view, therefore, that the revised BTS/SIGN guidelines should reflect this and recommend the use of tests that clinical evidence has shown to be safe, minimally invasive and potentially useful (e.g. FeNO, blood eosinophils), alongside the collection and reporting of data on their utility. This would allow evidence to be collected through routine use, rather than waiting for the results of more clinical trials. The respiratory community needs to be responsive to the adoption of new technologies to transform the diagnosis and treatment of asthma and to prevent under - and over-treatment, whilst remaining mindful of the need for patient safety. This, importantly, aligns with the NHSE Long Term Plan which calls for better adoption of new technologies. | The use of FeNO and blood eosinophils in monitoring asthma is covered in sections 4.3.2 and 4.3.3 (now 4.4.2 and 4.4.3). | |
| | SCRR | See above wrt type 2 inflammation markers | The diagnosis of asthma was not covered by this update. Section 3.2.4 reviews the evidence about FeNO and inflammatory markers and has a recommendation about use. | |
| **3.3** | BTS | Could Tables 4 and 5 be referenced here as well? | No. These tables are referenced appropriately in section 3.3.2. | |
| | SCRR | No comment on disconnect between FEV1 and markers of small airways function | The diagnosis of asthma was not covered by this update. | |
| **3.3.2** | BTS | Add "Locate previously performed spirometry for comparison" GPP at top of page – bullet starting "assess the status....2 This paragraph should read "assess the status with a validated symptom questionnaire before and after treatment corroborated by domiciliary serial peak flows and, if possible, by FEV 1 at symptom baseline at clinic visits" | The diagnosis of asthma was not covered by this update. The second bullet point in the GPP has been amended. | |
| | BTS | Query if FEV1 measurements widely separated in time are helpful even as supporting evidence. Surely demonstration of continuous data involving improvement in symptoms, airflow variability and a visual representation of frequently collected should be advocated as best practice? | The diagnosis of asthma was not covered by this update.<br><br>If a person improves with treatment, then the only evidence of airways obstruction may be retrospective. | |
| | SCRR | See above wrt small airways | No response needed. | |

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| | Cir | This section states: "Adults and children with a typical clinical assessment including recurrent episodes of symptoms (‘attacks’), wheeze heard by a healthcare professional, historical record of variable airflow obstruction and a positive history of atopy (see Table 2) and without any features to suggest an alternative diagnosis (see Tables 4 and 5) have a high probability of asthma."<br><br>Although objective testing is only suggested for intermediate probability patients, this section for high probability mentions "historical record of variable airflow obstruction" which is an objective test.<br><br>We suggest that objective tests including spirometry and biomarkers be incorporated in the initial assessment to properly phenotype asthmatic patients as aligned with NICE NG80 guidelines for all patients. This has been shown to be cost effective by NICE in the context of asthma care in the United Kingdom. We propose both Spirometry and FeNO measurement where relevant as initial assessment and as suggested in NICE NG80 guideline to provide a baseline for assessing response to and initiation of treatment and exclusion of alternative diagnosis even for high probability patients. Asthma is a highly heterogenous disease and initial assessment would not be complete without inclusion of objective testing. See also comments in section 2.1 regarding objective testing for asthma. | The diagnosis of asthma was not covered by this update. | |
| **3.3.3** | BTS | GPP: With respect this is not logical; if asthma is a low probability differential it must have been replaced as working diagnosis by another differential. Surely, given the adage of confirming the working diagnosis and refuting the differential we should be looking to confirm the new working diagnosis? Trying to confirm asthma having decided it is a low likelihood differential is surely futile and an example of the law of diminishing returns?<br><br>Point 2:<br>Surely something should be said about measuring airflow during symptoms as well as twice daily if the initial lung function is normal.<br><br>Another issue is communication with primary care colleagues ensuring that the treatment plan and the rationale behind it as well as what their role is are all clear. | GPP - We agree, and this is what we were trying to say in section 3.3.3. For clarity, we have now rephrased as ‘investigate for the alternative diagnosis, reconsidering asthma if the clinical picture changes or an alternative diagnosis is not confirmed’.<br><br>Point 2 - This is addressed in Table 2, but is now also emphasised in the re-worded second bullet point of the GPP in 3.3.2. | |

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| | | Should we advocate a review of all patients starting a trial of outpatient treatment with the asthma nurse prior to commencement as best practice? Re-enforcement of process, rationale, inhaler technique as well as a friendly face and a contact card would surely not go amiss?<br><br>Point 7:<br><br>"titrating down the dose of inhaled steroid"<br>? at not less than 3 monthly intervals. | The issue of follow-up is addressed in Table 3, but the point about communication and where the responsibility lies for follow-up is well made.<br><br>Point 7 - We have not specified the time frame for stepping down as this will vary. In stable conditions 3-monthly might be appropriate, but when treatment is started at a higher dose in a more acute context, more rapid tapering may be appropriate. | |
| | SCRR | See above wrt small airways | No response needed. | |
| **3.3.4** | BTS | Recommendation:<br>in adults who have baseline obstructive lung function | The diagnosis of asthma was not covered by this update. In the view of the GDG, the existing recommendation is appropriate. | |
| | Cir | This section recommends that patients require full clinical assessment and investigation before a diagnosis of asthma can be made, unless the clinical condition is acute, before treatment is commenced or continued. As discussed in section 2.1, there is a risk of over, and under-diagnosis of asthma, therefore a combination of clinical evaluation as well as objective testing needs to be considered for all asthmatic patients as detailed here, even for the high probability patients. The approach as suggested by NICE NG80 guideline has been shown to be cost effective in the context of asthma care in the UK. NICE quality standard propose objective testing to support asthma diagnosis. The rationale as per NICE is that "Asthma can be misdiagnosed, which means that people with untreated asthma are at risk of an asthma attack, and people who do not have asthma receive unnecessary drugs. Objective tests can help healthcare professionals to diagnose asthma correctly. The basis on which a diagnosis of asthma is made should be documented." (NICE Quality Standard Draft Consultation 2018). In addition, it would be beneficial to get alignment on asthma care for the benefit of patients, and to better guide healthcare professionals | The diagnosis of asthma was not covered by this update. | |

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| **3.3.3** | Cir | See comments in section 3.3.2 relevant to clinical assessment and objective testing as aligned to NICE NG80 guideline. | No response needed. | |
| **3.3.4** | Cir | This section recommends that patients require full clinical assessment and investigation before a diagnosis of asthma can be made, unless the clinical condition is acute, before treatment is commenced or continued. As discussed in section 2.1, there is a risk of over, and under-diagnosis of asthma, therefore a combination of clinical evaluation as well as objective testing needs to be considered for all asthmatic patients as detailed here, even for the high probability patients. The approach as suggested by NICE NG80 guideline has been shown to be cost effective in the context of asthma care in the UK. NICE quality standard propose objective testing to support asthma diagnosis. The rationale as per NICE is that "Asthma can be misdiagnosed, which means that people with untreated asthma are at risk of an asthma attack, and people who do not have asthma receive unnecessary drugs. Objective tests can help healthcare professionals to diagnose asthma correctly. The basis on which a diagnosis of asthma is made should be documented." (NICE Quality Standard Draft Consultation 2018). In addition, it would be beneficial to get alignment on asthma care for the benefit of patients, and to better guide healthcare professionals. | The diagnosis of asthma was not covered by this update. | |
| **3.4** | ALUK | There are too few allergy services in the UK to investigate if Allergic triggers are exacerbating asthma and access to immunotherapy or biologicals is an issue. | No response needed. | |
| | BFS | We as manufacturers are concerned about the non-alignment in the major guidelines and how it impacts both patient care and GP's as this may be confusing to both patient and GPs alike. Even in these guideline, section 3 seems to advocate FeNO in conjunction with other tests (especially in secondary care) but section 4 contradicts this entirely. | Use of FeNO in diagnosis and monitoring of asthma are separate issues and are covered in Sections 3.2.4 and 4.3.2 (now 4.4.2), respectively. | |
| | NPRANG | 'Asthma is the by far the commonest cause' - typo in sentence | This phrase appeared in section 3.3.4 and has already been re-worded. | |
| **3.5** | NPRANG | A raised specific IgE to wheat, egg white, or inhalant allergens such as house dust mite and cat dander, predicts later childhood asthma.<br><br>Wheat IgE is a notoriously poor indicator of allergy to wheat. | The diagnosis of asthma was not covered by this update. | |

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| | | Does raised IgE perhaps suggest an increase risk of childhood asthma rather than predict? | | |
| **Section 4** | | | | |
| **General** | ALUK | The accepted first line management for all allergic manifestation is avoidance of 'trigger' allergens. Are you rewriting the 'rationale' for this? Which has huge implications.<br><br>Patient education on avoidance measures need to be multifactorial and extensive to be of benefit ie via a factsheet.<br><br>UK has the highest rates of asthma in the world and also exceedingly high rates of allergic rhinitis. Uncontrolled asthma is a serious risk factor in fatal food induced anaphylaxis, so taking a multipronged perspective is key.<br><br>Housedust mite if an important driver of asthma as are pet allergens in susceptive sensitised individuals. So reduction/avoidance measures are a key part of non-pharmacological management. A recent study: *Preventing Severe Asthma Exacerbations in Children. A Randomized Trial of Mite-Impermeable Bedcovers, by Murray et al in 2017* , showed in its conclusions that: Mite-impermeable encasings are effective in reducing the number of mite-sensitized children with asthma attending the hospital with asthma exacerbations but not the number requiring oral prednisolone. This simple measure may reduce the health care burden of asthma exacerbations in children.<br><br>We also know that housedust mites are killed by washing bedclothes above 60 degrees Celsius, the drive to wash at lower temperatures that are more environmentally friendly do not kill the dustmites. | Trigger avoidance is discussed in detail in chapter 6 (non-pharmacological management) which is referenced in Table 7 as a component of asthma monitoring. We have now specified some of the key topics in Table 7.<br><br>This paper was included in the Leas 2018 systematic review considered by the GDG in section 6.2.1.<br><br>This is beyond the scope of the guideline. | |
| | ARNS | Table 7 is a good guide to what should be included in an annual review. The risk tables 9a and 9b are much clearer than previously with good links to levels of evidence. | Thank you. | |
| | BTS | Should one include specific questions on control: (Daily salbutamol use, EIB, morning dipping and QOL impairment)? | The GDG consider that section 4.1 (now 4.2) adequately covers assessment of asthma symptom control. | |

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| | NPRANG | Asthma is best monitored by routine clinical review on at least an annual basis – obviously this would probably be fine for the 'well controlled long term, knowledgeable asthmatic' but there is no emphasis that this would need to be more often for newly diagnosed, younger children who are growing and developing or children who have social issues or previous severe attacks etc.<br><br>A list of things to consider when planning the duration between reviews may be useful to encourage more individual care. | The use of 'at least' implies that more frequent review may sometimes be necessary. The appropriate frequency will depend on the individual patient. | |
| | PCRS | Why state doctor or nurse? Monitoring is best carried by a healthcare professional with the appropriate training in asthma management. This could be a community or practice based pharmacist or physician's assistant for example as long as they have appropriate training.<br><br>Does this need to include other meds such as betablockers or NSAIDs? | Agreed. 'Nurse or doctor' changed to 'healthcare professional'.<br><br>The need to consider multi-morbidity and polypharmacy have been added to the 'Management' section of Table 7. | |
| | SCRR | The place of monitoring type 2 inflammation using FeNO and blood eos needs to be made more prominent | Use of FeNO is covered in section 4.3.2 (now 4.4.2) The use of blood eosinophils has been added to an amended section 4.3.3 (now 4.4.3) | |
| | SF | "Monitoring" and asthma reviews must also review reliever use and adherence, as noted in the new table 7. Recommended methods at present include only prescription pick-up checks and (for inhaler devices with dose counters) dose-counting. Hopefully we will have smart-inhalers as well by the next update. | No response needed. | |
| | Cir | There is evidence to support the role FeNO in various aspects of the management of Asthma.<br><br>1. FeNO could be useful in evaluation of responsiveness to inhaled steroid (ICS). Patients respond to various asthma treatments differently depending on their underlying disease characteristics. Understanding the phenotypic characteristics of the disease has also become important since it helps clinicians individualize treatment accordingly. Patients with T2 phenotype have increased airway inflammation associated with eosinophils compared | The evidence summary in section 4.3.2 (now 4.4.2) concluded that the routine use of FeNO testing to monitor asthma cannot be recommended at the present time. | |

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| | | to T helper 1 (T1) phenotype that is associated with more neutrophilic infiltration (Fajt 2015), and are more likely to respond to ICSs. Up to 45% of asthmatic patients may not benefit from ICS therapy as they exhibit non-eosinophilic Th1 asthma (Spahn 2016). The following studies support the utility of FeNO in evaluation of steroid responsiveness:<br><br>• Price et al (2017) investigated the use of FeNO in predicting response to treatment with inhaled corticosteroids in difficult to manage patients with undiagnosed, non-specific respiratory symptoms. A higher baseline FeNO was associated with an increased likelihood of a positive response to inhaled corticosteroid treatment in terms of ACQ7 score, severity of cough, FEV1 and a global evaluation of treatment effectiveness. In addition, the authors found that baseline FeNO was a better predictor of clinical improvement in cough than peripheral blood eosinophils; importantly neither FEV1 nor clinical opinion of asthma were associated with response to treatment.<br>• Price et al (2013) demonstrated that adult and paediatric patients who initially present with an increased FeNO value will more likely have a positive response to inhaled corticosteroids. Conversely, patients who have a low FeNO value are less likely to respond to ICS therapy. This study is applicable to the UK settings.<br>• Smith et al. (Smith 2005a) studied 101 patients referred to a respiratory specialist for treatment. Steroid response was evaluated using spirometry (FEV1, peak flow, bronchodilator response), and bronchial challenge in addition to FeNO. Baseline FeNO provided greater sensitivities and negative predictive values than each of the other predictors. More specifically, a baseline FeNO >47ppb predicted steroid response better than any of the other tests.<br>• FeNO measurement predicts the likelihood of steroid responsiveness more consistently than spirometry, bronchodilator response, peak flow variation, or airway hyper responsiveness to methacholine. (Knuffman 2009, Szefler 2002).<br><br>2. FeNO could also be valuable in optimising the doses of ICS for asthmatic patients on treatment. Current asthma guidelines recommend periodic clinical assessment of patients and adjustment of medications by either stepping-up or -down therapy (NHLBI 2007, NICE 2017, GINA 2018). Asthma severity and symptoms fluctuate depending on the patient's lifestyle, exposure to environmental triggers and genetic tendencies. Therefore, periodic re-assessment is needed to help individualize drug | | |

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| | | therapy according to the patient's asthma symptoms, degree of airway inflammation and to minimize adverse effects from medications.<br><br>• Smith et al. (2005b) compared a FeNO based approach to one where traditional clinical monitoring (symptoms, spirometry, etc) was used. The ICS dose of fluticasone was lower in the FeNO monitored group compared to the control group (mean 370 µg vs 641 µg). More importantly, asthma control was better in the FeNO group with 45.6% less exacerbations compared to the standard care group. Exposure to high doses of ICS was also reduced in this study by using a FeNO based strategy to step patients down; 48% of the standard care group were receiving 1,000ug of fluticasone daily at the end of the study compared to 20% in the FeNO group.<br>• LaForce et al (2014) demonstrated that without knowledge of the patient's FeNO, the clinicians did not recognize the presence of significant airway inflammation in 50% of patients. Measurement of FeNO substantially altered treatment decisions in more than one third of subjects, notably stepping up medication in 20% and stepping down medication in 16% of the patients studied.<br>• Hanania et al (2018) showed in a 7000 patient real world observational study that the physician's ability to detect the presence of significant airway inflammation using traditional office based clinical tools was only able to recognize the likelihood of the FeNO being > 50 ppb in 1/3 of patients, affirming the findings from the LaForce study. However, once the physician knew that the patient had an elevated FeNO (> 50 ppb), anti-inflammatory treatment was then stepped up in 96% of patients underlining how important this knowledge is to the treating physician.<br>• ATS Guideline (Dweik 2011) recommendations for the use of FeNO monitoring states that a FeNO > 50 ppb (> 35 ppb in children) be used to indicate that eosinophilic inflammation is likely and, in symptomatic patients, responsiveness to corticosteroids is also likely (strong recommendation, moderate quality of evidence). (Dweik 2011)<br><br>3. FeNO could also be used to monitor adherence to ICS, or to uncover non-adherence to treatment. Guidelines and consensus statements on the diagnosis and assessment of patients, especially with difficult-to-treat asthma, unanimously stress the importance of identifying and addressing non-adherence in this population (Bousquet 2010, Bel 2011, GINA for severe asthma 2018).<br>• Beck-Ripp et al (2002) found a significant relationship between | | |

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| | | budesonide dosing and a reduction in FeNO levels in fifty-four paediatric and adolescent patients who were followed for 8 weeks during treatment with budesonide or placebo. The treatment phase following a 4-week washout period. No effect was observed on FEV1, and the reduction in FeNO levels was positively correlated to budesonide compliance.<br>• Delgado-Corcoran et al (2004) investigated the relationship of FeNO to asthma control and medication adherence in 30 pediatric and adolescent patients that were followed periodically for 2.5yrs using NHLBI Guidelines. FeNO levels correlated to improved asthma control and were significantly reduced in subjects with good compliance to steroids compared with patients with poor and moderate compliance. FEV1 levels were not substantially different between compliance groups.<br>• In a study by McNicholl et al (2012), patients received 7 days of direct observed administration of their ICS medication (DOICS). Those patients who had a history of poor adherence as measured by ICS refills of less than 50% experienced a greater reduction in FeNO following 7 days of DOICS compared to the group of adherent patients who had > 80% history of ICS refills (47 +/- 21% versus 79 +/- 26%) of baseline measurement (P < 0.003).<br>• Kaminsky et al (2008) evaluated 27 children who attended a summer camp for asthma. Throughout the one-week duration of the summer camp, children were administered their usual medications brought from home in an observed manner. While the duration of the summer camp was too short to see an effect on asthma outcomes, there was a significant decrease in the patient's FeNO that was attributed to improved adherence (via direct observed administration).<br><br>4. Incorporating FeNO measurement in asthma treatment paths may reduce the likelihood of asthma exacerbations in patients at risk for future events. The relevant references on FeNO and exacerbations are discussed in section 4.2 below.<br><br>5. The recently published Global Initiative for Asthma (GINA) guideline for difficult to treat and severe asthma suggest the use of markers of Type 2 inflammation including FeNO for assessment of the severe asthma phenotype. They also recommend, based one their evidence evaluation, FeNO and other markers of Type 2 inflammation as factors that predict good response to anti-IgE treatment. FeNO is also recognised among other markers as relevant for objective assessment of adherence to corticosteroids, and they suggest that tapering of corticosteroids may be supported by internet-based monitoring of symptom control and FeNO. | | |

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| | | 6. There is also a possible role of FeNO in identification of patients for biologic therapy, and monitoring of biologic treatment response. The most compelling evidence published is with the anti-interleukin-4 receptor monoclonal antibody dupilumab. In the phase III Liberty Asthma Quest Study, dupilumab decreased asthma exacerbations 46-48% across all patients. However, in patients with baseline FeNO > 25ppb, exacerbations were reduced 61-65%; and an even greater reduction in exacerbations was seen in patients with baseline FeNO of > 50ppb (mean 70%). (Castro 2018). | | |
| **4.1** | NPRANG | When asking questions it would be useful to encourage practitioners to ask the child (even young children) directly as well as the parents as the information gained is not always the same. The parent may not be aware of all the symptoms and SABA use (separated parents, whilst out with friends etc) | Agreed. A new GPP has been added to section 4.1 (now 4.2). | |
| | PCRS | States that the RCP 3Q's may be useful but goes on to say asthma control best measured using ACT agree.<br><br>However, the 2 tick/bullet points go on to include the RCP 3Q's and using a validated questionnaire, so not really reflecting the above comment. Many think RCP 3Q's are a validated questionnaire. | Agreed. Text and GPP modified. | |
| **4.2** | PCRS | The inclusion of assessing future risk is very welcome and in line with GINA recommendations.<br><br>9a table. Does smoking really only cause a 'slight increase in risk'? This is underplaying the evidence.<br><br>Recent BTS audits show that around 50% of people admitted for asthma are classified as current or ex-smokers.<br><br>We would expect high SABA use to be mentioned as a risk factor for future attacks under 'moderately increased risk' – in adults as well as children | Thank you.<br><br>Yes, this is what the evidence showed.<br><br>No response needed.<br><br>It is already included in Table 9a (adults). Clarity improved by changing it to a separate bullet point. In Table 9b (children), SABA use is covered by the text in italics after 'Sub-optimal drug regimen'. | |

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| | SCRR | ACQ is a strong predictor of future exac risk (JACI 2011 ;127:167) (Ann Allergy Asthma Immunol. 2016 ;116: 112) | The ACQ is already included in Table 9a as a predictor of future risk. | |
| | Cir | The current draft guideline lists FeNO as having equivocal evidence as a risk factor for predicting future risk of asthma attacks. We note the references quoted in the current draft guidelines. However, there is further evidence to support the predictive value of elevated FeNO for asthma care and prediction of asthma exacerbations as follows:<br><br>1. GINA 2018 guidelines recognise an elevated FENO (in adults with allergic asthma taking ICS) as a risk factor for exacerbations, even in patients with few asthma symptoms.<br><br>2. In a 3-year longitudinal study examining loss of lung function, a persistently high FeNO level of >40 ppb was independently associated with an accelerated decline in FEV1. (Matsunaga 2016).<br><br>3. An accelerated decline in FEV1 (>54.2 mL per year) was associated with nasal polyps, number of blood and sputum eosinophils, body mass index, and level of exhaled nitric oxide. Only body mass index and FeNO identified patients at highest risk using body mass index (BMI) ⩽23 kg·m−2 and cut-off values of FeNO ⩾57 ppb (Coumou 2018).<br><br>4. Syk et al (2013) compared a FeNO guided anti-inflammatory treatment algorithm to standard care in 187 non-smoking asthmatic patients. Using FeNO to guide anti-inflammatory treatment significantly reduced the exacerbation rate and improved asthma symptom control, without increasing overall inhaled corticosteroid use. There was significant change in the Asthma Control Questionaire (ACQ) in the FeNO guided treatment group (-0.17 [interquartile range {IQR}, -0.67 to 0.17] vs 0 [-0.33 to 0.50]; P = .045), which was clinically important in subpopulations with poor asthma control at baseline (P=0.03). Asthma exacerbation rates were reduced about 50% in the FeNO guided group (0.22 [CI, 0.14-0.34] vs 0.41 [CI, 0.29-0.58]; P = 0.024).<br><br>5. Zeiger 2011 et al (2011) showed that the addition of monitoring FeNO, a biomarker of airway inflammation, to usual clinical assessments during routine asthma visits such as asthma control patient questionnaires and spirometry, helps to identify patients at risk for future exacerbations. | The evidence summary in section 4.3.2 (now 4.4.2) concluded that the routine use of FeNO testing to monitor asthma cannot be recommended at the present time.<br><br>Tables 9a and 9b show that, at present, there is insufficient evidence to recommend using FENO to monitor airway inflammation at routine reviews.<br><br>The discussion in Petsky said: “While these new data are somewhat supportive of authors who previously advocated using FeNO levels to tailor medications,[40] we do not believe there is currently sufficient evidence to universally use FeNO to monitor airway inflammation recommended by others.[41]” | |

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| | | 6. The Seasonal Asthma Exacerbation Predictive Index (saEPI), which was developed based on data from 2 National Institute of Allergy and Infectious Diseases trials, identified 8 variables (including FeNO) as risk factors for asthma exacerbations. Exacerbations in children were associated with a higher saEPI along with higher markers of allergic inflammation, ICS treatment and a history of a recent exacerbation (Hoch 2017).<br><br>7. A 2016 Cochrane Systematic Review on "Exhaled Nitric Oxide Levels to Guide Treatment for Adults with Asthma" included 7 randomized controlled trials and 1,700 adult participants (Petsky 2016a). By monitoring FeNO, the number of exacerbations were reduced by 40% and the exacerbation rates by at least 41%. The number of people having one or more asthma exacerbations was significantly lower in the FeNO group compared to the control group (odds ratio (OR) 0.60, 95% confidence interval (CI) 0.43-0.84). Those in the FeNO group were also significantly more likely to have a lower exacerbation rate than the controls (rate ratio 0.59, 95% CI 0.45 – 0.77). The quality of the evidence to support the effect of monitoring FeNO on reducing asthma exacerbations was determined to be moderate, even though exacerbations were not defined using a common definition across all the studies included in the analysis. Although additional secondary endpoints examined in the meta-analysis (symptoms, ICS dosing and measures of asthma control such as spirometry) were not found to be statistically significant, the lack of consistency of reporting data across the 7 studies on secondary outcome measures affected the ability to accurately compare groups using meta-analysis methodology.<br><br>8. In a second 2016 Cochrane Systematic Review focusing on paediatrics, Petsky and colleagues (2016) evaluated the efficacy of tailoring asthma interventions based on monitoring FeNO, in comparison to management based on clinical symptoms (with or without spirometry/peak flow) or asthma guidelines (or both), for asthma-related outcomes. This meta-analysis included 9 randomized controlled trials and 1,426 children. Using traditional monitoring, 40 out of 100 children experienced at least one exacerbation over 48.5 weeks, compared to 28 out of 100 children where treatment was guided by FeNO (OR 0.58, 95% CI 0.45 to 0.75; 1279 participants; 8 studies; p< 0.0002). (Petsky 2016b) Of note, the number needed to treat to benefit (NNTB) over 52 weeks was clinically relevant and very low; 12 in the adult and 9 in the paediatric meta-analyses. | | |

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| | | 9. Wang et al (2017) concluded following the Petsky metanalyses that using asthma management algorithms that incorporate FeNO testing reduced the risk of exacerbations (strength of evidence: High), and possibly the risk of exacerbations requiring oral steroids (strength of evidence: Moderate).<br>10. Kimura et al (2018) conducted a 3 year multicenter observational cohort study in 127 patients to characterize the clinical and biomarker features associated with asthma exacerbations in severe asthma. Subjects were classified into 3 clinical groups: consistent non-exacerbators (CNE), consistent frequent exacerbators (CFE) and intermittent exacerbators (IE). FeNO concentrations were significantly higher in the CFE group than in the other 2 groups (P = 0.013), and a multivariate analysis showed that FeNO was an independent factor associated with CFE (P=0.013) irrespective of "past exacerbation status". Blood eosinophils showed a statistical trend in both analyses, suggesting that FeNO measurement may more accurately reflect airway inflammation predisposing to exacerbations. The effect of FeNO on exacerbator status remained significant over the follow up period (p=0.007).<br><br>11. Petsky et al (2018) conducted a systematic review that combined 3 Cochrane reviews with 22 included studies (16 included studies of FeNO-based management [seven in adults] and 6 of sputum based management [five in adults]) in 3500 adults and children. The review aimed to evaluate the evidence for tailoring asthma medication based on eosinophilic inflammatory markers (sputum analysis and FeNO) for improving asthma related outcomes in children and adults. In both adults and children, the number of participants with exacerbations (during the follow-up period 18–52 weeks) in the group whose treatment was adjusted according to FeNO were significantly lower than the control group; in adults, OR was 0.60 (95% CI 0.43 to 0.84, p=0.003; participants=1005; studies=5) and in children the OR was 0.58 (95% CI 0.45 to 0.76, p<0.0001; participants=2284; studies=8), translating to a number needed to treat (NNT) of 12 (95% CI 8 to 32) in adults and 9 (95% CI 6 to 15) in children. However, there were no significant group differences for either strategy in secondary endpoints including daily inhaled corticosteroids dose (at end of study), asthma control or lung function.<br><br>12. Elevated FeNO (> 50ppb) has been shown to be a significant independent risk factor for uncontrolled asthma (Malinovischi 2016). | | |

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| | | References:<br><br>1. *Global Initiative For Asthma (GINA). Global Strategy for Asthma Management and Prevention 2018 Update*<br>*2. Matsunaga K, Hirano T, Oka A et al. Persistently high exhaled nitric oxide and loss of lung function in controlled asthma. Allergology International 2016; 65:*<br>*3. Coumou H, Westerhof GA, de Nijs SB, et al. Predictors of accelerated decline in lung function in adult-onset asthma. Eur Respir J. 2018; 51: 1701785*<br>*4. Syk J, Malinovschi A, Johansson G, Undén AL, Andreasson A, Lekander M, Alving*<br>*K. Anti-inflammatory treatment of atopic asthma guided by exhaled nitric oxide: a*<br>*randomized, controlled trial. J Allergy Clin Immunol Pract. 2013 Nov-Dec;1(6):639-48.e1-8.*<br>*5. Zeiger RS, Schatz M, Zhang F, et al. Elevated exhaled nitric oxide is a clinical indicator of future uncontrolled asthma in asthmatic patients on inhaled corticosteroids. J Allergy Clin Immunol. 2011; 128 (2):412-414.*<br>*6. Hoch HE, Calatroni A, West JB, et al. Can we predict fall asthma exacerbations? Validation of the seasonal asthma exacerbation index. J Allergy Clin Immunol. 2017; 140(4):1130-1137.e1135.*<br>*7. Wang Z, Pianosi P, Keogh K, et al. The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management. Comparative Effectiveness Review No. 197 (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. 290-2015-00013-I).*<br>*8. Kimura H, Konno S, Makita H, Taniguchi N, Shimizu K, Suzuki M, et al. Prospective predictors of exacerbation status in severe asthma over a 3-year follow-up. Clin Exp Allergy 2018;21:21.*<br>*9. Petsky HL, Kew KM, Turner C, Chang AB. Exhaled nitric oxide levels to guide treatment for adults with asthma. Cochrane Database of Systematic Reviews. 2016a, Issue 9. Art. No.: CD011440.*<br>*10. Petsky HL, Kew KM, Chang AB. Exhaled nitric oxide levels to guide treatment for children with asthma. Cochrane Database of Systematic Reviews. 2016b, Issue 11. Art. No.: CD011439.*<br>*11. Petsky HL, Cates CJ, Kew KM, Chang AB. Tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils): a systematic review and meta-analysis. Thorax. 2018 Jun 1. pii: thoraxjnl-2018-211540. doi: 10.1136/thoraxjnl-2018-211540.*<br>*12. Malinovschi, A, Janson, C, Borres M. Simultaneously increased fraction* | | |

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| | | *of exhaled nitric oxide levels and blood eosinophil counts relate to increased asthma morbidity. J Allergy Clin Immunol. 2016 Nov; 138(5):1301-1308* | | |
| **4.2.1** | PCRS | We would expect high SABA use to be mentioned as a risk factor for future attacks under 'moderately increased risk' – in adults as well as children | The need to monitor SABA use is already in Table 9a (adults). For clarity, it has now been made a separate point. | |
| | SCRR | See above | See response to SCRR in 4.2. | |
| **4.2.2** | SCRR | Days off school should be mentioned here. | This is covered in Table 7 as a component of an asthma review. | |
| **4.2.4** | AZ | Currently severe asthma and difficult asthma appear to be used interchangeably.<br><br>Suggested change: Severe asthma, as a distinct subset of difficult asthma (see section 10.1), should be defined clearly in line with the ERS/ATS definition: "asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy". We also recommend that the NICE quality statement 5 regarding referral to specialist severe asthma centres should be included in this section. Please also state that at referral the phenotype should be identified or confirmed by the specialist. | Agree. The correct term here is 'severe asthma'; the existing definition is appropriate.<br><br>Additional sentence added to first paragraph to clarify that patients with severe asthma will usually be under the care of a specialist asthma clinic.<br><br>Difficult asthma is covered in Section 10. | |
| | SF | In severe asthma there is better evidence for the predictive benefit of FeNO, and the increased healthcare costs + disease burden in these patients should make it more easy to recommend (after all this should only be in specialist centres who are using it now anyway).<br><br>As well as the ref cited (134) see: -<br><br>*Zeiger RS, Schatz M, Zhang F, Crawford WW, Kaplan MS, Roth RM, et al. Elevated exhaled nitric oxide is a clinical indicator of future uncontrolled asthma in asthmatic patients on inhaled corticosteroids. J Allergy Clin Immunol. 2011;128(2):412-4.*<br><br>*Kupczyk M, ten Brinke A, Sterk PJ, Bel EH, Papi A, Chanez P, et al. Frequent exacerbators--a distinct phenotype of severe asthma. Clin Exp Allergy. 2014;44(2):212-21*. | Zeiger 2011 is a letter, rather than a full paper, and reports the predictive value of FeNO in 'allergist-diagnosed asthma' (described as 'persistent' rather than fitting our definition of 'severe asthma')<br><br>We did not identify Kupczyk amongst the six papers that looked at predictors of attacks specifically in patients with severe asthma. These papers looked at a number of predictors which we have reflected in the | |

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| | | For the same reason I would recommend qualifying the recommendation in 4.3.2. and making it specify “non-severe asthma” or “outside specialist asthma services” | bulleted list. For clarity, in section 4.2.4 (now 4.3.4) the statement about FeNO has been moved to the list of bullet points.<br><br>Agree. Wording of recommendation changed. | |
| **4.3.1** | PCRS | ARTP national register or certified practitioners could be mentioned here.<br><br>Pleased to see LLN mentioned for children but also relevant for teens and younger adults. Spirometry in children in terms of interpretation is an issue as the ECCS reference values are not representative of children or the population in general compared to GLI which hasn’t been adopted in the UK. Spirometry in children needs careful interpretation and certainly to be considered in line with the history. | The need for training in the use of spirometry is covered in section 3.2.2.<br><br>The statement about lower limit of normal applies to ages 5 and over, not just children. | |
| | SCRR | FEF25-75 is very volume dependent -hence need to know if pt has breathed out all the way to RV with a complete true FVC manoeuvre | Agree, but this is too much detail for an asthma guideline. Guidance on use of spirometry is available from the Association of Respiratory Technology and Physiology (ARTP). | |
| **4.3.2** | AUK | See comments from AUK under Section 3.2.4 | See response in Section 3.2.4 | |
| | BFS | The statement made here in this section:<br><br>‘The routine uses of FeNO testing to monitor asthma in adults or children is not recommended’.<br><br>This does not bear any alignment with the statement NICE have written in their 2017 Asthma: diagnosis, monitoring and chronic asthma management (NG80):<br><br>‘NICE is recommending objective testing with spirometry and FeNO for most people with suspected asthma. (pg. 27, putting this guideline into practice)’ As I have previously mentioned in section 3.4, having two conflicting guidelines (on what is already a difficult condition to diagnose) would cause | This section is about monitoring not diagnosis (covered in section 3) of asthma. The quote from NICE given here refers to diagnosis.<br><br>With regard to use of FeNO for monitoring asthma, SIGN and NICE are in agreement. | |

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| | | more confusion for patients. There really needs to be a clear cut pathway to aid diagnosis in asthma, not two guidelines with conflicting conclusions on FeNO. | | |
| | BH | I find measurement of FeNO useful, but understand why it is not recommended for routine use in all people with asthma. However, that negative recommendation does not tell the whole story. For example, you quote evidence that monitoring FeNO has value in those having frequent exacerbations and it would be appropriate to at least recommend that. | The recommendation in section 4.3.2 (now 4.4.2) has been amended to clarify that it relates to routine use of FeNO outwith specialist asthma clinics.<br><br>The use of FeNO for monitoring in specific sub-groups will be considered for inclusion in a future update. | |
| | JK | Whilst I appreciate the difficulties of writing a guideline for everyone from primary care to severe asthma centres, FeNO monitoring is something that is extremely useful for the difficult asthmatics (e.g. when trying to wean off high ICS or pred and for those in whom we are trying to phenotype). Even in those with less severe asthma (e.g. being followed up after a severe exacerbation) it is useful for guiding ICS dose. There are patients in whom symptoms don't particularly correlate with the amount of eosinophilic inflammation and what steroid treat is this inflammation, therefore I would argue FeNO is a very useful part of assessing and monitoring in asthma. | See response to BH, above. | |
| | PCRS | We agree with the conclusion here in respect of primary care. – but we are aware that some hospital units are using FeNO for asthma monitoring and developing the evidence base for the value of this in referral populations. Perhaps clarification about what you mean by ‘routine’ would help to manage people’s understanding that you acknowledge its value outside of routine monitoring in primary care. | See response to BH, above. | |
| | SCRR | Predictive value of raised FeNO only in ICS naive patients | The use of FeNO is described in section 3.2.4 and factors affecting FeNO levels are listed (including use of ICS). There is a cross reference to section 3.2.4 in section 4.3.2 (now 4.4.2). | |

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| **4.3.3** | SCRR | Not practical in most clinics | This existing text refers to the limited availability and technical demands of sputum eosinophil analysis and does not recommend its routine use. | |
| | SF | I'm surprised blood eosinophils have not been considered. Elevated levels are associated with poor asthma control, increased risk of exacerbations and hospital admissions, airflow obstruction and lung function decline, and again should be considered especially in severe asthma. See, e.g.:<br><br>*Price D, Wilson AM, Chisholm A, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. J Asthma Allergy. 2016; 9:1-12. 44.*<br><br>*Zeiger RS, Schatz M, Dalal AA, et al. Blood Eosinophil Count and Outcomes in Severe Uncontrolled Asthma: A Prospective Study. J Allergy Clin Immunol Pract. 2017; 5(1):144-153 e148. 45.*<br><br>*Price DB, Rigazio A, Campbell JD, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med. 2015; 3(11):849-858. 46.*<br><br>*Kerkhof M, Tran TN, van den Berge M, et al. Association between blood eosinophil count and risk of readmission for patients with asthma: Historical cohort study. PLoS One. 2018; 13(7):e0201143. 47*.<br><br>*Kerkhof M, Tran TN, Soriano JB, et al. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. Thorax. 2018; 73(2):116-124. 48.*<br><br>*Hancox RJ, Pavord ID, Sears MR. Associations between blood eosinophils and decline in lung function among adults with and without asthma. Eur Respir J. 2018; 51(4)* | Blood eosinophils are covered in Table 9a (equivocal evidence).<br><br>Agree, however, that they are not discussed in the text. Section 4.3.3 (now 4.4.3) has been amended to include blood eosinophils. | |
| | PCRS | We agree with the conclusion here | Thank you | |
| **4.4** | NPRANG | Monitoring of other atopic conditions should be included in each review eg rhinitis as poor control of these can impact on asthma control and symptoms. Optimising treatment of these could reduce need for escalating asthma medications. | Agree. Table 7 has been amended to include the need to consider multimorbidity and polypharmacy. | |

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| | SCRR | FOT - eg IOS or AOS needs to be mentioned here as an effort dependent way of measuring small airways dysfunction -eg R5-20 ,X5 or AX *(http://dx.doi.org/10.1016/j.anai.2017.04.009) (Lancet Respir Med 2014;2: 497–506) .Easier to perform that spirometry and more close related to control (http://dx.doi.org/10.1016/j.jaci.2015.12.1336)* especially in pts with preserved FEV1 (*Eur Respir J 2014; 44: 1353–1355)* | We found no evidence to support a role for FOT (forced oscillation technique) in routine monitoring of asthma. | |
| **Section 5** | | | | |
| **General** | ARNS | I have commented previously on these areas *(see comment under 5.2.3 below)* | See response under 5.2.3 below. | |
| | AUK | **Encouraging the use of digital technologies in asthma management**<br><br>In line with recent NHS England announcements on encouraging the use of digital technology in predictive prevention and patient self-management, we would like to see more emphasis in the BTS/SIGN guidance on the use of digital technologies to support self-management, including smart inhalers, which have proven potential in helping patients to better manage their asthma.[1, 2] Asthma UK would like to see a section included in the guideline that reviews the evidence for the use of smart inhalers in the management of asthma.<br><br>*Refs*<br>*[1] Asthma UK, Connected asthma: how technology will transform care, 2016*<br>*[2] Asthma UK, Smart asthma: real-world implementation of connected devices in the UK to reduce asthma attacks, 2017* | The use of smart inhalers was not covered by this update. | |
| | BTS | Could a definition of role management be added in brackets please? | No, as this is a direct quote. For details, refer to the cited reference. | |
| | WS | Use of epinephrine auto injectors for acute asthma? | There is currently no evidence to support this. | |
| **5.1** | BTS | PAAP:<br>Is it possible to include a glossary? | PAAP is defined in the text and in the list of abbreviations at the end of the guideline. | |
| **5.2** | ALUK | Recognition of allergic triggers and practicing avoidance measures where possible and where not, then reduction measures.<br><br>Pet allergen avoidance<br><br>Mould allergen reduction/ avoidance | This section was not covered by this update.<br><br>The need for education about trigger avoidance is already covered in the GPP in section | |

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| | | Occupational allergens such as latex | 5.2.2 and this has been enhanced to include occupational exposure. | |
| **5.2.2** | AM<br>PB | 1. Page 42 – Asthma Action Plans.<br><br>i) The example provided is not consistent with other parts of the guideline and potentially dangerous.<br><br>The PEF threshold suggested for patients starting oral steroids is 60% of best or predicted and for seeking urgent medical advice is 40% of best or predicted which is verging on life-threatening asthma.<br><br>The guideline elsewhere sensibly suggests that anyone with acute severe (or worse) asthma (i.e. PEF <50%) should be referred to hospital (section 9.2.5, page 91) and that all patients with an acute asthma attack (severity not defined, section 9.3.3, page 94) should receive oral steroids. In Leicester we believe that anyone whose PEF has fallen to less than 70% is likely heading for trouble, so this our AAP threshold for starting oral steroids, and we tell all patients to attend hospital if their PEF falls to 50% or less. The latter is consistent with the rest of your guideline. So please revise your example asthma action plan so that it is consistent with the rest of the guideline and safe.<br><br>ii) At PEF <80% you suggest increasing ICS but doubling ICS ineffective, and quadrupling ICS is also probably ineffective, but recommended as a treatment option in the last box on this page. You even suggest giving patients with a fixed dose combination an additional steroid inhaler, but this advice and the study by McKeever in the NEJM on which this recommendation is made are so flawed and not sensible.<br><br>Briefly the McKeever study was open label and likely due to unintentional bias. Furthermore, the intervention group had an action to follow before starting oral steroids, while the only option for the control group was to start oral steroids. It is well known (eg data from the FACET study) that many exacerbations resolve without oral steroids, so it is inevitable that the control arm would end up taking more ICS than the active arm. The NEJM editorial by Bardin states that caution and more data are required before following this approach, and we do not think this should be promoted as an option. | The self-management literature describes actions plans using a range of thresholds. The levels we used reflect typical thresholds. Note that at peak flows <60% patients are advised not only to start their oral steroids but also to seek medical advice. However, we agree that different thresholds risk causing confusion and have therefore adjusted the PEF threshold for seeking urgent medical advice to <50%.<br><br>The ‘Practical considerations’ boxes in the 2nd and 4th rows of Table 10 have been amended and cross-references added to relevant sections of the guideline. | |

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| | | In patients on combination inhalers, there is much stronger evidence that they benefit from an adjustable dosing or maintenance and reliever approach (MART) than the evidence provided in the McKeever study. This is likely due to the fact that about 50% of the exacerbation benefit is derived from prn formoterol as compared to a short-acting beta-agonist<br><br>*Tattersfield AE, Lancet. 2001;357:257- 61; Rabe KF, Lancet 2006; 368:744-75*<br><br>So in patients who are on fixed dose combinations who are still exacerbating, switching to an adjustable dose/MART combination would be more sensible that adding an additional ICS that is probably of no benefit. | Information on MART is given in section 7.3.5 and is also cross-referenced in Table 10.<br><br>This point is not about self management so is not relevant to this section. | |
| | PCRS | The addition of the quadrupling inhaled steroid option here is a welcome addition recognising the growing evidence that this intervention can be helpful – as it logically ought to be since beta agonist doses require substantial increase during exacerbations in order to be effective.<br><br>We believe however that this section of Table 10 is complicated and confusing.<br><br>“Adults may be advised to increase their inhaled corticosteroid dose fourfold (best achieved, in those using a combination inhaler, by adding a single ICS inhaler) at the onset of an attack.<br><br>Risk/benefit will need to be assessed in patients already taking high doses of ICS especially if they are stepping up multiple times a year.<br><br>It is unclear whether this step works in children.220,221 For those on MART regimes, see section 7.3.5. “<br><br>Instructions should be clearer and there should be a specified maximum dose (BDP equivalent, given the likelihood of a ceiling effect and the high potency of some inhaled steroids). It should be made clear that pMDI and spacer is the most effective method of administering high dose inhaled treatments during an asthma attack.<br><br>‘Personalised’ not adequately explored. Most of self-management section seems quite prescriptive. | Thank you.<br><br>Agree. Table 10 has been amended and cross-references have been added to the relevant sections of the guideline.<br><br>By definition, a PAAP is tailored to an individual patient. | |

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| | | While it is important that patients know how to recognise and address worsening symptoms, personalised self-management should involve the patient who may be concerned about their weight or may work night shifts and therefore the management of their asthma will be personalised to incorporate that. | | |
| | SCRR | Role here for AIR or MART in personalised action plans | This topic was not covered by this update. | |
| **5.2.3** | ARNS | Whilst in an ideal world people will read the whole of the guidelines, there is a concern that most will now just revert back to advising patients to quadruple ICS at the start of deteriorating symptoms without further follow up information on a PAAP. This is the only section in bold and so will draw the most attention. The other sections on those already adherent may also need to be written in bold to suggest the reader continues with all the relevant information. | The recommendation in section 5.2.3 has been amended to clarify that this advice forms part of a PAAP and should be used in that context. | |
| | AZ | New data on ICS/LABA as an as needed regimen should be included since it reflects an important change in treatment paradigm.<br><br>Suggested change: Two recently published studies [1, 2] describing data on the use of budesonide-formoterol as an as needed regimen have been missed. These two trials show that in patients with mild asthma, budesonide–formoterol used as needed was noninferior to twice daily budesonide with respect to the rate of severe asthma exacerbations during 52 weeks of treatment but was inferior in controlling symptoms. These effects seen with as needed budesonide–formoterol occurred at a median daily dose of inhaled glucocorticoid that was between 17 to 25% of that in the regular maintenance group. This could reduce the potential for glucocorticoid side effects and possibly improve the acceptability of the treatment regimen to glucocorticoid-averse patients, it may also have the potential to reduce costs[3]. The EMA license is expected to change for Symbicort to add this data in August 2019.<br><br>Therefore, these studies and the change in treatment paradigm are important inclusions in the BTS/SIGN guidelines 2019.<br><br>*1. O'Byrne PM, et al. n engl j med 2018 378;20 186576*<br>*2. Bateman ED, et al. n engl j med 2018 378;20 1877-87*<br>*3. Lazarus S. n engl j med 2018 378;20 1940-42* | This issue was not covered by this update and this is currently an unlicensed approach.<br><br>Papers by O'Byrne and Bateman were rejected as not relevant for the key question under consideration. | |

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| | BH | Personally I would re-word this recommendation: In Asthma Action Plans for adults, consider advising the quadrupling of ICS dosage at the onset of an asthma attack and for up to 14 days. | Agreed. Recommendation re-worded. | |
| | PCRS | 'Consider including quadrupling ICS at the onset of an asthma attack and for up to 14 days in action plans for adults in order to reduce the risk of needing oral steroids .'<br><br>See note above. One of our commentators felt that this wording was a little vague and non-committal for a guideline?<br><br>Another commented: 'this needs to be clearer as assumes a knowledge of MART which just isn't there in primary care from my experience and I have concerns about how practitioners decide on quadrupling ICS as very much subjective assessment of use and adherence. I think need to be specific re which LABA are suitable to increase as I still see Seretide doubled and quadruped in practice!'<br><br>Fourfold increase is likely to raise concerns amongst some clinicians, especially for generalists trying to identify who this may be appropriate for. Also, concerns over the practicality of adding an ICS for those on a fixed dose combination inhaler at the start of an attack. The patient would have the inconvenience of coming into the surgery at this point rather than 'selfmanaging'.<br><br>We wondered whether it might be helpful to add a table showing what dose of ICS is equivalent to oral prednisolone. This would help GPs/prescribers make decisions about what is a reasonable and safe course of action to take.<br><br>It would be useful to have a "good practice point" about what should be recommended in children in this circumstance.<br><br>In the section on acute asthma management in children it is stated that oral steroids should be used rather than high dose inhaled steroids . But given the frequency with which oral steroid courses are used in children with asthma exacerbations and given that 2,000mcg of beclometasone is a much lower steroid dose, the safety of using short term high dose inhaled steroids in the initial self management of an exacerbation could usefully be stated here. | See response to PCRS under section 5.2.2, above.<br><br>This topic was not covered by this update.<br><br>There is no evidence for this at present.<br><br>There is no pragmatic trial providing evidence for use of high-dose inhaled steroids in children. | |

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| **5.3.5** | SCRR | Increased prevalence of Arg-16 genotype in African pts -means possibility of worsening control with ICS/LABA and overreliance on SABA | Agree, but this was not covered by this update. It will be considered for inclusion in the next update. | |
| **5.4** | AZ | Currently it is stated that electronic monitoring of adherence is not normally available in routine practice.<br><br>Suggested changed: Revise guidance as there are a number of electronic monitoring tools either currently available or soon to be available including Turbo+ which has been approved as a medical device and will be included in the MHRA database in March 2019. | This topic was not covered by this update.<br><br>These tools are not currently available for routine clinical use. | |
| | SCRR | Role for AIR and/or MART in non-adherent pts means that in such pts use of controller and reliever are always concordant. | Agree. No action required. | |
| **5.4.3** | BTS | First para:<br><br>Is there any evidence for the hypothesis that patients are simply obeying the BTS guidelines i.e. tapering to the lowest dose required to control symptoms. | <br><br>No. No action required. | |
| | PCRS | The general discussion of problem of concordance and adherence in 5.4.1 and 5.4.2 is excellent 'Adherence to long term asthma treatment should be routinely and regularly addressed by all healthcare professionals within the context of a comprehensive programme of accessible proactive asthma care. '<br><br>There is an opportunity here to restate the need for additional training in respiratory care for health professionals conducting routine asthma reviews. There is considerable anecdotal evidence of health professionals in primary care having to conduct routine asthma reviews without sufficient training. (we note that this is stated in 5.3.1 )<br><br>The importance of sufficient time for HCPs to conduct asthma reviews, and the preferability of and patent preference for continuity of care should be mentioned here.<br><br>The UK operates with shorter primary care consultation times than any other country of comparable economic development. This is a huge barrier to the most effective care of chronic conditions of all kinds. | Thank you.<br><br>Disagree. This is covered appropriately in section 5.3.1.<br><br>Covered in section 5.3.1<br><br>Agree, but beyond the remit of the guideline. | |

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| | SCRR | Use of AIR and/or MART -see above | This topic was not covered by this update. | |
| **Section 6** | | | | |
| **6.1.1** | BH | Reference 282 is used to support 2 different points in adjacent paragraphs. I don't think it's the correct reference in the first paragraph (Cochrane review) | Agree. The reference in paragraph 2 has been corrected to:<br>*Maas et al Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma (Cochrane Database of Systematic Reviews: 2009 CD006480)* | |
| | BTS | For clarity, the sentence could be recast as follows:<br>A Cochrane review of trials comparing single (six studies) or multiple (three studies) interventions with a no intervention control, reported that in children at risk of developing childhood asthma, there may be a role of multifaceted interventions which involve both dietary allergen reduction and environmental change to reduce exposure to inhaled allergens. Such interventions reduced the odds of a doctor diagnosing asthma later in childhood by half (>5 years of age... etc.) | Agreed. Text reworded as suggested.<br><br>Note point above about incorrect reference for this paragraph. | |
| **6.1.10** | BTS | "antioxidant activity"<br>? ADD "rather than allergy" | Disagree. The text is correct as stated. | |
| **6.2.1** | Ai | Healthcare Improvement Scotland: This IMTO review 003/2015<br><br>Airsonett® is a temperature controlled laminar airflow device, with a base unit containing an air intake, filter and cooler, neck pipes and an air supply nozzle. The base unit is positioned next to the patient's bed with the air supply nozzle above their head principally designed to be used when the patient sleeps. The device draws air from the room through a filter that captures allergens and other particles.<br><br>This filtered air is then cooled to 0.5–10oC below the ambient room temperature, before being slowly expelled from the air supply nozzle. This cooler air is denser than the ambient room air and so it descends into the patient's breathing zone. The device provides cooled, filtered air to the patient's face through their sleep, breaking the natural body convection without creating draught or dehydration. In doing so, this gives both the | No response required. | |

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| | | lungs and immune system a rest from allergic stimulation all night, thereby allowing the body to react normally to allergens during the following day. The manufacturer describes this as the key feature that differentiates Airsonett® device from other devices designed to supply filtered air to the breathing zone. | | |
| | BSACI | The response below is based on comments by Professor Angela Simpson, reviewed by and concurred with by Professor Adnan Custovic and reflect the view of the BSACI and are submitted as such:<br><br>We have concerns about the evidence on which the recommendation that house dust mite avoidance measures should not be routinely recommended. The authors rely solely on systematic reviews, concurring with the view that all systematic reviews are good. The authors cite the Cochrane review from 2008 which has multiple flaws as summarised by *Platts-Mills in a review (Platts-Mills J Allergy Clin Immunol. 122(4) 694-696)*.<br><br>The Lead Cochrane author (Gotzsche, since removed from the organisation) was a proponent of the view that 'content' experts are not required on systematic review teams. Consequently there were methodological issues not identified by the non-expert including:<br><br>1) Data from studies of adults and children were combined (this approach of combining data form adults and children is not used in any other section of the draft asthma guidelines).<br><br>2) Studies included are very old (1980s) and included methods which had not been shown to reduce exposure to house dust mite<br><br>3) Some old studies were excluded because of the way the methods were reported – satisfactory in their time, but not rigorous in the way that modern RCTs are<br><br>4) Blinding is difficult/not attempted interventions are not easy to maintain without extensive education<br><br>5) Many studies were too short to have a realistic chance of showing a clinical effect ( based on data from studies of allergen avoidance at altitude)<br><br>6) Studies of multifaceted avoidance were excluded | We acknowledge that there are challenges with undertaking systematic reviews in this area. We are therefore removing the much criticised Gotzsche meta-analysis from the guideline. The more recent Leas meta-analysis is methodologically better and includes the more recent, better designed studies. In the text we now acknowledge that it is difficult to synthesis the studies in this area due to the heterogeneity of interventions (and their combinations).<br><br>Furthermore, in research recommendations we suggest that a further systematic review is required with a methodology that avoids the issues raised. This is likely to highlight the need for further primary research focused on the combinations of interventions that are mostly likely to be effective. | |

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| | | 7) Re-analysis of data from 1 study was undertaken ( splitting control groups) which rendered a previously positive study in children, negative<br><br>8) Many studies reported multiple clinical outcomes separately. Importantly many studies recorded allowed changes in medication (at the discretion of the usual physician) but used measure of lung function such as bronchial hyperresponiveness as an outcome. It is unlikely that you will see an improvement in bronchial hyperresposiveness as a consequence of an environmental intervention, if you allow reduction in inhaled corticosteroid dose at the same time.<br><br>The authors also use the meta-analysis of Leas et al published in 2018, covering mite and other allergens which has similar methodological problems, in addition to combining studies of adults and children<br><br>For example: when summarising evidence for Impermeable mattress covers compared with placebo covers or no intervention as a single measure and exacerbations, 3 studies are quoted. (1 paediatric on which Professor Simpson is senior author, and 2 adult studies).<br><br>*Luczynska et al* data is included in the exacerbation category, despite the fact that this outcome is not listed in the methods, does not form part of the power calculation and is not fully reported in the results ("There was also no change in the number of reported asthma attacks or use of medication (data not shown)". In the study by *Woodcock et al,* exacerbation was a secondary outcome not included in the power calculation and this was in fact a rare event. That is there has been no attempt to comment on this or adjust the analysis for underpowered secondary outcomes is problematic.<br><br>The BSACI thinks that on balance section 6.2.1 and section 6.2.2 would benefit from revision which acknowledges the limitations of the systematic reviews conducted and also acknowledges that it is impossible to blind a study of pet removal, and to acknowledge that data for adults and children should be assessed separately. | | |
| | BTS | 82 studies: This must be a typographical error - it was a systematic review of 72 studies (64 RCTs and 8 non-RCTs). | Corrected. | |

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| | CS | The UK has the highest rate of asthma in the world (1). Dust mites are the number 1 allergic asthma trigger in the world. The UK is not in a position to vary from other countries in relation to dust mite avoidance advice. The Committee should consider carefully whether the use of this evidence is still appropriate given that it has not been used by other countries and does not stand up to today's standards.<br><br>The link below explains why the evidence was not taken up by the US where dust mite avoidance is routinely recommended in relation to asthma control along with prescribed medication.<br>*https://www.jacionline.org/article/S0091-6749(08)01494-2/fulltext*<br>*https://royalsociety.org/people/thomas-platts-mills-12102/*<br><br>"The recent meta-analysis on dust mite avoidance appears to be seriously flawed because of the decisions about inclusion and exclusion as well as the way in which studies were evaluated"<br><br>Also there is new evidence which supports the use of anti-dust mite bedding and it would be useful to understand why has not been acknowledged or taken into consideration.<br><br>"The use of mite impermeable bedding in mite sensitised asthmatic children can significantly reduce the risk of severe exacerbations resulting in emergency hospital attendance."<br><br>The results obtained in this more recent evidence are consistent with what a dust mite allergy sufferer would expect, since multi-factor avoidance (not limited to bedding) is necessary to achieve minimisation of asthma for a dust-mite allergy subject.<br><br>*http://www.atsjournals.org/doi/abs/10.1164/rccm.201609-1966OC*<br><br>The inclusion of the statement in para B increases the risk of uncontrolled asthma and therefore also anaphylaxis in children who are multi-allergen allergic, as well as non-asthma dust mite related illnesses, which are considerable.<br><br>Consultant allergists and paediatricians routinely recommend methods of dust mite avoidance despite the guidelines as they and their patients have become aware of their effectiveness. | We have removed the Gotzsche meta-analysis from the guideline for the reasons highlighted above (see response above to BSACI comments).<br><br>The Murray study was included in the cited Leas meta-analysis. Our guideline methodology is to consider the totality of the evidence not individual studies. | |

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| | | The guidance should be changed to make recommendations to encourage the avoidance of dust mites by physical methods including the use of anti-dust mite bedding.<br><br>*(1)Mukherjee, M, Stoddart, A, Gupta, R, Nwaru, B, Farr, A, Heaven, M, Fitzsimmons, D, Bandyopadhyay, A, Aftab, C, Simpson, C, Lyons, RA, Fischbacher, CM, Dibben, C, Shields, M, Phillips, C, Strachan, DP, Davies, G, McKinstry, B & Sheikh, A. (2016).*<br><br>'The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases'<br><br>*BMC Medicine, vol 14, no. 113. DOI: 10.1186/s12916-016-0657-8* | | |
| | NPRANG | While the 2008 Cochrane review has been used to inform this section, it does not differentiate between adults and children, which is a weakness of the review. A 2017 study (below) demonstrated a significant reduction in exacerbations of asthma and emergency attendances in children who were randomised to the active group, using mite-impenetrable covers.<br><br>*Murray et al 2017 Preventing Severe Asthma Exacerbations in Children. A Randomized Trial of Mite- Impermeable Bedcovers American Journal of Respiratory and Critical Care Medicine*<br>https://doi.org/10.1164/rccm.201609-1966OC<br><br>I would consider rewording the recommendation and instead of reading 'should not be routinely recommended' to something a little more balanced. Such as 'Healthcare professionals may like to discuss avoidance measures with patients and families, however, the cost of purchasing such measures, such as bedding encasements should not be understated'. | We have removed the Gotzsche meta-analysis from the guideline for the reasons highlighted above (see response to BSACI comments).. This study is included in the new Leas 2018 systematic review discussed in the guideline.<br><br>The guideline says that house dust mite reduction measures "should not be routinely recommended". This means, therefore, that healthcare professionals can recommend this approach to patients where HDM reduction measures are practical and they are likely to be beneficial to the patient. | |
| | PCRS | Whilst the conclusions regarding house dust mite eradication techniques in asthma are agreed, there is evidence that such measures can help patients with perennial rhinitis *(Sheikh A et al Cochrane Review 2010).* Therefore the recommendation should specify that elimination procedures are not recommended for management of asthma (rather than a blanket "are not recommended") | Agree. Recommendation changed to clarify that it relates to asthma. | |

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| | SHTG | The National Institute for Health and Care Excellence (NICE) published a Medtech Innovation Briefing for Airsonett in August 2014 (https://www.nice.org.uk/advice/mib8)<br><br>SHTG published Innovative Medical Technology Overview: 003/2015 for Airsonett on 23 June 2015. Airsonett® is a class I, noninvasive, temperature controlled laminar airflow device indicated as an add-on therapy for children and adults with severe persistent allergic asthma whose disease despite pharmacotherapy remains poorly controlled (corresponding to Step 4 or above of the British Thoracic Society/Scottish Intercollegiate Guidelines Network stepwise treatment approach).<br><br>The manufacturer presented a phase III multi- centre double blind placebo randomised controlled study, where 312 patients with inadequately controlled persistent atopic asthma were randomised to receive add-on treatment with Airsonett® or placebo. Patients were aged between 7 and 70 years. The results demonstrate that patients who had treatment with Airsonett® had a statistically significant improvement in quality of life after one year.<br><br>The manufacturer also presented a one year observational study conducted in Germany. Data from 30 patients' medical records aged 8 to 70 years of age were examined comparing exacerbations and asthma control the year before and after treatment with Airsonett®. Patients in the study were children and adults with severe poorly controlled perennial atopic asthma. The results suggest that Airsonett® is associated with a reduction in severe exacerbations, accident and emergency (A&E) attendances, unplanned clinic visits and hospitalisations. Asthma control was also significantly improved. The manufacturer presented a costutility analysis over a one year time horizon. Airsonett® was compared to standard care in patients with severe poorly controlled perennial atopic asthma. The clinical data used to populate the model was taken from the German observational study. Airsonett® was found to be cost effective with an estimated incremental cost effectiveness ratio (ICER) of £8,998 per quality adjusted life year (QALY) based on an incremental cost of £553 and a QALY gain of 0.0615.<br><br>At its most severe, patients with persistent allergic asthma may be treated with omalizumab. For this reason, the NICE Medtech Innovation Briefing includes a costing statement comparing Airsonett® to omalizumab. Based | In the view of the GDG, there is currently no published evidence to support its use. | |

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| | | on an annual cost of Airsonett® of £2,088 per patient, the NICE costing statement reports that Airsonett® may lead to cost savings of £6,312 per year per patient based on the average dose used in trials and the list price of omalizumab.<br><br>While the Cochrane review cited in section 6.2.1 contains interventions such as ventilation, air filtration and ionisers, the Airsonett technology provides cooled, filtered air to the patient's face through their sleep, breaking the natural body convection without creating draught or dehydration. In doing so, this gives both the lungs and immune system a rest from allergic stimulation all night, thereby allowing the body to react normally to allergens during the following day. The manufacturer describes this as the key feature that differentiates Airsonett® device from other devices designed to supply filtered air to the breathing zone and supported the development of the SHTG Innovative Medical Technology Overview advice.<br><br>Advice may be downloaded from http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/topics_assessed/imto_003-2015.aspx | | |
| **6.2.2** | BSACI | The concerns about methodology of the systematic reviews as detailed above apply to this section too.<br><br>With regard to pets, Leas 2018 et al seem surprised that studies of pet removal are non-randomised and unblended. Shirai et al report 5.9-fold increase in the provocative concentration of methacholine causing a 20% fall in FEV1 was observed in the pet removal group compared with a 2.3-fold increase in the group keeping pets (p [1] 0.04), but Leas et al report this as inconclusive and the draft asthma guidelines do not reference this work, but cite other work which seems less relevant..<br><br>The BSACI thinks that on balance section 6.2.1 and section 6.2.2 would benefit from revision which acknowledges the limitations of the systematic reviews conducted and also acknowledges that it is impossible to blind a study of pet removal, and to acknowledge that data for adults and children should be assessed separately | There is a paucity of evidence around removing pets to improve asthma. Only one small (n=20), non-randomised study was identified in the Leas systematic review. Bronchial hyperresponsiveness was not an endpoint in this systematic review. There are only 2 multicomponent studies that included pet removal. So there are insufficient data to make conclusions in this area. | |
| **6.2.3** | BTS | First rec:<br>Suggest "People with asthma, THEIR PARTNERS and parents of children with asthma" | Disagree. The existing recommendation reflects the stated evidence. | |

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| | PCRS | It might be worth stating here that VBA (very brief advice) to stop smoking from healthcare professionals in primary care and pharmacotherapy-supported counselling to treat tobacco dependency is a highly cost effective health care intervention relevant to patients with asthma, especially since the local authority funding for smoking cessation services has been reduced in many areas.<br><br>There are several useful documents you could signpost to here:<br>Primary care respiratory society Pragmatic guide to Diagnosis and Management of Tobacco Dependency 2018<br>*https://www.pcrs-.org/sites/pcrsuk org/files/TD%20Pragmatic%20guide_Draft%20for%20Conference_WithAck now.pdf*<br>Royal College of Physicians Hiding in Plain Sight – Treating Tobacco dependency in the NHS 2018<br>*https://www.rcplondon.ac.uk/projects/outputs/hiding-plain-sight-treating-tobacco-dependency-nhs*<br>NHS England NHS Long term plan for England 2019 Smoking chapter<br>*https://www.longtermplan.nhs.uk/online-version/chapter-2-more-nhs-action-on-prevention-and-healthinequalities/smoking/* | This is beyond the scope of the guideline.<br><br>The recommendation in section 6.2.3 covers the need to offer appropriate support to stop smoking. | |
| **6.2.8** | PCRS | Leave this out if there is no evidence and you are not recommending it? | It was felt important to include a section on vitamin D and asthma as this is topical and evidence is available. The text has been shortened. | |
| | SCRR | Measuring Ca D3 and PTH should be part of work up in any uncontrolled pt | The evidence for this is inconclusive and it cannot therefore be recommended. Anyone found to be deficient would be treated in accordance with relevant national guidelines. | |
| **6.2.9** | BTS | First para:<br>Can one make this assertion with respect to asthma when there is good evidence for the benefit of weight loss in several other health domains? I would make this explicit and advocate a policy of encouraging weight loss on this basis.<br><br>Check Ciclesonide doses (usually one puff daily @160 mcg) | Yes, because the guideline is about asthma.<br><br>Unclear what this comment relates to. | |

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| | PCRS | Weight loss interventions (including dietary and exercise-based programmes) B CAN BE considered for overweight and obese adults and children with asthma 'Can be' ought to be changed to 'should be' | Agreed. Wording changed. | |
| **Section 7** | | | | |
| **General** | ARNS | Tables 11 and 12 are useful to generalists in practice to understand the doses of ICS they may be prescribing. To my understanding the paediatric table (figure 3) is up to 12 years old. If so then are you classing Tiotropium now licensed from 6yrs and upwards as a high dose therapy and only for specialist initiation, as if not then it should be in the additional add on therapies box. | Table 12 and Figure 3 do not specify an overall age range because different treatments are approved for children of different ages. When prescribing, the summary of product characteristics should be checked to ascertain the age range for which the product is suitable.<br><br>Tiotropium is not mentioned in Table 12 but is covered in section 7.4.3 (now 7.5.1). However, the use of tiotropium in children was not covered by the current update. | |
| | AZ | AstraZeneca would like to thank you for the opportunity to comment. We would like to highlight 5 key changes that we believe will ensure the guideline is up to date and provides guidance for best-practice patient care for asthma patients of all severities:<br><br>1. "Severe asthma" needs to be defined clearly in line with the ATS/ERS guidelines.<br><br>2. The recommendation that "patients needing frequent or continuous use of oral corticosteroids should be referred to a specialist clinician" should be included in the main body text.<br><br>It is encouraging to note that the draft guidelines recommend that patients requiring frequent or continuous use of oral corticosteroids should be referred to a specialist clinician, unfortunately this is only mentioned in figures 2 & 3 and not in the text of section 7.6; it is suggested that this wording is also included in the main body of text to ensure clarity. | Agree. See response to AZ comments in sections 4.2.4 and 10.<br>Agree. Statement added to section 7.6 (now 7.5.3).<br><br>Figures 2 and 3 have been amended and the column relating to frequent or continuous use of oral steroids has been removed. | |

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| | | 3. SABA over-reliance is mentioned, but the threshold should change to ensure that patients prescribed 2 or more SABA inhalers per year are reviewed in line with a maximum of 3 SABA uses per week for a controlled patient.<br><br>4. New data on ICS/LABA as an as needed regimen should be included since it reflects an important change in treatment paradigm<br><br>5. Guidance on the use of anti-IL5s needs to be aligned to NICE guidance (and forthcoming SMC guidance) *(for detailed comments see 7.7.2).* | See response to AZ comments in sections 7.1.1 and 9.1.2.<br><br>See response to AZ comments in section 5.2.3.<br><br>See response to AZ comments in section 7.7.2 (now 7.5.4) | |
| | CH | In the 'High dose therapies' section we think there should be the same direction provided to the clinician as is provided in the previous steps (i.e: 'Regular preventer, Initial add-on & Additional add-on therapy sections). While the line ' Refer patients for specialist care' has been moved up and made more prominent, the practical reality is that a number of general clinicians will manage patients who require 'High dose therapies' in Respiratory and subsequently guidance should be provided for them as to what medication classes to consider as per the earlier steps in order to ensure patients receive the optimal treatment at this step.<br><br>The comments made above should also apply to this Figure. We would suggest that guidance and direction is added to the 'High dose therapies' in this section as well in the interests of safety and providing patients with the optimal treatment. | Additional text has been added to section 7.5 to highlight the need for these patients to be under specialist care and the 'Frequent or continuous use of oral steroids' column has been removed from Figures 2 & 3.<br><br>The previous Section 7.6 (Continuous or frequent use of oral steroids) has been moved to become section 7.5.3 under the re-named section 7.5 'Specialist therapies'. This change reflects the fact that alternatives to oral steroids may now be more appropriate for these patients. | |
| | GSK | Table 11: Adult doses of inhaled corticosteroids:<br>GSK believes that Relvar Ellipta (fluticasone furoate/vilanterol; FF/VI) 92/22 mcg should be specified across the whole of the low dose and medium dose columns within the BTS/SIGN inhaled corticosteroids table (Table 11) to bring this is in line with the latest clinical trial safety data, marketing authorisation and its specification within international guidelines.<br><br>GSK believes that in line with the positioning of the inhaled corticosteroid/long acting beta2 agonist (ICS/LABA) class it would now be appropriate to position FF/VI 92/22 mcg, as suitable treatment for all low | Table 11 is based primarily on efficacy rather than safety and as stated here, efficacy is | |

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| | | and medium dose eligible patients.<br><br>In terms of efficacy and safety the benefit : risk profile of FF/VI 92/22 mcg as both a low and mid-dose ICS/LABA is favourable. In particular, lung function efficacy is similar to a medium dose ICS/LABA, whilst the impact on the hypothalamic pituitary axis (HPA) is more consistent with a low dose ICS/LABA<br><br>*(Allen et al. 2013; Busse et al. 2013; Woodcock et al. 2013; Busse et al. 2016).*<br><br>Please find below the key points as to why it is appropriate to classify FF/VI 92/22 mcg as both a low and a medium dose ICS/LABA:<br><br>FF/VI 92/22 mcg safety data that supports low dose ICS/LABA positioning<br><br>FF/VI is indicated for patients who are uncontrolled on ICS alone<br><br>GINA asthma guideline recommends FF 92 mcg to be used as a low dose ICS<br><br>Evidence that supports the use of FF/VI 92/22 mcg as a low-to-mid dose ICS/LABA in the context of<br>efficacy<br><br>Point 1<br>FF/VI 92/22 mcg safety data that supports low dose ICS/LABA positioning.<br><br>In 2016, during the development of the previous guidelines BTS/SIGN responded to GSK's query regarding the positioning of FF/VI 92/22 mcg across the low and medium dose in the adult ICS table.<br><br>BTS/SIGN stated that FF/VI only partially covered the low-dose section due to a lack of available safety data and that FF/VI had the Black Triangle symbol in place.<br><br>FF/VI's safety profile has been assessed and has led to the removal of the Black Triangle (June 2018) through agreement with regulatory bodies who have appraised the entirety of the safety data. Since marketing authorisation there has been a total of 2,083,923 patient-years of exposure | equivalent to a medium dose, so in the view of the GDG the positioning in Table 11 is correct as it reflects this but takes into account that safety is consistent with a low dose.<br><br>The Busse 2016 paper, the only one of the references suggested here that was published since the last update of the guideline was published, concentrates mainly on the safety of Relvar, rather than the equivalence of FF/VI with any other ICC. It is clear from the paper that FF/VI is safe but it is difficult to make any comment about equivalence.<br><br>*T* | |

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| | | (GSK DoF RF/FFT/0101/17).<br><br>In addition, the European Medicines Agency (EMA) has granted a license extension with broadened indication, which GSK believes further supports the confidence in this medicine.<br><br>The benefit/risk of FF/VI has now been evaluated in a robust 52-week RCT that included patients representative of those seen in everyday clinical practice (n=4,233). Eligible patients were on either ICS or ICS/LABA maintenance treatment prior to randomisation. Initiation of FF/VI was shown to be superior to continuing on usual care on asthma control, as measured by the Asthma Control Test at Week 24 (ACT; OR 2.00, 95% CI 1.70, 2.34; p<0.001). The safety profiles were comparable between the treatment arms (SAE incidence 13% for FF/VI and usual care). This supports FF/VI's balanced efficacy : safety profile in a real-world setting.<br><br>In clinical trials, FF 92 mcg has not demonstrated any clinically significant cortisol suppression.<br><br>*(Busse et al. 2012; Bleecker et al. 2012, Bateman et al. 2012, Allen et al. 2013; Busse et al. 2013, Busse et al. 2016)*<br><br>The effect of the marketed doses of FF/VI on the HPA axis has been assessed in multiple studies evaluating 24-hour serum and urinary cortisol levels. In a 6-week study that compared once-daily FF/VI 92/22 mcg or 184/22 mcg, placebo or an active control group, no effect of FF/VI at both marketed doses on serum cortisol levels were observed (n=185 - see Graph 1 in e-mail) (Allen et al 2013).<br><br>This effect was also observed in the dose ranging studies which demonstrated no significant impact on urinary cortisol levels at the marketed doses of FF (100 mcg/200 mcg)<br><br>*(Bateman et al. 2012, Bleecker et al. 2012 and Busse et al. 2012)*.<br><br>In fact, cortisol suppression was only observed at FF doses of ≥800 mcg in a dose ranging study by *Busse et al. 2012* (see Graph 2 in email).<br><br>A single study showed cortisol suppression for FF/VI 92/22 mcg but not FF 92 mcg vs placebo. This was not considered to be a clinically relevant | | |

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| | | safety signal, as this effect was not observed in the FF monotherapy arm and the adverse event safety profile was comparable between the arms in the study.<br><br>*(Bleecker et al. 2014)*<br><br>This finding is further supported by modelling data to identify the dose of FF at which 20% serum cortisol suppression was evident, which is below the level of suppression associated with systemic adverse effects. In this model, FF was estimated to result in 20% cortisol suppression at a daily dose of 580 mcg which is approximately 6 times higher than the low-to-medium licensed dose of FF/VI of 92/22 mcg per day (*Daley-Yates 2015* - see Graph 3 in e-mail).<br><br>Point 2<br>FF/VI is indicated for patients who are uncontrolled on ICS alone (Relvar Ellipta SPC 92/22 mcg; Relvar, Ellipta SPC 184/22 mcg; GINA 2018).<br><br>The clinical trial data for FF/VI has been assessed and approved by the European Medicines Agency (EMA) and is indicated for the regular treatment of asthma in patients ≥12 years where a combination product (ICS/LABA) is appropriate: patients not adequately controlled with ICS and 'as needed' inhaled short acting beta2-agonists (SABA); patients already adequately controlled on both ICS and LABA.<br><br>Section 4.2 of the SmPC states: "A starting dose of Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting beta2-agonist."<br><br>Point 3<br>The ‘Global Strategy for Asthma Management and Prevention’ (GINA) asthma guideline recommend FF 92 mcg to be used as a low dose ICS GINA (Global Initiative for Asthma) specify FF 92 mcg as a low dose ICS (FF 184 mcg as a high dose ICS) for the treatment of adults & adolescents (12 years & older) in the ‘Global Strategy for Asthma Management and Prevention’ (Box 36, P44).<br><br>Point 4<br>Evidence that supports the use of FF/VI 92/22 mcg as a low-to-mid dose | | |

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| | | ICS/LABA in the context of Efficacy.<br><br>The benefit : risk profile of FF/VI 92/22 mcg as low and mid-dose ICS/LABA is favourable in terms of efficacy as well as safety FF/VI 92/22 mcg has been shown to be efficacious as both a low and a medium dose ICS/LABA. FF/VI 92/22 mcg is efficacious in patients who are not well controlled on low-to-moderate dose ICS monotherapy<br><br>*(Busse et al. 2012, Bleecker et al. 2012, Bateman et al. 2012, Bleecker et al. 2014, Bateman et al. 2014)*<br><br>The licenses for FF/VI are based on a programme of Phase II and III studies which established its efficacy and safety profile. These lower dose studies evaluated the efficacy and safety of FF/VI 92/22 mcg in patients who were not well controlled on low-to-moderate dose ICS [200-500 mcg/day fluticasone propionate (FP) or equivalent].<br><br>These studies demonstrated that in patients not well controlled on 200-500 mcg/day FP or equivalent, FF/VI 92/22 mcg provided improvements in lung function and symptomatic measures and reduced the frequency of exacerbations.<br><br>FF/VI 92/22 mcg demonstrated similar efficacy to FP/SAL 250/50 mcg – a medium dose ICS/LABA.<br><br>*(Woodcock et al. 2013)*<br><br>A 24-week Phase III study (n=806) comparing the efficacy of FF/VI 92/22 mcg OD with FP/SAL 250/50 mcg BD over 24 weeks showed that FF/VI was similar to FP/SAL with regards to improving lung function in patients with persistent asthma (341mL and 377mL, respectively - the primary superiority endpoint was not met (treatment difference 37mL; 95% CI -88, 15; p=0.162).<br><br>The above evidence demonstrates that FF/VI 92/22 mcg has a Benefit : Risk profile that supports its use as a low to mid dose ICS/LABA.<br><br>Indeed, FF has not demonstrated clinically significant cortisol suppression at the dose contained within low-to-mid-dose FF/VI 92/22 mcg. | | |

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| | | *(Allen et al. 2013; Busse et al. 2013; Busse et al. 2016).*<br><br>GSK believes that FF/VI 92/22 mcg should be specified across the entirety of the low and medium dose columns within the BTS/SIGN inhaled corticosteroids table (Table 11), as reflected in its license and the evidence base for FF/VI (BTS/SIGN 2016; Relvar Ellipta EPAR 2013).<br><br>SK is aware of the sphere of influence that the BTS/SIGN asthma guideline has and that the inhaled dose columns within the BTS/SIGN inhaled corticosteroids table (Table 11), as reflected in its license and the evidence base for FF/VI (BTS/SIGN 2016; Relvar Ellipta EPAR 2013).<br><br>GSK is aware of the sphere of influence that the BTS/SIGN asthma guideline has and that the inhaled corticosteroids table is widely regarded as a reference point for prescribing. In the interest of health care professionals' clarity and practical application, we are committed to ensuring that this medicine is prescribed correctly. | | |
| | PCRS | FIGURE 2:<br><br>Given the major discrepancy between BTS/SIGN and NICE on first choice add-on treatment after ICS, some comment on the analysis leading to the continued BTS/SIGN LABA recommendation would be worthwhile.<br><br>There is evidence that LTRAs are valuable as first choice add-on option in atopic patients with other atopic conditions.<br><br>It is only in Figs 2 and 3 that the change in advice to refer patients for high dose therapies and frequent or continuous use of OCS is made clear. Should this not also be explained in the text at 7.5 and 7.6?<br><br>Has the potential impact on secondary care/ community based specialist capacity and waiting lists been modelled? It is important that referral is to someone with respiratory expertise, but we have concerns over the increase in referrals and the impact on patients.<br><br>Is it worth a reminder that referral to a specialist does not necessarily mean a referral to secondary care, but could include specialists outside that setting? Indeed integrated respiratory teams are using interventions such as virtual clinics to deliver specialist review. | The evidence was reviewed and it is considered that LABAs are the more effective treatment.<br><br>The advice was based on current evidence.<br><br>Agree. New text added to make the need for specialist referral clear.<br><br>No, the potential impact of this has not been modelled.<br><br>Agree. The term 'secondary care' has been replaced by 'specialist care' where appropriate throughout the | |

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| | | FIGURE 3:<br><br>Again, the recommendation of referring to specialist care before high dose therapy- this could lead to an increase in referrals to secondary care which already has a long waiting time. Although, it is essential that high dose therapy is not started lightly.<br><br>Consider providing a cut-off point above which referral for specialist opinion should be made | guideline.<br><br>Agree, but evidence does not support provision of a specific cut-off point. The term 'secondary care' has been replaced with 'specialist care', where appropriate in the guideline, as specialist care may be provided in a primary care setting, eg by a specialist GP or asthma nurse, or in hospital, eg by a respiratory specialist, or in a specialist asthma centre by a team of healthcare professionals. | |
| | SF | Figure 2: It is not clear why medium dose ICS is preferred over a trial of LTRA+low dose ICS, after (or in addition to) LABA trial. Cochrane-level evidence shows they are equivalent, so why isn't an alternative anti-inflammatory preferred over med dose ICS, or at least given the same recommendation? The consequence is that we reduce the chances of finding LTRA-responders, as they will only be tried on top of LABA + med dose ICS, where they are much less likely to be effective. The other problem that this leads to is that step 3 ("additional add-on therapies") becomes very crowded and confusing. I would solve this by rewriting:<br><br>Step I (regular preventer) unchanged<br><br>Step II (initial add-on therapy):<br>i. Add inhaled LABA to low-dose ICS<br>ii. If no response to LABA: stop LABA and try LTRA<br>iii. If partial response to LABA: continue, and try LTRA<br>(NB Step II now comes very close to NICE (but prioritises LABA over LTRA) – and so might be a compromise that they can agree on) | Figure 2 has been amended and simplified to reflect the fact that addition of LTRA or an increase in ICS can be considered as 'Additional controller therapies' in patients inadequately controlled on low-dose ICS+LABA (see renamed 'column and section 7.4)<br>The appropriate treatment approach for LABA non-responders was not covered by this update but will be considered for the next update. | |

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| | | Step III (medium dose ICS + add-on therapy):<br>i. Continue LABA +/- LTRA if partial benefit, and increase ICS to medium dose<br>ii. If control still inadequate, consider sequential trial of LAMA, then SR theophylline<br><br>Step IV + V – I agree that patients should be referred on at this stage, but at least they will have had trials of all treatments short of high dose steroids by then. These steps (IV + V) should actually be merged to make this point clearer. Also, PLEASE remove b-agonist tablets from the guidance completely.<br><br>In my opinion it is MUCH more helpful to be able to refer to "steps". If necessary, "prn SABA only" could easily be referred to step 0. Steps II and III could also be divided into A and B (IIA – trial of LABA; IIB – trial of LTRA; IIIA – med dose ICS; IIIB – trial of further add-ons) | Agree. The final column has been removed from Fig 2 & 3. B-agonist tablets have been removed from the text<br><br>Disagree. This change was made in 2016 | |
| | TeUK | Relvar 92/22 mcg is listed across low dose inhaled corticosteroids - this is inappropriate and may affect patient safety if recommended and used as a low dose inhaled corticosteroid. the SmPC for Relvar states the following:<br><br>Prescribers should be aware that in patients with asthma, fluticasone furoate (FF) 100 micrograms once daily is approximately equivalent to fluticasone propionate (FP) 250 micrograms twice daily.<br><br>As is seen in the same table 11 - this dose of fluticasone propionate is equivalent to beclometasone dipropionate (non extrafine) of 1000mcg daily - and both these doses of flucticasone and beclometasone (non extrafine) are considered medium ICS doses. In addition - the doses need to highlight whether they are metered or delivered doses - this could add to confusion without. For example Fobumix easyhaler and DuoResp Spiromax are delivered doses whereas Symbicort Turbohaler is metered dose. there is no metered dose listed in the SMPC for Fobumix, other than the SmPC states With the Fobumix Easyhaler device the delivered dose (the dose that leaves the mouthpiece) contains a similar quantity of active substance as the metered dose.<br><br>There are in addition some minor typographical errors in that the product names are not correctly capitalized as per registered names.<br>Qvar Autohaler | See response to GSK above)<br><br>Spelling corrected as indicated. | |

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| | | Qvar Easi-Breathe<br>Aerivio Spiromax | | |
| **7.1.1** | AM<br>PB | Page 64, 7.1.1<br><br>i) The wording regarding the use of SABA regularly four times daily could be interpreted as suggesting this is acceptable. There is overwhelming evidence that in some patients regular SABA may be detrimental, and there is no rational for this when LABAs are available and known to improve outcomes. So this should be reworded i.e. "SABA should only be used as required for the relief of symptoms. There are concerns that the use of SABA regularly 4 times a day may reduce asthma control in some patients".<br><br>ii) Allowing one SABA prescription per month is far too generous. Good asthma control equates to just over one SABA inhaler per year. Please revise. | This issue was not covered by this update.<br><br>However, we agree that this text is potentially misleading and does not reflect current thinking. The first paragraph has been deleted and the second has been extended to say: "SABA should only be used as required for the relief of symptoms.<br><br>The threshold in the GPP comes from the recommendations in the published NRAD report cited in section 9.1.2.<br><br>This issue will be considered for inclusion in the next update.<br><br>NICE also have an 'Option for local implementation' that states: "Review all people with asthma who have been prescribed a quantity of more than 12 short-acting reliever inhalers in the previous 12 months." (*NICE. Asthma Medicines safety priorities. nice.org.uk/guidance/ktt5 Last updated March 2019)* | |
| | AZ | Currently it is stated that anyone prescribed more than one short acting bronchodilator inhaler device a month should be identified and have their asthma assessed urgently and measures taken to improve asthma control if this is poor. | This topic was not covered by this update.<br><br>The threshold in the GPP comes | |

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| | | Suggested change: This number should be in line with the maximum number of SABA uses for a controlled patient of 3 per week as stated in the current BTS/SIGN guidelines Section 7.2.1 page 65.<br><br>Therefore, based on the licensed doses of short acting beta agonists, the maximum number of exacerbations per week for controlled patients and the number of doses per canister this number should be 2 SABA inhalers per year, not 12[1].<br><br>[1]. Asthma Slide Rule, Asthma Right Care PCRS accessed https://www.pcrs-uk.org/asthma-right-care<br>January 2019 | from the recommendations in the published NRAD report cited in section 9.1.2 and is intended to highlight the need for urgent review.<br><br>Anyone using a SABA more than three times a week is not a controlled patient, hence the recommendation in 7.2.1 to trial ICS.<br><br>This issue will be considered for inclusion in the next update. | |
| | NPRANG | If SABA is used > 4 doses per day, need to clarify that this is for 'sick days' only and should refer to PAAP for when a medical review is indicated.<br><br>A patient using > 6 SABA refills per year should be identified as a potential risk and interventions put in place at this stage -before they become a higher risk with use of SABA > 12 refills per year (RCP, 2014). | This point is too detailed.<br><br>The number in the GPP comes from the published NRAD report (cited in Section 9.1.2).<br><br>NICE also have an 'Option for local implementation' that states: "Review all people with asthma who have been prescribed a quantity of more than 12 short-acting reliever inhalers in the previous 12 months." (*NICE. Asthma Medicines safety priorities. nice.org.uk/guidance/ktt5 Last updated March 2019)*<br><br>This issue will be considered for inclusion in the next update. | |
| | PCRS | 7.1.1 'Anyone prescribed more than one short acting bronchodilator inhaler device a month should be identified and have their asthma assessed urgently and measures taken to improve asthma control if this is poor.' | The threshold in the GPP comes from the recommendations in the published NRAD report cited | |

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| | | Given the recommended frequency of SABA use and the concerns at excessive SABA use as a marker of poor control - should this threshold be lower? Six inhalers per year rather than twelve? After all, NRAD identified 12 per year as a marker of those who had such severe asthma that they died | in section 9.1.2 and is intended to highlight the need for urgent review.<br><br>NICE also have an 'Option for local implementation' that states: "Review all people with asthma who have been prescribed a quantity of more than 12 short-acting reliever inhalers in the previous 12 months." (*NICE. Asthma Medicines safety priorities. nice.org.uk/guidance/ktt5 Last updated March 2019)*<br><br>This issue will be considered for inclusion in the next update. | |
| **7.2** | PCRS | Table 11 - These tables are very important and useful. As stated above the need for practitioner awareness of variation in inhaled steroid potency and dosage is suboptimal and the need for such awareness needs greater emphasis in the text of the guideline and in summaries. | Thank you. In the view of the GDG it is clear from section 7.2.2 that treatment should start at an appropriate dose (low for adults, very-low for children) and be titrated to the lowest effective dose.<br><br>Table 11 and Table 12 have been updated to reflect more recent information. | |
| **7.2.1** | AM<br>PB | Page 65, 7.2.1<br><br>The current guidance for stepping up or initiating ICS is too lenient. Nocturnal waking once a week is a sign of poorly controlled eosinophilic inflammation and daytime symptoms twice a week suggests that the airways are not stable and the patient is at risk. GINA have moved to allowing symptoms twice a month which seems more sensible, and I would urge you to do the same. | This topic was not covered by this update. | |
| | NPRANG | Need to clarify the time period on a specified dose of ICS when a low dose adrenocorticotropic hormone test should be performed in children. Suggest adding this requirement on PAAP. In addition, there is a need to clarify | This topic was not covered by this update. | |

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| | | when the same test would be recommended with specified number of courses of OCS , intranasal and topical corticosteroids.<br><br>Figure 3<br>Clarify when Secondary and Tertiary care are indicated on summary. | There is no evidence on when an ACTH test is needed.<br><br>As stated in Figure 3, any child requiring high-dose therapy should be referred to specialist care (which may or may not be secondary or tertiary care). | |
| | PCRS | 7.2.1 'Inhaled corticosteroids should be considered for adults, children aged 5–12 and children under the age of five with any of the following features: using inhaled β2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, ICS should be considered in adults and children aged 5–12 who have had an asthma attack requiring oral corticosteroids in the last two years.438-442 '<br><br>We think that this should be more clearly worded to make it clearer that any regular requirement for SABA or continuing symptoms warrants the use of regular preventer treatment. | Disagree. Text clear as it is. | |
| **7.2.2** | NPRANG | Should specify a suitable review period after initiation of ICS. | Already covered in Table 3 and section 7.3. | |
| | PCRS | 7.2.2 'In mild to moderate asthma, starting at high doses of ICSs and stepping down confers no benefit.443'<br>It is interesting when the evidence leads to a conclusion at variance with experience in primary care.<br><br>When initiating inhaled corticosteroids, the vital thing is to demonstrate benefit to the patient or parent.<br><br>Starting at a higher does and stepping down makes it more likely that despite inhaler technique and adherence issues at the outset of treatment, a benefit with regular inhaled therapy is perceived by the patient, making subsequent adherence more likely. Absence of evidence is not evidence of absence for this very important consideration. | Disagree. Text clear as it is. | |
| **7.2.3** | SMC | Give inhaled corticosteroids initially twice daily (except ciclesonide which is given once daily. **Ciclesonide is licensed for adults and adolescents aged 12 years and older)"** | This topic was not covered by this update. | |

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| | | The boxes next to this piece of advice indicate this advice applies to all three age categories: adults and adolescents aged 12 and over, children aged 5-12, and children aged <5. Ciclesonide is only licensed for and accepted by SMC for children aged over 12 and adults as per the license. Although it is true ciclesonide is only given once daily, it shouldn't be used in children <12. Is this worth clarifying? See suggestion in bold. | No change required. HCPs should refer to the SPC for licensed indications. | |
| **7.2.4** | AZ | Currently the guidelines state Fluticasone propionate provides equal clinical activity to BDP and budesonide at half the dosage. The evidence that it causes fewer side effects at doses with equal clinical effect is limited. Mometasone appears to provide equal clinical activity to BDP and budesonide at half the dosage.448 It is difficult to establish the exact equipotent dose of fluticasone furoate.449,450.<br><br>Suggested change: Remove paragraph as it is misleading as it does not refer to BDP equivalence and it is unsubstantiated in referring to safety differences. | Disagree. The text as stated is factually correct and was not reviewed for this update | |
| | CI | Inhaled steroids are included as a first choice treatment. In section 7.2.4 differences between steroids are discussed, yet there is no mention of the difference in potency between extrafine formulations and non-extrafine formulations. This could easily result in patients receiving brands that are either not potent enough or too potent (compare Clenil 50mcg and Kelhale 50mcg). This is clear in the BNF. | This topic was not covered by this update. However, dose equivalence is covered in Tables 11 and 12.<br><br>No published evidence is available on extrafine formulations. This will be considered for inclusion in the next update. | |
| | GSK | FF/VI 92/22 mcg is a low daily dose required to achieve the efficacy thresholds within a wide therapeutic index.<br><br>*(Bateman et al. 2012; Bleecker et al. 2012; Busse et al. 2012; Daley-Yates et al 2015)*<br><br>GSK believes that the ICS equipotency model has now been superseded based on data generated since the writing of the 2016 guideline. The comparison with BDP as a measure of potency cannot be directly applied to FF/VI. | See response to GSK under Section 7 – General, above. | |

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| | | Within section '7.2.4 comparison of inhaled corticosteroids' with reference to the last sentence "it is difficult to establish the exact equipotent dose of fluticasone furoate", the more recent evidence demonstrates that FF/VI 92/22 mcg has a wide therapeutic index. Therapeutic Index is the comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes toxicity. Well-tolerated drugs demonstrate a wide therapeutic index between the doses required to produce a therapeutic effect and those producing adverse effects. FF/VI 92/22 mcg provides a low daily dose required to achieve the efficacy thresholds within a wide therapeutic index<br><br>*(Bateman et al. 2012;)*<br>*Bleecker et al. 2012; Busse et al. 2012; Daley-Yates et al. 2015).*<br><br>There are two main pharmacological properties of FF that account for this wide therapeutic index.<br><br>1. Low oral bioavailability (1.26%) meaning less potential for systemic exposure (Relvar Ellipta SPC 92/22 mcg; Relvar Ellipta SPC 184/22 mcg; Daley-Yates 2015).<br>2. Higher glucocorticoid receptor occupancy in the airways at lower doses (higher potency) resulting in lower daily doses for equivalent efficacy compared with other ICS *(Daley-Yates 2015).*<br><br>These pharmacological properties have been shown to be consistent with the results of asthma patient studies where the wide therapeutic index of FF 92 mcg has been demonstrated through equivalent efficacy on lung function to mid dose ICS (FP 250 mcg) with no evidence of clinically significant HPA suppression consistent with low dose ICS treatments (see below).<br><br>Note that GINA has moved away from comparing ICS doses according to BDP equivalence. (GINA 2018)<br><br>GSK are committed to examining the Benefit : Risk profile of FF and FF/VI and further supportive equivalence data is due to be published in the near future. Based on existing evidence, FF/VI 92/22 mcg is a low daily dose required to achieve the efficacy thresholds within a wide therapeutic index. *(Bateman et al. 2012; Bleecker et al. 2012; Busse et al. 2012; Daley-Yates et al. 2015)* | | |

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| | PCRS | 7.2.4 'Fluticasone propionate provides equal clinical activity to BDP and budesonide at half the dosage.'<br><br>Practitioners are not all aware of this and the point about the need to be aware of the differing potencies of inhaled corticosteroids and consequent dose differences needs greater emphasis as a good practice point. | This is the purpose of Tables 11 and 12. | |
| **7.2.5** | NPRANG | Need to clarify the time period on a specified dose of ICS when a low dose adrenocorticotropic hormone test should be performed in children. Suggest adding this requirement on PAAP. In addition, there is a need to clarify when the same test would be recommended with specified number of courses of OCS , intranasal and topical corticosteroids.<br><br>7 Figure 3<br>Clarify when Secondary and Tertiary care are indicated on summary. | There is no evidence on when an ACTH test is needed.<br><br>As stated in Figure 3, any child requiring high-dose therapy should be referred to specialist care (which may or may not be secondary or tertiary care). | |
| | PCRS | 7.2.5 It has been suggested that steroid warning cards (for example the High Dose Inhaled Corticosteroid Safety Card developed by the London Respiratory Network for NHS England451) should be issued to patients on higher dose ICS, but the benefits and possible disadvantages, particularly with regard to adherence, to such a policy remain to be established.'<br><br>The BNF contains advice to use such cards at higher inhaled steroid doses. This should perhaps be mentioned. The value is as a reminder to practitioners and patients of the desirability of reducing inhaled steroid dose to the minimum compatible with good control.<br><br>'Titrate the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is maintained. '<br><br>The importance of stepping down to the lowest dose that will achieve control deserves greater emphasis, as does the efficacy of spacers when pMDIs are being used to allow dose minimisation by achieving greater efficacy of treatment. | No change required.<br><br>No change required. | |
| **7.2.7** | AZ | Currently Relvar 92/22 is positioned as low/medium dose in the table. However the NICE evidence summary (esnm34) states that "in patients with asthma, fluticasone furoate 92 micrograms once a day is approximately | | |

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| | | equivalent to fluticasone propionate 250 micrograms twice a day". It then goes on to say that "The British guideline on the management of asthma (SIGN guideline 101) published jointly by the Scottish Intercollegiate Guidelines Network and British Thoracic Society and accredited by NICE indicates that 250micrograms fluticasone propionate twice a day is approximately equivalent to 1000micrograms beclometasone dipropionate per day"<br><br>Suggested change: Relvar 92/22 should not straddle low dose and medium dose in table 11. Relvar 92/22 should be clearly within the medium dose field of table 11. | See response to GSK under Section 7 - General, above. | |
| | JK | My view is that SR theophylline should not be listed as an option for add on when on moderate dose ICS/LABA. It has limited efficacy and a poor side effect profile. It certainly isn't something I would like to see GPs adding on before 'step 4' and potentially instead of LTRA. The option of beta2 agonist tablets again is odd... I doubt any asthma specialists ever prescribe these, and in my view non-specialists should not be prescribing them. | This section relates to alternatives to ICS as the regular preventer and evidence is cited to support use of theophylline. Use of theophylline as add-on therapy is covered in section 7.5 (now 7.5.2)<br><br>Beta2 agonist tablets are not mentioned in this section but have now been removed from elsewhere in the guideline. | |
| **7.3** | SF | I agree that LABA should be first line add-on after low dose ICS, although I do not feel that enough emphasis is placed on the need to withdraw this treatment if it doesn't work, before trying a 2nd add-on. We do not actually know the true response-rates to low-dose ICS+LABA in this group as (almost) al studies have included only people with reduced lung function and marked SABA reversibility (and therefore pre-selected to respond to a LABA), whereas we know in mild-moderate asthma 50-75% (even more in children) will have normal lung function and/or minimal reversibility. | Treatment options for LABA non-responders were not covered by this update but will be considered for inclusion in the next update. | |
| **7.3.4** | PCRS | 7.3.4 'Combination inhalers are recommended to:<br><br>• guarantee that the longacting β2 agonist is not taken without inhaled corticosteroid<br>• improve inhaler adherence '<br>What is the signal to reduce inhaled corticosteroids if a daily bronchodilator | Current advice on decreasing | |

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| | | is also being given? Given the concerns about overdiagnosis and overtreatment of asthma it might be advisable to restate the criteria (ie absence of symptoms) for stepping down treatment here. | treatment is relevant here. See section 7.6 (previously section 7.10) | |
| **7.3.5** | PCRS | Opinion among our commentators varied. Some are convinced by the evidence for the value and efficacy of this approach to management and feel that it needs more prominent placement in the guideline and the management tables. Others felt that the undoubted advantages of flexible dosing to deal with symptoms fluctuation and the onset of exacerbations can often be achieved within self management plans using less expensive non-combination inhalers. We note that the great majority of the evidence for the effectiveness of MART regimens comes from industry sponsored studies. We feel that there is an important research need for non-industry funded comparisons of these differing approaches to management, which should include health economic analysis.<br><br>One commentator states:<br><br>The summary diagram states that if control is not achieved on low dose ICS/LABA then the next option is to increase ICS dose or add in a second controller. The text of the guideline acknowledges that MART therapy should be considered for exacerbating patients at this stage and indeed studies such as *Rabe KF et al Chest 2006 129(2) 246* state that SMART therapy at low dose of ICS has better outcomes than increasing the dose of ICS.<br><br>There is an important need to consider the compatibility of MART regimens with self-management plans for high dose inhaled treatment via MDI and spacer in exacerbations. The Asthma UK leaflet on this advises patients on MART regimens not to use the advice but to ask their health professional.<br><br>However, patients on MART regimens continue to experience exacerbations and need to know what to do when their MART regimen has failed to control and exacerbation.<br><br>The text of 7.3.5 is very clear but it is not reflected in Fig 2 page 76... There needs to be alignment between text and algorithms in case busy HCPs only look at one or the other. It is grade A evidence but isn't obvious from looking at the summary figure. | Agree. MART now included under 'Initial add-on therapy' in Figure 2. | |

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| | SCRR | More prominence needs to be given to MART throughout as a way of enforcing ICS adherence | Agree. MART now included under 'Initial add-on therapy' in Figure 2. | |
| **7.4.1** | BTS | This is the first opportunity for tailored therapy. Those who are FeNO high likely to respond to higher dose ICS, others not. This could be explored | Agree this is interesting but there is currently no evidence to support it. We will consider this for inclusion in the next update. | |
| **7.4.4** | AM<br>PB | Page 74, 7.4.4<br><br>There is no role for oral beta agonists in the modern management of asthma. They are less effective than topical treatment and associated with a lot more side effects. The lack of effect of topical treatment is not due to a lack of agonist binding to beta2 receptors. It should be made clear they are not an option, or their mention should be deleted. | Agree. Paragraph on beta2-agonist tablets removed and GPP amended. | |
| **7.5** | BH | Technically, I don't think the tiotropium reference here should be level D. | Agree, but the D grade relates to the overall level of evidence supporting the recommendation rather than that supporting its component parts. | |
| | BTS | Again choice of add on at this stage is increasingly directed by phenotype – not mentioned | This topic was not covered by this update. | |
| **7.6** | AZ | Currently the guidelines only state the recommendation that patients requiring frequent or continuous use of oral corticosteroids should be referred to a specialist clinician in figure 2 and figure 3 and not in the text of section 7.6.<br><br>Suggested change: This recommendation is also included in the main body of text to ensure clarity. | Agree. Statement added before the GPP and a new GPP added (now all in section 7.5.3). | |
| **7.6.1** | AUK | **Criteria for referral of asthma patients to secondary/specialist care**<br><br>Asthma UK strongly supports the provisions in the new NICE Quality Standard 25 that any patient with asthma who has had more than two courses of high-dose oral corticosteroids in a year, should be referred for a specialist review because of the cumulative side effects of using oral steroids and the adverse impact on patients' long-term health. Asthma UK's | A sentence reflecting the need for referral to specialist care has been added (now in section 7.5.3). | |

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| | | 2018 report *Slipping through the net*[1], revealed that people are not getting the referrals they need to secondary or tertiary care and that there is also a wide variation in referral criteria and behaviours amongst clinicians. We are therefore calling for standard guidelines to be adopted for the referral of patients to specialised care, as well as for standard guidelines within specialised care, both for people with confirmed severe asthma and for those with difficult to control asthma who have not yet had a severe asthma diagnosis.<br><br>In the light of this, and because there are now four biologics available (with more on the way) we believe BTS/SIGN should consider developing a new dedicated guideline for the management of severe asthma that is updated annually.<br><br>*Ref*<br>*[1]Asthma UK, Slipping through the net: the reality facing patients with difficult and severe asthma, 2018* | | |
| **7.7.1** | BTS | Worth mentioning control of Anti -IgE through regional severe asthma networks (it is included for anti IL5 at 7.7.2)<br><br>No mention of Azithromycin – should be commented on after AMAZES trial? | Agree. GPP added (now in 7.5.4)<br><br>Agree. Existing text on macrolides in section 7.7.3 deleted.<br>*New guidance on macrolides from BTS is pending, and will be referenced in 7.5.5 if published in time.* | |
| | ER | The following statement is no longer current "Due to risk of anaphylaxis, omalizumab should only be administered to patients in a healthcare setting under direct medical supervision".<br><br>Xolair has had it's license amended to include self-administration (in patients with no history of anaphylaxis). Patients with no known history of anaphylaxis may self-inject Xolair or be injected by a caregiver from the 4th dose onwards if a physician determines that this is appropriate (see section 4.4). The patient or the caregiver must have been trained in the correct injection technique and the recognition of the early signs and symptoms of serious allergic reactions. Patients or caregivers should be instructed to | Agree. Text in 2nd paragraph (now in 7.5.4) amended to clarify that this applies to the first three doses only. | |

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| | | inject the full amount of Xolair according to the instructions provided in the package leaflet.<br><br>Type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab, even after a long duration of treatment.<br><br>However, most of these reactions occurred within 2 hours after the first and subsequent injections of Xolair but some started beyond 2 hours and even beyond 24 hours after the injection. The majority of anaphylactic reactions occurred within the first 3 doses of Xolair.<br><br>Therefore, the first 3 doses must be administered either by or under the supervision of a healthcare professional. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration.<br><br>Therefore for patients with a known history of anaphylaxis, Xolair must be administered by a health care professional, who should always have medicinal products for the treatment of anaphylactic reactions available for immediate use following administration of Xolair. If an anaphylactic or other serious allergic reaction occurs, administration of Xolair must be discontinued immediately and appropriate therapy initiated.<br><br>Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur. Self-administration at home refers to administration by a patient as well as administration by a lay caregiver in a home setting. | See point above. | |
| | PCRS | This section would be more useful of it gave clear guidelines for when patients should be referred for assessment for MABS.<br><br>Recommendation of initiating omalizumab in specialist centre has been removed, why is this? | Patients being considered for MABS should be under the care of an asthma specialist who can consider all the options available.<br><br>Agree. This was an error. The GPP has been reinstated and augmented and now appears with the recommendations at the end of Section 7.5.4. | |

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| | SF | BT should be grouped with the other therapies for severe asthma (i.e. immunotherapy should be moved out of this section). In fact it would be better to have a new section at position 7.5. called “Potential treatments for severe asthma” and include: high dose ICS; systemic CS; monoclonals; BT; (maybe macrolides too??). | Section 7.7 has been re-organised and headings changed and is now section 7.5‘Specialist therapies’. Bronchial thermoplasty has been moved from section 7.9 to section 7.5.7 and immuotherapy has been moved from Section 7.8 to 7.5.6.<br><br>Severe asthma is not considered as a separate topic in the current guideline but consideration will be given to including such a section in the next update. | |
| | SMC | For guidance on when to consider treatment see NICE technology appraisal guidance TA278" (in reference to omalizumab).<br><br>This is appropriate because SMC advice regarding omalizumab has been superseded by NICE MTA appraisal.<br><br>(https://www.scottishmedicines.org.uk/medicines-advice/omalizumab-150mg-powder-and-solvent-for-injection-xolair-resubmission-5906-1/) | No response needed. | |
| **7.7.2** | AZ | Point 5/5. Guidance on the use of anti-IL5s needs to be aligned to NICE guidance (and forthcoming SMC guidance)<br><br>Currently the guidelines state that mepolizumab (subcutaneous), reslizumab (intravenous) and benralizumab (subcutaneous) may be considered in eligible patients with a high steroid burden. This is inaccurate in relation to available evidence and the NICE recommendation as due to a lack of evidence, reslizumab does not have a recommendation for OCS (oral cortico-steroids) sparing and therefore can’t be used in patients receiving continuous OCS; furthermore, mepolizumab and benralizumab can be used in patients with or without continuous OCS. The guideline should state that mepolizumab (SC), reslizumab (IV) and benralizumab (SC) should be considered for patients with severe eosinophilic asthma in line with their NICE and SMC recommendations | The final paragraph before the recommendation (now in section 7.5.4) has been revised to reflect the need for England & Wales and Scotland to take account of advice from NICE and SMC, respectively. | |

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| | | From a patient perspective it is important to include the frequency of administration of the medication.<br><br>Benralizumab is licensed for dosing every 8 weeks (following the first 3 doses which are every 4 weeks) compared with mepolizumab which is continuously administered every 4 weeks.<br><br>Therefore, benralizumab offers the advantages and convenience of less frequent injections for patients. | | |
| | GSK | "An RCT looking at the potential steroid-sparing effect of mepolizumab including 135 patients with severe eosinophilic asthma receiving 100 mg of mepolizumab subcutaneously every four weeks, reported a significant glucocorticoid-sparing effect with mepolizumab compared with placebo (28% v 11%, respectively), improved secondary outcomes including fewer exacerbations and improved ACQ-5 scores, and a similar safety profile."<br><br>GSK believe that taking into account the level of drug exposure is important when considering maintenance oral corticosteroid (mOCS) use in this group of patients. We feel that better clarity is provided by not only considering the proportion of patients who were able to achieve near-complete reduction in daily mOCS use, but also calling attention to the proportion of patients who achieved lower, but still significant, reductions in daily mOCS use.<br><br>The publication by Bel et al (referenced in the draft guidelines), as well as wider factors which are a reality of day-to-day patient care, suggest that some patients with long-term mOCS dependency will see significant results, but will not achieve the magnitude of reduction being quoted. Currently the draft guidelines refer to the proportion of patients achieving a 90-100% reduction in their daily mOCS dose (23% when treated with mepolizumab vs. 11% with placebo).<br><br>To this end we would like to draw attention to the proportions of patients achieving lower, but still significant reductions in daily mOCS use. In the SIRIUS trial, 63% of patients treated with mepolizumab were able to achieve any reduction in daily mOCS dose by the end the treatment period, compared to 45% of placebo-treated patients. Similarly, 53% of mepolizumab patients were able to achieve a reduction of 50% or more, compared to 34% in the placebo arm. This represents a 2.39 greater chance of achieving daily mOCS dose reduction for patients using | In the view of the GDG, this is adequately covered by the existing text. | |

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| | | mepolizumab compared to placebo.<br><br>As well as showing a benefit with regards to the number of patients who were able to achieve a significant reduction in their mOCS dose, the publication also provides insight into the degree of daily mOCS dose reduction which could be seen in these patients overall, showing that the median reduction in OCS dose was 50%. | | |
| | SF | See comment in 7.7.1 | Response as for 7.7.1. | |
| | SMC | For guidance on when to consider treatment see NICE technology appraisal guidance, on mepolizumab (TA431), reslizumab (TA479) and benralizumab (TAXYZ) (available at www.nice.org.uk/guidance)."<br><br>As noted previously, the relevant advice for NHSScotland is the SMC advice, so reference to SMC advice should be included in the guideline. Mepolizumab is accepted for restricted use in Scotland for adults (see 1149/16), and an abbreviated submission for 6+ (including adults) is in process (SMC meeting date 5th March 2019).<br><br>Reslizumab is not recommended for use by SMC (see 1233/17). The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.<br><br>Benralizumab has not been reviewed yet by SMC, but a submission has been received. | Agree. Final paragraph before the recommendation (now in section 7.5.4) re-worded to read:<br><br>'Guidance on use of mepolizumab, reslizumab and benralizumab differs in England/Wales and Scotland and the relevant NICE or SMC advice should, therefore, be checked prior to considering these treatment approaches. | |
| **7.7.3** | AM<br>PB | Page 79, 7.7.3<br><br>There is no role for gold, cyclosporine or methotrexate in the modern management of asthma.<br><br>Methotrexate is ineffective (*Bilocca D, Chron Respir Dis. 2018; 15:85-87.*). The others are toxic. There is better evidence for the use of macrolides which you suggest should be avoided (*Gibson PG, Lancet. 2017; 390:659-668*). | This topic was not covered by this update.<br><br>Paragraph on use of macrolides has been deleted as it does not reflect current evidence.<br><br>*New guidance on macrolides from BTS is pending, and will be referenced in 7.5.5 if published in time.* | |

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| | JK | I realise this was not part of the update, but I don't think BTS can issue new guidance that totally ignores macrolides so long after publication of the AMAZES trial... Please re-think! | Agree. See response above, | |
| **7.9** | SCRR | Trials urgently needed to compare BT with biologics | Agree. This has been added as a research recommendation. | |
| | SHTG | Note that NICE published Interventional Procedures Guidance 635 in December 2018 on bronchial thermoplasty, available at https://www.nice.org.uk/guidance/ipg635 | No response needed. | |
| | SF | See comment in 7.7.1 | Response as for 7.7.1. | |
| **7.11.2** | AM<br>PB | Page 83, 7.11.2<br><br>Again, please delete oral beta agonists. | Agreed. Bullet point and recommendation relating to use of beta agonist tablets have been deleted (remaining text now in section 7.7.2). | |
| **7.11.3** | NPRANG | There may be insufficient evidence for improving asthma with intranasal steroid treatment but what is the evidence for recommending LTRA for improving both AR and asthma and overall QOL ? Should this be a treatment recommendation? | This topic was not covered by this update but will be considered for a future update. | |
| | SCRR | More emphasis needs to be given wrt ARIA | ARIA is not specifically covered by the guideline although allergic rhinitis is mentioned (eg in section 7.7.3), usually in relation to atopy. | |
| **7.11.6** | SF | Type 'OESOPHOGEAL' | Spelling corrected. | |
| **7.11.7** | SCRR | There are new data wrt safety of BB in asthma.<br><br>*Heart2014;100:219–223.*<br>*Am J Respir Crit Care Med Vol 187, Iss. 12, pp 1308–1314, Jun 15, 2013*<br>*Clinical Science (2014) 127, 635–643 doi: 10.1042/CS20140249* | Thank you. This topic was not covered by this update. | |
| **Section 8** | | | | |
| **General** | ARNS | Nothing else to add | No response required. | |

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| **8.1** | BTS | First rec:<br>Should upper airway clearance of ics by gargling (MDI) and pre-meal dosing (DPI) should be mentioned separately? | This topic was not covered by this update. | |
| **8.2.1** | AM<br>PB | You say there is no evidence regarding the use of MDI + spacer in acute severe asthma, but the Cochrane review you cite (ref 542) looks at the efficacy in the more severe patients (FEV1 <30% predicted) and found the results were the same – MDI and spacer is as effective as nebuliser. You also say on page 93 that "In patients with acute asthma without life threatening features, β2 agonists can be administered by repeated activations of a pMDI via an appropriate large volume spacer or by wet nebulisation driven by oxygen, if available (542). So please amend page 85 accordingly. | Agree there is inconsistency. The text in section 8.2.1 has been revised to indicate that there are 'insufficient data' rather than 'no data'. The second paragraph in section in 9.3.2 has also been amended to improve clarity. | |
| | NPRANG | What is a "mild" asthma attack? There is no classification of this level of severity of acute asthma anywhere in the guideline so use of the term in this section is unhelpful and confusing.<br><br>Why, if there is no basis for a recommendation in acute severe asthma, do the annexes guide to the use of B2agonist via pMDI and spacer? | There is no accepted definition of a mild asthma attack. The use of the term in the guideline reflects its use in the supporting evidence.<br><br>Annexes 2, 5, 6 and 7 have been amended to reflect the updated text. | |
| | NPRANG | Some discussion around appropriate inhaler use in children <5 years should be included, clinicians rely on these guidelines to support their clinical practice (ref tips in 8.4) | This topic was not covered by this update. | |
| | WS | ? Cite<br>Sellers WFS<br>*Allergy Asthma Clin Immunol (2017) 13:30*<br>*DOI 10.1186/s13223-017-0202-0* | Unclear as to what this comment relates. No action required. | |
| **8.3** | NPRANG | Should spacer be included with pMDI in the paragraph about inhaler use in 5-12 year olds? It currently reads as though meaning pMDI alone which presumably is incorrect (pMDI Vs Clickhaler and Turbohaler)<br><br>Some discussion around appropriate inhaler use in children <5 years should be included, clinicians rely on these guidelines to support their clinical practice(ref tips in 8.4) | This topic was not covered by this update.<br><br>This topic was not covered by this update. | |

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| | PCRS | 8.3 INHALED CORTICOSTEROIDS FOR STABLE ASTHMA<br><br>What about acute asthma?<br><br>Given the growing recognition of the value of higher dose inhaled steroids for the initial management of exacerbations (reflected in the guideline now) the point needs to be made that pMDI and spacer is likely to be the most effective way of administering high does inhaled steroid for the control of exacerbations. | This topic was not covered by this update. | |
| **8.4** | PCRS | 8.4 Prescribing devices<br><br>The advantages of spacers for increasing the effectiveness of medication administered via pMDI have been consistently understated and under-emphasised in guidelines for many years. They should feature far more prominently in this section. Lung deposition with spacer use is substantially higher and normal deposition much reduced even in patients with good technique. Wider use of spacers would improve treatment results.<br><br>In exacerbations spacers are indispensable for effective inhaled treatment so every person with asthma who is liable to exacerbations should have one and know how to use it.<br><br>The following statement should be reconsidered with this in mind. 'pMDI and spacer should be available and taught for exacerbations even when routine treatment is with other devices.'<br><br>'Prescribing mixed inhaler types may cause confusion and lead to increased errors in use. Using the same type of device to deliver preventer and reliever treatments may improve outcomes.'<br><br>This will be of increasing importance if considerations raised in 8.6 lead to more widespread use of DPIs. | This topic was not covered by this update. | |
| **8.5** | NPRANG | Monthly rather than weekly washing of spacers sentence is a little unclear – does it mean monthly washing is recommended no matter what the manufacturer instructions say or monthly rather than weekly and washed as per manufacturers instructions | This topic was not covered by this update. | |

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| **8.6** | Ch | This section feels overly dramatic and misleading in terms of the relative impact on the environment.<br><br>It is true that CFCs were potent greenhouse gases but the replacement HFAs have a much lower impact than the CFCs. The CFCs were 'phased out' under the Montreal Protocol and therefore this guidance should use that phrase and not emotive language such as 'banned'. Therefore we recommend that the title of this section is amended to 'Environmental impact of metered dose inhalers' to redress the bias in the language. This will also therefore apply to the contents page (page 4) as the title will need changed here as well.<br><br>The term 'potent greenhouse gases' was originally used for ozone depleting substances (ie. CFCs), with the transition to HFC/HFAs there is considerably less potency and therefore the term 'potent greenhouse gases' should not be used for HFAs.<br><br>Acknowledging that the fluorinated gases have a high global warming potential, the UK Government and Montreal Protocol committees refer to HFAs as having a high Global Warming Potential (GWP) and therefore this is the term that should be used in this document. Slightly concerned that the 'potent greenhouse gases' statement is not a true interpretation of the reference included. From a search of reference 553 there doesn't appear to be a mention of the term 'potent greenhouse gases' and yet this is the assigned reference for this statement in the document. Somewhere in this section there needs to be guidance which states that patient safety, patient choice and ensuring symptom control/disease management should not be compromised in favour of the environmental impact of the inhaler device. Please refer to the Usmani, Scullion, Keeley paper (Our planet or our patients—is the sky the limit for inhaler choice?) in order to understand the importance of the inclusion of this statement. (*https://publications.parliament.uk/pa/cm201719/cmselect/cmenvaud/469/469.pdf*)<br><br>We also suggest that the last point in this section - 'Patients should be informed that they can recycle their.....' is re-written as 'Patients should be encouraged to return their inhalers at any community pharmacy'. The gases in some inhalers can be reused if disposed of correctly at the pharmacy and this wording removes the words 'selected pharmacies' which could | Agree. Title and contents page heading changed as suggested.<br><br>Agree. 'Potent' changed to 'high global warming potential'<br><br>The GPP states that inhalers with low global warming potential should be used when they are likely to be equally effective.<br><br>Disagree. Only some community pharmacists participate in this scheme. GPP re-worded to raise awareness of the issue. | |

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| | | discourage patient recycling.<br><br>There is a typo in reference 554 on page 180 - it should read Creagh (as in Mary Creagh) - Chair of the environmental audit committee. https://publications.parliament.uk/pa/cm201719/cmselect/cmenvaud/469/469.pdf Currently it is referenced incorrectly as 'Creach'. | Spelling of name corrected. | |
| | PCRS | 8.6<br><br>A broader statement about how to reduce the overall GWP contribution of asthma treatments would be desirable. This would cover a variety of issues: better education and adherence with preventer use in asthma, routine spacer use if using MDIs, minimising propellant per dose where the change is patient-acceptable, switching from pMDI to DPI where the change is clinically appropriate, safe and patient-acceptable. A multifaceted approach of this kind is more likely to be effective in reducing propellant use. It should also be mentioned that alternative low GWP propellants for MDIs are under development. Reference: *Parliamentary Environmental Audit committee UK progress on reducing Fgas emissions 2018*<br><br>It should be emphasised that any inhaler device change should be undertaken in consultation with individual patients and that routine inhaler type switches should not take place. There is a risk of adverse clinical consequences from an uncritical or wholesale shift to DPIs from MDIs as well as significant cost pressures for the NHS given the higher cost of DPIs.<br><br>'Where there is no alternative to MDIs, lower volume HFA134a inhalers should be used in preference to large volume or HFA227ea inhalers.'<br><br>This point should be clarified, as many prescribers will be unaware of the different amount of propellant per puff in different inhalers – Where would clinicians find data on relative global warming potential (GWP) of different inhalers? - a table of some kind would be the easiest way of explaining this.<br><br>Another intervention that would reduce propellant use would be for the very common regimen of beclometasone 100 x 2 puffs twice daily to be instead prescribed as beclometasone 200 x one puff twice daily. This would halve propellant use for this preparation and also halve prescription costs for prescription charge payers. | This is beyond the scope of the guideline.<br><br>If PCRS would like to draft something, the GDG would be happy to consider it with a view to possible inclusion in a future update.<br><br>The GPP states that inhalers with low global warming potential should be used when they are likely to be equally effective.<br><br>These suggestions will be considered for a future update. | |

| **Section 9** | | | | |
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| **General** | ARNS | I have commented earlier on the relevant sections. | No response needed. | |
| **9.1.2** | AZ | (Point 3/5) Currently it is stated that anyone prescribed more than 12 SABA inhalers per year should be identified and have their asthma assessed urgently and measures taken to improve asthma control if this is poor. Suggested change: This number should be in line with the maximum number of SABA uses for a controlled patient of 3 per week as stated in the current BTS/SIGN guidelines Section 7.2.1 page 65.<br><br>Therefore, based on the licensed doses of short acting beta agonists, the maximum number of exacerbations per week for controlled patients and the number of doses per canister this number should be 2 SABA inhalers per year, not 12[1].<br><br>[1]. Asthma Slide Rule, Asthma Right Care PCRS accessed https://www.pcrs-uk.org/asthma-right-care January 2019 | The figure of 12 SABA inhalers per year is a recommendation in the cited NRAD 2014 report. | |
| | PCRS | 'Heavy or increasing use of 2++ β2 agonist therapy was associated with asthma death. 556-560,563,564'<br><br>It is VERY IMPORTANT to make clear that this evidence relates to heavy or increasing routine use of beta agonists over time and not to the appropriate and necessary use of high dose beta agonists for acute exacerbations. There is a very real risk that in the public and health professional mind this statement may act as an inhibitor to the (necessary) use of high dose beta agonists in the initial management of exacerbations.<br><br>Table 13 should include ongoing high/routine use of beta agonists as a risk factor. | This topic was not covered by this update.<br><br>The text relates directly to the cited findings.<br><br>Heavy use of beta-2-agonist is already included in Table 13. | |
| **9.3.5** | WS | Please cite: Intravenous magnesium sulphate prevents intravenous salbutamol tachycardia in asthma. *Sellers WFS et al doi:10.1093/bja/aeq329*<br><br>Case report evidence in similar vein to case report use of Sevoflurane. Also; Sellers WFS inhaled and intravenous treatment in acute severe and life-threatening asthma doi:10.1093/bja/aes444 | There is no usable evidence to support this. | |

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| **9.3.12** | WS | Using IV enoximone. Beute J. Emergency management of status asthmaticus with enoximone https://doi.org/10.1093/bja/aeu048 | No response needed. | |
| **9.7.2** | NPRANG | PULSE OXIMETRY – add in statement regarding use of appropriate probe selection according to child's weight. https://improvement.nhs.uk/news-alerts/risk-of-harm-from-inappropriate-placement-of-pulse-oximeterprobes/ | This topic was not covered by this update. | |
| **9.8.2** | NPRANG | Clarity is needed when patient is on a combination therapy as we would not advocate stopping background therapy during an attack.<br><br>Two to four puffs of salbutamol (100 micrograms via a pMDI + spacer) might be sufficient for mild asthma attacks, although up to 10 puffs might be needed for more severe attacks. Single puffs should be given one at a time and inhaled separately with five tidal breaths. ** Add in...The inhaler should be shaken in between doses. Relief from symptoms should last 3–4 hours. | This topic was not covered by this update. | |
| **9.9.3** | WS | As for adults | No response needed. | |
| **9.9.4** | Ai | It would be useful to include the findings on preventing asthma with the help of Airsonett®.<br><br>A class I1, non-invasive, temperature controlled laminar airflow device indicated as an add-on therapy for children and adults with severe persistent allergic asthma whose disease despite pharmacotherapy remains poorly controlled.<br>*Reference: Inovative Medical Technology Overview: 003/2015*<br>*NICE - https://www.nice.org.uk/advice/mib8/chapter/Summary* | This topic was not covered by this update. | |
| **9.9.5** | WS | As for adults; Enoximone IV | No response needed. | |
| **Section 10** | | | | |
| **General** | BTS | Difficult asthma is an old term – severe difficult to treat is better | The section on difficult asthma will be considered for review as part of the next update to the guideline. | |
| **10.1** | ARNS | Not changed so no comments to be made. | No response needed. | |

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| | AZ | Currently severe asthma and difficult asthma appear to be used interchangeably.<br><br>Suggested change: Severe asthma, as a distinct subset of difficult asthma, should be defined clearly in line with the ERS/ATS definition: "asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy".<br><br>We also recommend that the NICE quality statement 5 regarding referral to specialist severe asthma centres should be included in this section. Please also state that at referral the phenotype should be identified or confirmed by the specialist in sections 4.2.4 and 2.8. | The definition of severe asthma in section 4.2.4 (now 4.3.4) has been clarified.<br><br>The need for specialist care has been added to section 4.2.4 (now 4.3.4).<br><br>Phenotyping was not covered by this update. | |
| | SF | General comment (apologies!):<br><br>I feel this section really needs overhauling, perhaps in time for the next update. It should aim to be a useful resource for someone wanting to understand the assessment and management of difficult asthma, and as such it should include the investigation and treatment of severe disease, including moving treatments from chapter 7. | Agree. The section on difficult asthma will be considered for review as part of the next update to the guideline. | |
| **10.2.1** | SCRR | See above wrt MART | Unclear as to what this comment relates. | |
| **10.2.4** | ALUK | Allergic triggers need to be identified and proactively reduced. If this is completely unavoidable then antiallergy medication as well as asthma medication needs consideration. There should be recommendation that a referral for allergy assessment is necessary | The section on difficult asthma will be considered for review as part of the next update to the guideline. | |
| | SCRR | see above wrt ARIA | Unclear as to what this comment relates. | |
| **10.2.5** | SCRR | See above wrt IOS | Unclear as to what this comment relates. | |
| **Section 11** | | | | |
| **11.1** | ARNS | Not changed so no comments to be made. | No response required. | |

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| **11.2** | NPRANG | End of section re questionnaires states 'see Table 6' which relates to Diagnostic indications for specialist referral. Surely it should state 'see Table 8' which relates to the questionnaires. | Thank you. Table number corrected. | |
| **11.3.4** | SCRR | See above wrt IOS being used in conjunction with Spiro especially in pts with preserved FEV1 | This topic was not covered by this update. | |
| **11.4.4** | SCRR | There is now much data in competitive swimmers wrt Cl2 as a trigger -this should be included | This topic was not covered by this update. | |
| **11.7** | NPRANG | Clinician's should also discuss potential issues with career choices being unobtainable due to the diagnosis/treatment for asthma e.g. UK armed forces will not accept applications if treatment taken within last 4 year period.<br><br>Adolescents have been known to stop taking medication to fulfil criteria. | This topic was not covered by this update. | |
| **11.8.1** | NPRANG | ECigarettes not mentioned – ? if this would be relevant | This topic was not covered by this update. | |
| **11.11.3** | NPRANG | It should be highlighted that some adolescents will transition to the care of the GP. The adolescent should be prepared for managing their condition within primary care and equipped with the knowledge the referral to adult health services in secondary or tertiary care is available if required. | This topic was not covered by this update. | |
| **11.11.4** | NPRANG | 'The involvement of adult physicians prior to transfer supports attendance and adherence to treatment' does not highlight their significance in the process. It is imperative that adult physician's other key workers within the adult healthcare team take part in the transition process by offering joint appointments, meeting the patient, offering a unit visit etc. Children's services can prepare the adolescent but adult services can and should assist. | This topic was not covered by this update. | |
| **11.12.2** | SCRR | See above wrt use of MART | This topic was not covered by this update. | |
| **Section 12** | | | | |
| 12.1 | ARNS | Not changed so no comments to be made. | No response required. | |

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| 12.3 | SCRR | See below wrt ICS | This topic was not covered by this update. | |
| 12.3.2 | SCRR | Use of ICS with shorter elimination T1/2 such as BUD or BDP cf FP or FF results in lower fetal exposure | This topic was not covered by this update. | |
| **Section 13** | | | | |
| **13.3** | SF | Why is the phrasing "Adults with airflow obstruction …." used? People with asthma may not have airflow obstruction documented, especially those with only symptoms at work. Suggest change to "Adults with suspected asthma….." | Agree. Test of GPP changed to 'Adults with suspected asthma or unexplained airways obstruction should be asked…' | |
| **13.4** | BTS | General Respiratory physicians often get asked about respiratory protective equipment. Will the authors consider answering the question: Is the incidence of occupational asthma reduced by respiratory protective equipment?<br><br>*Cullen MR, Redlich CA, Beckett WS, Weltmann B, Sparer J, Jackson G, Ruff T, Rubinstein E, Holden W*<br><br>Feasibility study of respiratory questionnaire and peak flow recordings in autobody shop workers exposed to isocyanate-containing spray paint: observations and limitations.<br><br>*Occup Med (London), 1996 ; 46 : 197-204. Grammer LC, Harris KE, Yarnold PR , Effect of respiratory protective devices on development of antibody and occupational asthma to an acid anhydride , Chest , 2002 ; 121 : 1317-1322*<br>*Petsonk EL, Wang ML, Lewis DM et al , Asthma-like symptoms in wood product plant workers exposed to methylene diphenyl di-isocyanate , Chest , 2000 ; 118 : 183-193* | Use of respiratory protective equipment (RPE) is not covered by the guideline. A review of RPE up until 2010 is, however, included in the British Occupational Health Research Foundation guidance (ref 893 in the SIGN guideline), which generally concludes that RPE use does reduce occupational asthma incidence but does not completely prevent it.<br><br>The GDG suggest that if patients enquire about the use of respiratory protection at work, it should be stressed that this should be seen as part of a set of measures to reduce harmful exposures at work. They should discuss RPE with their workplace, and general RPE advice is always available on the HSE website http://www.hse.gov.uk/respiratory-protective-equipment/ | |

| **Section 14** | | | | |
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| 14.1 | ARNS | Not changed so no comments to be made. | No response required. | |
| 14.2 | NPRANG | Educational Outreach visits require appropriately trained professionals from within the local area where training is being delivered, building links and establishing strong/effective collaborative relationships.<br><br>Adoption of the PACE intervention with children would provide further experience and information about approaches best suited to clinical practice and education in the UK. Asthma Champions and/or outreach nurses could support this approach.<br><br>Training needs to be ongoing and sustainable. | This topic was not covered by this update. | |
| 14.3.1 | NPRANG | Strong evidence for structured review but further trials needed to test the impact of clinics run by specialists in asthma care. This should link in with educational outreach within primary care. | This topic was not covered by this update. | |
| 14.4 | NPRANG | Supporting self-management is well documented via various IT modalities. IT approaches with children could be more significant as access and engagement directly with the young person is increased through this approach but systems/processes/ personalised feedback needs additional resources and support specifically for children/young people. | This topic was not covered by this update. | |
| 14.5 | NPRANG | School based asthma interventions should be delivered by appropriately trained professionals/ students.<br><br>Children and young people spend a good proportion of time in school and therefore recognition of this as ‘a captive audience’ and an opportunity to impact on their asthma care/self-management as an alternative to ‘health setting’ delivered care should be supported. | This topic was not covered by this update. | |
| 14.6 | NPRANG | Further studies in the UK needed. | This topic was not covered by this update. | |
| 14.7 | NPRANG | Any lay-led interventions need to recognise that the needs of young people are different to that of the parents/family and outcome measures need to be specific depending on who is being targeted. | This topic was not covered by this update. | |

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| 14.8 | SCRR | Use of FeNO | This topic was not covered by this update. | |
| | NPRANG | Pharmacists provide an additional opportunity to deliver education and training needs to be supported. | This topic was not covered by this update. | |
| **Section 15** | | | | |
| **General** | ALUK | Allergy UK has factsheets and information for healthcare professionals and the public | No response required. Allergy UK are already listed as an organisation providing additional information. | |
| 15.1 | ARNS | You may wish to add something in this section to ensure HCPs are aware many patients are illiterate and so provision of written materials is not appropriate especially their PAAP. | Disagree. All HCPs should be aware of this possibility. | |
| | ALUK | We have an asthma tool on our website to think about potential allergic triggers of asthma | No response required. Allergy UK are already listed as an organisation providing additional information. | |
| 15.2 | Ai | Innovative Medical Technology Overview 003/2015<br><br>"This IMTO review document describes an impartial review of the strengths and weaknesses of the submission by Airsonett UK Limited regarding the following medical technology. Arisonett" | This is not relevant for this section which relates to other publications from SIGN. | |
| 15.3.1 | ALUK | Allergy UK | No response required. Allergy UK are already listed as an organisation providing additional information. | |
| **Section 16** | | | | |
| 16.1 | Ai | https://www.nice.org.uk/advice/mib8/chapter/Summary IMTO 003/2015 Bjermer L, Eriksson G, Radner F, Peterson S, Warner JO, Time to onset of improvement in Quality of Life from Temperature-controlled Laminar Airflow (TLA) in severe allergic asthma (Respiratory Medicine), February 2019 URL: https://www.sciencedirect.com/science/article/pii/S0954611118303950?dgcid=coauthor | Not relevant here. | |
| | WS | The Cochrane review of IV versus Nebulised beta2 agonists is severely flawed and requires re-assessment. The doses of IV magnesium sulphate | Not relevant here and topic not covered by this update. | |

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| | | (1.2-2g over 20 mins) are too low and slow to reach adequate serum levels for smooth muscle relaxation. Overdose is highly unlikely. | | |
| 16.2 | SCRR | Use of IOS to predict long term control | Not relevant here as this section relates to recommendations for research identified by the GDG during the guideline development process. | |
| | SF | It's not clear where these recommendations come from, but they appear rather thrown together and without any logical order/ categorisation. A couple of them are poorly written and/or grammatically unclear, e.g.: "<br><br>Large, long-term trials of FeNO are required to identify cut offs, asthma severity, management protocols, ethnic groups and less affluent settings."<br><br>"In considering treatment with extracorporeal membrane oxygenation (ECMO) what is the definition of life-threatening or standard care?"<br><br>This looks like its copied from a non-UK list:<br><br>"What is the impact of poverty, urban/rural living, ethnicity and different rates of state/private/no medical insurance in the non-US setting?" This is not pharmacologically accurate:<br><br>"Does suppression of IgE or IL5 have any long term effects on the recipient's immune function?"<br><br>In my opinion there are a disproportionately high number of questions related to allergen exposure +/- immunotherapy<br><br>This seems very specific and extremely unlikely to ever be answered by research:<br><br>"What is the clinical effectiveness and safety of ECMO treatment in patients with asthma taking anticoagulants?"<br><br>(typo: "monocloncal") | This section relates to recommendations for research identified by the GDG during the guideline development process.<br><br>The wording and balance of recommendations for research will be finalised prior to publication.<br><br>Spelling of 'monoclonal' corrected. | |
| | PCRS | Non industry funded research comparing MART regimens with alternative regimens allowing dose variation for exacerbations using less expensive inhalers. | Not relevant here as this section relates to recommendations for research identified by the GDG | |

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| | | Cluster randomised trial of the routine provision of emergency pMDI and spacer packs for patients at risk of attacks. | during the guideline development process. | |
| | WS | 1. IV Enoximone is used for status asthmaticus in half of Dutch Hospitals and is in helicopter retrieval guidelines.<br>2. Dose of IV magnesium sulphate which will prevent tachycardia of subsequent IV beta2 agonists<br>3. Use of epinephrine auto-injectors for acute asthma | Not relevant here as this section Not relevant here as this section relates to recommendations for research identified by the GDG during the guideline development process. | |
| Annex 1 | | | | |
| | ARNS | Information not available in the draft so unable to comment. | Annexes were available separately on the consultation webpage throughout the consultation period. | |
| Annex 2 | | | | |
| | ARNS | Not included in draft | Annexes were available separately on the consultation webpage throughout the consultation period. | |
| Annex 3 | | | | |
| | ARNS | Not included in draft | Annexes were available separately on the consultation webpage throughout the consultation period. | |
| Annex 4 | | | | |
| | ARNS | Not included in draft | Annexes were available separately on the consultation webpage throughout the consultation period. | |
| Annex 5 | | | | |
| | ARNS | Not included in draft | Annexes were available separately on the consultation webpage throughout the consultation period. | |
| Annex 6 | | | | |
| | ARNS | Not included in draft | Annexes were available | |

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| | | | separately on the consultation webpage throughout the consultation period. | |
| Annex 7 | | | | |
| | ARNS | Not included in draft | Annexes were available separately on the consultation webpage throughout the consultation period. | |
| Annex 8 | | | | |
| | ARNS | Not included in draft | Annexes were available separately on the consultation webpage throughout the consultation period. | |
| Annex 9 | | | | |
| | ARNS | Not included in draft | Annexes were available separately on the consultation webpage throughout the consultation period. | |
| Annex 10 | | | | |
| | ARNS | Not included in draft | Annexes were available separately on the consultation webpage throughout the consultation period. | |