COMMENTS RECEIVED FROM EXTERNAL REFEREES AND OTHERS

British guideline on the management of asthma

Section	Comments received	Development group response
General		
	Summary AstraZeneca acknowledges some of the issues surrounding the use of beclomethasone dipropionate (BDP) equivalence as a means of comparing the relative potency of inhaled corticosteroids but considers it remains the best method of comparing relative potency in spite of its flaws. AstraZeneca recognise that Figure 2 is extremely important as it likely to be the most utilised aspect of the new SIGN guidelines as a quick reference guide to the treatment pathway and as such AstraZeneca considers that it needs to be able to "stand alone AstraZeneca disagree with the current recommendations for Maintenance and Reliever Therapy (S/MART) and believes this approach is a clinically appropriate and effective treatment option for uncontrolled patients on low dose ICS. **References** Cates Christopher J, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2013(4) DuoResp Spiromax 160/4.5 Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/medicine/29186 Fostair 100/6 Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/medicine/21006 Kew Kayleigh M, Karner C, Mindus Stephanie M, Ferrara G. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. Cochrane Database of Systematic	*See response to AZ under section 7.*

	Reviews 2013(12) Kuna P et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract 2007; 61: 725–736 NRAD: Royal College of Physicians. Why asthma still kills. The National Review of Asthma Deaths (NRAD) May 2014 (available from https://www.rcplondon.ac.uk/sites/default/files/why-asthma-still-kills-full-report.pdf) O'Byrne PM et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005;171(2):129-36. Rabe KF et al. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet 2006; 368(9537): 744-753. Schulte M et al. Handling of and Preferences for Available Dry Powder Inhaler Systems by Patients with Asthma and COPD. J Aerosol Med Pulm Drug Deliv 2008; 21(4): 321-328. Symbicort Turbohaler 200/6 Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/medicine/4821	
	As layperson I am of course primarily concerned with Patient Versions of outcomes and have not commented indepth on detailed clinical information Training seems vital to ensure consistently high and safe care for patients Embraces advances and looks at range of evidence Outcomes should improve as a result of adherence particularly in teenage groups	*Agree.* *Thank you.*
	Thank you for the opportunity to comment. I believe the document changes are comprehensive and accurate. The presentation and layout are clear and easy to follow. Regards	*Thank you.*
	Excellent, easily readable guideline with many helpful new additions now based on 964 refs -	*Thank you.*

	a far cry from 2 separate papers in the BMJ in 1990! Well done to all.	
	As I've said above, this document is a great text for those interested in asthma - great for researchers looking for ideas - it needs to be redesigned for practising generalist clinicians - much simpler and devoid of inconsistencies and should include a short practical summary	*Thank you. A Quick Reference Guide, summarising the main points, will be published at the same time as the full guideline.*
	Getting rather long to read (even for respiratory interested, keen individuals) we are not sure if this can be achieved - but an abridged version should be considered	*The accompanying Quick Reference Guide is a very abridged version of the full guideline.*
	Overall a good development on the previous guide, but certain sections could do with being more prominent. Maybe this will be in the executive summary when published.	*Not specified which sections should be more prominent, but see comments on other sections.*
	Thank you for allowing me to comment on this update. The guideline is of high quality and provides a great resource for clinicians. Thank you to the GDG members involved in updating this guideline.	*Thank you.*
	This is a welcome and helpful update to the long established and widely respected BTS/SIGN guideline. The comprehensive nature of the guideline, its established rigorous methodology and the extensive range of expertise and experience behind its production should prompt a re-assessment of the wisdom and value of NICE undertaking the production of separate guidelines on the diagnosis/monitoring and management of asthma. NB – we conducted an online survey of our members via Survey Monkey and had 28 responses. Wherever percentages are given of our members' views, they relate to this survey. We have only included results for questions where the number of respondents was 20 or more. Overall 52% of responders to our survey considered the guideline update to provide practical guidance in a useful format. (scoring 8/9/10 out of 10) A further 38% scored 5/6/7 out of 10. In broad terms we think the changes to the guideline will be received well. The main points of contention are: - reliance on trial of treatment for diagnosis - when evidence is poor and this will be at odds with GINA - and possibly NICE.	*Thank you.* *A Quick Reference Guide highlighting key points in the guideline will be published along with the full guideline.* *Thank you.* *The term 'trial of treatment' should not have appeared in the text as it has been replaced with the term*

	- loss of BDP as a reference product - in favour of banding ICS into strength categories. This is only helpful if products placed into bands are actually placed accurately and consistently, and are easily accessible to clinicians at the point of prescribing. There is a danger this will cause confusion, and on balance we think this could be more confusing than retaining the BDP reference system. Certainly if the new system of ICS banding by strength is adopted the rationale /evidence for that categorisation must be transparent (e.g as an appendix) and a system set up for categorisation of new ICS drugs that is equally transparent. Serious thought should be given to how the banding could be made easily accessible by working with BNF and the GP computer companies to disseminate this through their channels/systems. - loss of numbered steps in favour of descriptive labels - and division of current step 3 into 2 separate steps - unclear whether this will cause confusion in real world - lower threshold for referral - may increase numbers of referrals to secondary care - the GINA principles of assessment and management have not been adopted i.e the concept of optimising current control and reducing future risk. Some commented that it is getting very long and wordy and there is a need for an abbreviated version for those without a specialist interest in asthma. Unfortunately some of the lessons learnt from the National Review of Deaths (NRAD…Royal College of Physicians London 2014) seem not to have been recognised in the Assessment part of this document e.g the use of >12 short-acting beta-2 agonists per year as an indicator of high risk. Summary of PCRS-UK views overseen by Dr Duncan Keeley and Dr Kevin Gruffydd Jones.	*'monitored initiation of treatment' which is described in Table 3, and this has now been corrected.* *The problem is that there is no gold standard diagnostic test. At some point, the clinician has to decide that the probability of asthma is high enough that they are going to commence treatment. Because of the lack of absolute proof, it is important this initiation of treatment is monitored closely.* *No response needed.* *Thresholds for referral in Figures 2 and 3 have been adjusted.* *This is a monitoring issue and was not within the scope of this update.* *A Quick Reference Guide will be published at the same time as the guideline.* *The point about use of >12 SABA in 12 months has now been added to section 9.1.2.*
	As a patient I found some of this difficult to understand, and hope my comments are in the right boxes, and have been helpful, and I have not wasted your time.	*The full guideline is written for healthcare professionals, however, comments from non-specialists are welcome. Updated versions of the accompanying patient booklets will be available following publication of the full guideline*
	RCP is grateful for the opportunity to respond to the above consultation. We wish to	*This relates to sections 6.1.10 and 6.2.4 which were not within the*

	highlight the recently published joint working party of the RCP and Royal College of Paediatrics & Child Health (RCPCH), Every breath we take: the lifelong impact of air pollution. We would strongly recommend changes in line with our comments and would be happy to discuss further the development of any tools for clinicians to discuss air pollution with their patients.	*scope of the current update. This topic will be considered for review in the next update.*
	I am commenting on behalf of the RCP/RCPCH working party on air pollution. I represented (as vice chair) the RCPCH on the working party and co-authored the 2016 report "Every Breath we take; the lifelong impact of air pollution". We strongly recommend that the Guideline's comments about air should take into account our report (based on a comprehensive review of recent publications). We would be happy to support re-drafting of this section.	*This relates to sections 6.1.10 and 6.2.4 which were not within the scope of the current update. This topic will be considered for review in the next update.*
	Sorry, there was no box for commenting on section 1.3.2. "Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards." There is now a competency framework for all prescribers - currently being updated by RPS (originally published by NICE in 2012) and due for publication June 2016. http://www.rpharms.com/what-we-re-working-on/single-competency-framework-for-prescribers.asp "Healthcare professional" versus "health professional" - differing terminology used throughout - should a consistent approach be taken?	*This is standard text in all SIGN guidelines and is taken from the BNF.* *Specific frameworks or other documents are effectively encompassed by the existing statement.* *Agree. 'health professional', changed to 'healthcare professional'.*
	Thank you. Logical and readable.	*Thank you.*
	Questionnaire could've been less exhaustive.	*This may be referring to the consultation comments form.*
Section 1		
1.1	Significant and increasing numbers of patients with this condition. Particular challenges presented with children and especially teenagers. Compliance Issues - need for Patient Information on treatments and in particular variations in inhalers	*No response required.* *Agree* *Agree. This is outwith the scope of the guideline. Information on treatments and inhalers will be included in the updated patient*

		booklets.
	Clear and helpful	*Thank you.*
	NPPG wish to support this guideline which will have health benefits for both children and adults with asthma.	*Thank you.*
	Asthma management, care and treatment are changing rapidly as is the evidence base and the SIGN/BTS guideline puts research into practice in a pragmatic acceptable way. Concentrating on a few areas rather than the whole guideline allows relevant timely updates. This time a complete revision of the section on diagnosis, a major update to the section on pharmacological management of asthma, and updates to the sections on supported self-management, non-pharmacological management of asthma, acute asthma, difficult asthma, occupational asthma, and organisation and delivery of care. I particularly like the change from asthma exacerbation to asthma attack.	*Thank you.* *Updates are based on the results of scoping searches to identify where relevant new evidence is available.* *Thank you. This change was made in SIGN 141, published Nov 2014.*
1.1.1	Date and advances since	*Unclear as to what this comment relates.*
	Clear & concise	*Thank you.*
	No major change – no comment.	*No response needed.*
	Useful but could include key areas that do not yet have adequate evidence for clear recommendations and remain of concern	*Not stated what key areas this comment refers to. Recommendations for research are listed in section 16.2.*
	Robust evaluation of the most up to date evidence	*Thank you.*
1.2.1	Comprehensive and covering developments since last guideline regarding patient involvement in self management and their awareness of drug and inhaler variations and effects	*Thank you.*
	Clear	*Thank you.*
	No major change – no comment.	*Thank you.*
	Helpful	*Thank you.*
	The SIGN guidelines advise that the guides are British guidelines which may cause some confusion with the Draft NICE guidelines.	*The SIGN/BTS guideline has always been a British guideline and was first published in 2003, then updated annually until 2012 and*

		biennially since.
	Remain unchanged and relevant.	*Thank you.*
1.2.2	Primarily clinicians across a wide spectrum in acute and community settings	*Covered by existing first sentence.*
	Clear	*Thank you.*
	No major change – no comment.	*Thank you.*
	If this is intended for use by GPs and nurses (i.e. non-asthma specialists) then the document needs major revision. It is a good resource for clinicians with an interest in asthma. So I suggest amending the description of the guidelines target audience	*A Quick Reference Guide, summarising the key points will be published along with the guideline.* *We would be pleased to co-operate with GP/nursing/other groups wishing to develop summaries specific to the needs of their membership.*
	Appropriate, should also include education staff with regard to GIRFEC for children in Scotland	*Teachers are mentioned in the existing text.*
	Unchanged from previous guideline	*No response needed*
Section 2		
General	Detail on diagnosis, monitoring, self management and range of pharmacological interventions comprehensive and useful as fed down to patients	*Thank you.*
	Clear	*Thank you.*
	Should include mention of environmental pollutants to be reduced or avoided by individuals with asthma and children at risk. Include specific advice to have a cumulative record of systemic steroid exposure for children who have several viral induced asthma attacks over the winter, many issued by out of hours services	*A detailed consideration of environmental pollution was not within the scope of the current update. Currently, no recommendations are made about environmental pollutants so cannot be included in key recommendations.* *This relates to section 7.6.1 which was not within the scope of the current update. It is unclear what benefit would arise from recording this information unless recording was linked to specific triggers or actions.*
	More needs to be said about the Asthma patient who is not wheezing, but is still struggling to breathe. Beware the silent chest.	*A silent chest is already explicitly highlighted as a sign of life-threatening asthma (table 11, 12, 13, and the text in section 9.7.1)*
	Unchanged.	*Key recommendations have been*

		updated in line with changes in the guideline.
2.1.1	Good definition Organisation of diagnostic services vital	*Unclear what this refers to as no definition is given in this section.* *We have described some existing diagnostic services but there is no evidence of which model is the most effective.*
	Third Grade D recommendation - not sure why there is breathlessness and dyspnoea?	*Agree. This should have read 'chest tightness'; dyspnoea deleted.*
	I felt that effective inhaler technique was not deemed as important as it should be. p5"if response is poor.....and inhaler technique AGAIN..." might be suffucient. Add word again.	*Disagree. This GPP relates to initial diagnosis.*
	Page 5, section 2.1.1: 3rd and 4th bullets points of the GPP are open to variable interpretation. What is a "good objective" response? What is "poor? In most peoples' minds there could there be a middle category between the two? I would suggest define as best you can what constitutes a good response, and say that other patients need further assessment as described in the 4th bullet.	*Agree. Definitions have been added to Table 3.* *'Good' is 'substantial increase in lung function and/or clinically important improvement in symptoms'.* *Poor now includes 'or equivocal'.*
	No mention of PEF here - though it is referred to repeatedly throughout the document - not logical to omit PEF completely. Secondly as asthma is a chronic remitting/relapsing condition it seems illogical to promote spirometry so strongly (despite stating in 3.3.2 that it is unreliable in 50% of cases tested) without a very clear strategy for busy generalists for dealing with cases suspected of having asthma, where the spirometry test is normal in clinic. In these cases, as suggested in the document later (in a number of places) a home PEF meter may be helpful in confirming the presence of reversible airflow obstruction.	*We have now specified both spirometry and PEF in table 3.* *Variable PEFs and spirometry are highlighted in table 2 as providing useful corroborative evidence. We have also added this to the GPP in section 3.3.2.*
	In relation to both occupational risk and insurance etc it would be helpful to clarify how the official status of 'inactive asthma' - i.e. a history of childhood asthma now requiring no regular prophylactic treatment *(sic)*	*Our definition of inactive asthma is the pragmatic one of 'asthma code ever' plus no prescription in the previous 12 months (section 3.1.3). We have not considered the evidence for future risk (section 3.5).*

	NPRANG is please to see that the NICE quality standards are incorporated into the guidelines. Assess status with a validated symptom questionnaire and/or lung function... suggests that it is ok to rely on a questionnaire - maybe should be amended to explain that peak flows/ spirometry alongside a validated questionnaire would be best.	*Thank you. These were added to the previous update (Nov 2014).* *The advice is applicable to children as well as adults, some of whom may not be able to undertake lung function tests. The structured clinical assessment recommendation states 'ideally corroborated by variable PF'. We have now used this wording in the GPP related to initiation of treatment.*
	54% of our member survey responders felt that the key recommendations for diagnosis would be straightforward or easy to implement. 21% felt they would be difficult to implement while 25% were unsure. While it was felt that a balance of clinical judgement with objective testing was right, others raised logistical issues – the time required to implement diagnosis in line with the guideline in primary care, having to repeat tests/visits over time since it is a fluctuating condition, and catching patients to carry out spirometry when unwell/symptomatic was considered a challenge.	*Thank you for this helpful overview of responses.* *The initial structured clinical assessment is based on historical PEFs/spirometry readings (so making good use of past information, not generating new readings). We have added the word 'historical' to table 2* *'Catching patients to carry out spirometry when unwell/symptomatic' is a major practical limitation of spirometry. However, PEF is a crucial component of assessing the severity of an exacerbation and may very conveniently be compared to PEF when the patient is recovered. This is reflected in the initial structured clinical assessment, and has been added as a GPP in section 3.2.3.*
	Excellent guideline to see that FeNO monitoring and or diagnostic use has been labelled as a mainly secondary care tool. This emphasises that there is no gold standard test and has a very useful table outlining the negative and positive predictive values of each test. The concept that making a diagnosis of asthma may evolve over time is very useful and that repeated measurements may be needed.	*Thank you. The GDG felt that these were important points to get across.*
	Good to see objective testing and a pragmatic approach with a focus on looking at variation over time. Clinical assessment remains important and trials of treatment. Focus on obesity very important.	*Thank you.*

2.1.2	Useful support for practices especially practice nurses essential this is presented to patients as easily accessible	*The patient booklets will be updated in line with the main guideline.*
	Risk should be included here. Key recommendation of NRAD and described nicely in Table 10. If the guideline is intended to change behaviour, in my view, this is one of the two areas needing change – recognition of risk (the other is a post attack review with optimisation of care)	*This GPP is from section 4.4 on monitoring which was not within the scope of this update.* *Assessing future risk will be considered for inclusion in the next update.*
	What is meant by asthma training for monitoring asthma in Primary Care? There should be a record of all the asthma medications received by the patient and not solely what is prescribed and dispensed via Primary Care to allow accurate review of overall control. Some patients receive more than a single dose of medication in ED at hospital or via Out of Hours services or when away from home and may self manage on stored medications.	*Unclear to what this comments relates.* *This GPP is from section 4.4 on monitoring which was not within the scope of this update.*
	Unchanged	*No response needed.*
2.2	Will improve outcomes as compliance and other issues covered	*Thank you.*
	As above - advise that all community pharmacists have asthma training as they are now offering advice to many patients	*Unclear to what this relates. With the exception of section 5.4, Section 5 was not within the scope of the current update.*
	Napp fully support the concept of patient self-management. With the encouragement of patient self-management through personal asthma action plans, we believe that patients should have access to inhalers with easy to understand dose counters to enable them to monitor use and order a repeat prescription when necessary. Without a dose counter, and with the introduction of flexible dosing product licenses, patients may be using an empty inhaler without realising. Dose counters are an important feedback mechanism that can help to enhance patient adherence, reduce wastage and enhance self-management	*These possibilities are all covered in section 5.4.2. We have now added dose-counters and reminders to the GPP in section 5.4.3.*
	Unchanged	*No response needed.*
2.3	Area of great importance with relevance to exercise regimes.	*Thank you.*

	A useful section, I think including strategies in this section that improve nasal airway function should be emphasised as part of the 'one airway' approach for asthma control	*With the exception of section 6.1.8 and 6.2.8 on weight management, Section 6 was not within the scope of the current update.*
	Agree.	*Thank you.*
	Weight management section highly relevant and good to see this included. Rarely addressed.	*Thank you.*
2.4	Good description of range of medications and devices	*Thank you.*
	I welcome the specific advice to avoid generic prescriptions as have had patients adversely affected by this change made by pharmacy adviser in Primary Care	*Thank you.*
	The section on pharmacologic management rightly provides recommendations to increase inhaled corticosteroid doses in sub-optimally controlled asthma - however, could this section also introduce the concept of stepping down treatment in appropriate patients with well controlled asthma?	*'Stepping down' is covered in section 7.10.*
	Are we pushing for use of combination products earlier? Do the guidelines push any more than the last did in respect of getting the device right and changing device before increasing doses – in that respect, this pushes HCPs even more down the combination route and potentially still on an MDI – shame they don't tackle lack of correct use of MDI. HCPs revert to MDI and spacer again. It is still not clear that if a pMDI fails, or is unable to be used by a patient that DPIs can be used, DPIs can be used prior to a pMDI and certainly prior to a combination product (when HCPs go to a DPI invariably). Still saying MDI and spacer for children aged 5 – 12 and then for adolescents only accepting a move away from MDI and spacer for bronchodilator away from home. Any child can hate the spacer and they acknowledge that many DPI's equally as effective as MDI and spacer – why can children also use a DPI, when they are licensed for children as well? Could this section also say "walk in centre" NICE quality statement 10: People who received treatment in hospital or through out-of-hours services for an acute exacerbation of asthma are followed up by their own GP practice within two working days of treatment.	*It is unclear as to what these comments specifically relate.* *Inhaler devices are covered in section 8 which was not within the scope of the current update.*
	Excellent attempt to try and unravel particularly	*Thank you.*

	the equivalent doses of inhaled steroids. Also good to see clear evidence on how and where to use combination inhalers. (Ian Williams)	
	Agree.	*Thank you.*
2.5	AstraZeneca welcomes the move by SIGN to recognise the importance of prescribing by brand name linking to patient adherence and safety. The inhaler market is increasingly complex, and with the entry of an increasing number of branded generics in different inhaler devices, there is a need for highly respected organisations such as SIGN to provide this guidance. When a patient is inadvertently switched at community pharmacy level, there is a risk they will not receive counselling from their healthcare provider about the new medication and device: this may result in poor inhalation technique.[Schulte] In addition, two different devices albeit containing the same molecules may have differences in their licenses. For example, the combination of budesonide and formoterol is available in both the Turbohaler and the Spiromax device, however they differ in licensed age range and method of operation of the inhaler. Therefore, whilst we welcome this addition to the guidance, due to the seriousness of the potential consequences of generic prescribing of inhalers in terms of patient safety and unlicensed prescribing, we urge SIGN to provide stronger guidance around this point. AstraZeneca suggests: "Branded prescribing of inhalers is recommended whenever possible as this will ensure the patient receives the device that they have been trained to use. Generic prescribing may lead to patients being given an unfamiliar inhaler device which they are not able to use properly, which may have an impact on their adherence and outcomes". References: Schulte M et al. Handling of and Preferences for Available Dry Powder Inhaler Systems by Patients with Asthma and COPD. J Aerosol Med Pulm Drug Deliv 2008; 21(4): 321-328.	*See response to AZ in section 8.4.*
	Coverage of the implications of generic inhalers essential. Commend	*Thank you.*
	Include the need for children to have specific teaching and help for adults to help the child to use inhaled medications #Also advice to rinse the mouth and wipe around the mouth for children who use face mask with spacer	*This relates to section 8 which was not within the scope of the current update.*

	Napp support the recommendation made in sections 2.5 and 8.4 that generic prescribing of inhalers should be avoided due to the risk of substitution with an unfamiliar device for some preparations. Also, as stated in response to the self management section; Napp believe that patients should have access to inhalers with easy to understand dose counters to enable them to monitor use and order a repeat prescription when necessary. Without a dose counter, and with the introduction of flexible dosing product licenses, patients may be using an empty inhaler without realising.	*Thank you.* *Dose-counters, reminders and other strategies to improve adherence are discussed in section 5.4.*
	We would like to see the evidence base for this statement as the prescribing of many branded inhalers can be equally challenging. However, there have been cheap imports of variable quality and perhaps this is what this refers to.	*This is a GPP and not a recommendation because evidence to support it is lacking but the GDG agreed it was an important point that needed to be made.*
	I welcome the statement on generic prescribing of inhalers. In my Health Board (NHS Fife), the Respiratory MCN recommends that all inhalers are prescribed by brand (except salbutamol MDI) due to device variability. May I ask the committee to consider whether it is acceptable that salbutamol MDI is an exception to the recommendation to prescribe by brand?	*Thank you.* *The guideline group suggest that no exceptions are made.*
	Agree with emphasis on advice against generic prescribing. Unfortunately this is happening. Often due to medicines management or dispensaries.	*Thank you.*
2.6.1	Commend range and detail	*Thank you.*
	Page 7, section 2.6.1: Grade C rec about oxygen admin. The 2nd sentence is incorrect; literally interpreted it is telling people to seek a lack of pulse oximetry. I know that people will understand what is really meant, but how about: “Do not delay oxygen admin in the absence of pulse oximetry, but commence monitoring of SaO2 as soon as it becomes available”?	*Agree. Text changed as suggested.*
	Insert ‘via a spacer’ after deliver high dose inhaled B2 agonists.	*No change required. The method of delivery – via spacer or nebulised – depends on the initial assessment of the patient.*
	Happy with changes.	*Thank you.*
	Emphasise the 48 hour review - to decide on length of oral steroid Px and to optimise care	*NICE quality statement 10 that emphasises review within two*

	on the basis of risks identified (table 10)	*working days is included with 2.6.3.*
	The RCGP welcomes the recommendations on oral steroids doses which are clear and higher than many of us are used to in Primary Care.	*Doses are not specified here but are in the related text in section 9.3.3 which has not changed.*
	Agree, but it is important to stress that "controlled" does not imply that if the PaC02 is high this is in an indication to lower the Fi02 i.e. avoid any confusion with the management of COPD.	*See response to RCPE in section 9.3.1.*
	Should the 4th point be oral steroids?	*No. While oral steroids are used in the majority of circumstances (see 9.8.4 where use of oral steroids is emphasised) there are situations, eg vomiting, where IV steroids may be appropriate.*
2.6.2	Detail on outreach to children in variety of settings useful and essential	*Unclear as to what this comment relates.*
	Very good	*Thank you.*
	Happy with changes.	*Thank you.*
	Emphasise the 48 hour review - to decide on length of oral steroid Px and to optimise care on the basis of risks identified (table 10)	*NICE quality statement 10 that emphasises review within two working days is included with 2.6.3.*
	Specify the need to use of appropriate size probes for oxygen saturation recording for children Recommend use of humidified oxygen when high flow rates are used to reduce risk of drying the nasal mucosa with consequent adverse effect on lower airways Clarify if clinically determined duration for systemic steroids can be reduced as well as extended The section on viral wheeze in infants is confusing and rationale for change of advice is not explained. The acute severe section is much better than last guidleine	*1 & 2) These relate to section 9.8.1 which was outwith the scope of the current update. Such decisions depend on local factors, such as the particular oximeter used, and as such are too detailed for inclusion in a guideline .* *Children rarely require high flow rates for prolonged periods. Most oxygen will be administered with cold water humidification.* *3) The GDG consider that this is covered by the existing section 9.8.4.* *4) There is no section on viral wheeze in infants but viral wheeze in children is discussed at various points, including section 9.8.4, and existing text reflects current evidence.* *5) Thank you.*
	Easy to remember doses of oral steroids.	*Thank you.*

	No changes.	*No response needed.*
2.6.3	Advances outlined	*Unclear as to what this comment relates.*
	Emphasise the 48 hour review - to decide on length of oral steroid Px and to optimise care on the basis of risks identified (table 10)	*NICE quality statement 10 that emphasises review within two working days is included with 2.6.3.*
	Good section on high risk groups, there should be advice for those who do not read in relation to PAAPs, for children the PAAP should be copied for Nursery or school, updated annually or after any change of treatment	*Unclear as to what this comment relates.* *PAAPs are covered in section 5.2.2.*
	NPRANG would like to raise that although we agree primary care are informed within 24 hours of A/E visit by fax/ email and is and should be gold standard many of the GPs we have in the areas we work (we are a national group) do not have a secure emails system.	*This implementation issue is outwith the scope of the guideline.*
	There is much said about the wheeze, but little about Asthma where the patient does not wheeze, but still is struggling to breathe. The silent tight chest, which is not universally known as a danger sign and symptom of severe Asthma.	*Unclear as to what this comment relates as wheeze is not mentioned here or in the related text in section 9.6.3.*
	No changes.	*No response needed.*
2.7	Issues such as over oxygenation Consideration of drugs for those not responding (MgSO4). General increased vigilance and support outlined	*This is covered in detail in the acute section.*
	Clear & easy to read	*Thank you.*
	Apart from adherence check the inhaler device has not been changed. The mention of swimming pool asthma is welcome - could include advice that the effect of chlorinated water is worse later in the day when fumes accumulate especially when the atmosphere has been warm all day	*This is covered in section 2.5 and section 8.* *This may relate to section 11.4.4 which was not within the scope of this update.*
	See above. I am pleased to see the advice for NHS111, but they also need to know that it is pointless to keep telling someone to keep taking their inhaler,when they are already using Salbutamol nebulizer, and at this point an Ambulance rather than an hour wait for a	*Unclear as to what this comment relates.* *NHS 111 is mentioned in section 9.2.3 but not in the context of difficult asthma to which section 2.7 relates.*

	doctor is more appropriate.	
	No changes.	*No response needed.*
2.8	Comprehensive section including recommendation on breastfeeding	*Thank you.*
	Suggest additional asthma reviews during pregnancy as respiratory function changes	*Asthma in pregnancy was not within the scope of the current review.*
2.9	Excellent considering workplace issues today	*Thank you.*
	Please include school exposure as a form of occupational asthma for some individuals	*Unclear as to what this comment relates.*
	Agree.	*Thank you.*
	Not really sure of the difference between occupational or other work-related asthma.	*Occupational asthma refers to asthma thought to have been caused by exposure to a specific substance at work (eg flour in bakers). Work-related asthma is where exposure to a substance in the workplace is thought to aggravate existing asthma.* *The GPP has been amended to remove reference to work-related asthma as section 13 does not cover this and this was outwith the scope of this update.*
Section 3		
General	All the sections below are satisfactorily covered	*Thank you.*
	I was delighted to see the new Diagnosis chapter - it is certainly a major advance on the 2011 version and much more practical than the tortuous NICE algorithms published in Jan 2016. The amalgamation of Diagnosis in Adults and in Children also helps to reduce repetition. Well done to Hilary and her team!	*Thank you.*
	Good	*Thank you.*
	I fully appreciate the difficulty of capturing a complex process in simple, accurate recommendations. I like the structure of the chapter with overarching principles, data on the tests, and then a practical approach. However, there are places in the chapter, particularly section 3.3, where the advice is not precise as it could be.	*Precision is difficult in the context of probabilities and in the absence of pragmatic evidence.* *We hope that the revisions we have made to the tables and GPP have now improved clarity*

	Helpful and improved from last edition	*Thank you.*
	The extensively revised section on diagnosis is important and very useful. In particular, in its emphasis on the need for the use of time and repeated multi-modality assessment in making and reviewing an asthma diagnosis , and the fact that all tests – including spirometry and FeNO, may be normal in persons with asthma . This emphasises that there is no gold standard test and has a very useful table outlining the negative and positive predictive values of each test. The concept that making a diagnosis of asthma may evolve over time is very useful and that repeated measurements may be needed. Section 3.3 The practical approach to diagnosis laid out logically and the initial clinical assessment section very practical and thorough. The value of exercise testing is stated but the text does not state which exercise tests can be used in everyday clinical practice (rather than in the specialist setting). 71% of our member survey responders considered the guidance on diagnosis to be clear or very clear (20/28). 18% considered them somewhat unclear. Some commented that they liked the flexibility to use their clinical judgement. While others liked the clarity and simplicity of Fig 1 – the diagnostic algorithm.	*Thank you. The GDG felt that these were important points to get across.* *Thank you.* *Thank you* *There is no evidence to support a statement on practical exercise tests in primary care.* *Thank you.* *Thank you.*
	Agree that diagnosis should be clinically based.	*Thank you.*
3.1.1	good	*Thank you.*
	Asthma is not defined in SIGN/BTS - suggest use the new GINA definition here Also need to define, discuss differentiation and explain: Chronic Asthma with Fixed Airflow Obstruction (Read Code H335 - which was created during NRAD because a number of consultants and GPs had erroneously diagnosed COPD in people with longstanding, chronic asthma that had become fixed. (This is a very important omission from this diagnosis section)	*The GDG agreed that there is no clear definition of asthma, hence the 'definition' given in section 3.1.1.* *Key diagnostic features of COPD are included in Table 5. A comment about fixed airflow obstruction in asthma has now been added to section 3.3.4.*

	Also suggest a table (like GINA) to help generalists differentiate asthma from COPD from ACOS ? and identify Chronic Asthma with Fixed Airflow Obstruction	
	Agree.	*Thank you.*
	Symptoms important and good to see the recognition that both objective tests and clinical assessment isn't always robust.	*Thank you.*
3.1.2	We welcome the clear affirmation that there is 'no single diagnostic test for asthma'. The guideline should note the aspiration for more accurate diagnostic tools and the urgent need for research in this field. The guideline could helpfully recommend research such as the development of appropriate diagnostic tools that can identify biomarkers for different asthma phenotypes.	*Agree. The recommendations for research in section 16.2 have been rationalised and now explicitly include development of new biomarkers, as well as more accurate diagnostic tests.*
	Very useful	*Thank you.*
	3.1.2, Page 9, para 1, line 3: Why say "and/or"? Ideally we would like evidence of both reversible airway obstruction and airway inflammation. I appreciate it is hard to achieve, but that is what we should seek to demonstrate if possible.	*And/or changed to 'or; because individual tests only address one of the two objectives.* *The GDG consider that the existing text is appropriate because whilst variable airflow obstruction is central (see 'definition' in 3.1.1), evidence of airway inflammation cannot always be found, especially in children.*
	Agree.	*Thank you.*
	Important factor of false positives and negatives with push for FeNO diagnostics.	*Thank you.*
3.1.3	We welcome the emphasis that 'diagnostic tests are typically performed at a single point in time whereas asthma status varies over time' (para 1). Asthma is highly variable and symptoms will change over non-specific timeframes thereby making a diagnosis from a single snapshot in time near impossible. We welcome the emphasis on repeat investigations in the event of diagnostic uncertainty. Trial of treatment and repeat review of diagnosis and are an essential part of formal diagnosis. Tests such as measurement of peak expiratory flow (PEF), for instance, can be very helpful in diagnosing asthma when conducted sequentially by an engaged and appropriately trained patient.	*Thank you.* *Thank you.*
	Useful	*Thank you.*

	3.1.3, Page 9, para 2, line 1: Better expressed as “more likely to result in false negatives”	*Agree. Text changed to “...an ‘inactive’ period may result in false negatives.”*
	Agree, and this is very important.	*Thank you.*
	Variable disease recognition important and lack of gold standard test.	*Thank you.*
3.2	Useful	*Thank you.*
	The text might flow better if the 2nd (starting after the short 1st sentence) & 3rd paras are moved to under a new heading 'Objective Tests' put after Spirometry and BDR. Then Direct & indirect challenge tests and PEF monitoring and Tests to Detect Eosinophilic (Airway) Inflammation would follow logically.	*Symptoms/signs were separated from objective tests in an early version, but were moved to this format to emphasise that symptoms/signs/lung function/inflammatory markers are all aspects of the diagnostic process.*
	good	*Thank you.*
	Please put table 1 into an appendix - this is great for pundits and those keen on 'analysis paralysis' (as Eric Bateman stated once to try persuade guideline developers to focus on practicalities rather than high flying academia). This table only serves to confuse - the text states that the data is confusing and unhelpful in making clinical decisions - suggest stick to that and refer to it in an appendix.	*Guidelines have many audiences. Clearly a matter of preference, but on balance the table seems to be appreciated by many reviewers. Section 3.3 provides practical advice for those who do not want the detail.* *We have deliberately signposted the function of the different sections at the beginning of the chapter.*
	very useful	*Thank you.*
	Agree.	*Thank you.*
	Reinforcement of the importance of individualising diagnosis.	*Thank you.*
3.2.1	We suggest that the following statement could cause confusion: ‘Almost all children with asthma have a cough, wheeze and/or exercise induced symptoms, but only about a quarter of children with these symptoms have asthma.’ (Paragraph 1) The studies cited do not clarify this statement. We note that wheeze is often viewed by healthcare professionals as synonymous with asthma. Anecdotally, people with asthma have told us that their healthcare professional had initially discounted an asthma diagnosis on the basis of an absence of wheeze. While wheezing is one of the most common symptoms of asthma and is indicative of	*We have clarified that these symptoms will be intermittent to avoid the concern that asthma might be discounted if a patient does not have wheeze at the time of the consultation.*

	obstruction of the airways, asthma can occur without wheezing when obstruction involves predominantly the small airways (Morris, 2016). Gong (1990) notes that 'the absence of wheezing in an asthmatic may indicate either improvement of the bronchoconstriction or severe, widespread airflow obstruction'. Clarification that an absence of wheeze is not sufficient to rule out a diagnosis of asthma would be helpful. Additionally, guidance could be given on how to undertake quality auscultation of chests. References Morris (2016), Asthma Clinical Presentation. Medscape: WebMD. Available at:http://emedicine.medscape.com/article/296301-clinical Gong H JR.. Wheezing and Asthma. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990. Chapter 37.Available at: http://www.ncbi.nlm.nih.gov/books/NBK358/	*The guideline already emphasises the need to establish what patients/parents mean when they use the term 'wheeze'. Guidance on how to undertake auscultation is outwith the remit of the guideline.*
	Essential in all diagnostic settings	*Thank you.*
	Well written	*Thank you.*
	Clear	*Thank you.*
	Need to emphasize the need for clinical assessment and consistency of examiner to help confirm or refute the diagnosis - children often see each health professionals only once and rely on the adult to describe their symptoms and signs	*We accept that patients may see different healthcare professionals and have therefore emphasised the importance of maintaining good clinical records both to inform the initial structured clinical assessment (3.3.1), and also to record the basis on which a diagnosis was made (GPP and Table 3).*
	Tight quiet chest.	*This is of more relevance to the acute section. A silent chest is highlighted as a sign of life-threatening asthma in both adults and children*
	Agree.	*Thank you.*
	No comment happy with this. Physician confimed wheeze important.	*Thank you.*
3.2.2	The following statement may cause confusion:	

	‘In adults with obstructive spirometry, an improvement in FEV1 of 12% or more, together with an increase in volume of 200 ml or more, is regarded as a positive test, although some people with COPD can have significant reversibility. A >400 ml improvement in FEV1 to either β2 agonists or corticosteroid treatment trials strongly suggests underlying asthma. In children, an improvement in FEV1 of 12% or more is regarded as a positive test.’ (Paragraph 6) We note that an increase in volume of 200 ml could be due to better performed spirometric technique rather than indicative of asthma. Starren et al (2012) note that erroneous diagnosis of respiratory conditions may be common in primary care due poor spirometric technique (and underuse of spirometry). The above statement might benefit from clarity on the importance of each value to diagnosis, perhaps differentiating between adults and children. If volume is used as a complementary value to aid diagnosis, we recommend specifying that forced vital capacity (FVC) is noted, as per Kim et al (2012) cited in the NICE draft diagnosis guidance to which the above statement refers. References to the importance of good spirometric technique and adherence to appropriate quality standards to allow accurate interpretation would also be helpful. We note that NHS Wales has recently decided to invest in ARTP training to accompany its rollout of spirometry machines for all of primary care – highlighting the importance of training to effective spirometry use. The inclusion of evidence on the increase in volume of 200ml and retention of the second sentence re >400 ml improvement in FEV1 may confuse healthcare professionals as to what each volumetric measure means for an asthma diagnosis. While the reference to >400 ml has been long-standing advice, its meaning - being more strongly associated with a diagnosis of asthma – could usefully be clarified given the preceding sentence. References Starren, E. et al (2012). A centralised respiratory diagnostic service for primary care: a 4-year audit. Prim Care Respir J. 2012 Jun;21(2):180-6. Available at:	*We agree that the thresholds are potentially confusing. This reflects the distinction between a technically significant difference in FEV1 and the substantial difference that is clinically significant. We have adopted the approach used in the NICE COPD guidelines to differentiate a significant difference that is consistent with a diagnosis of COPD, and substantial difference (>400mls) indicative of asthma.* *We completely accept that spirometry must be performed to high quality standards, and this underpins many of our statements. We have now added the words ‘quality-assured’ to the recommendation in 3.2.2.*

	http://www.ncbi.nlm.nih.gov/pubmed/22430040 Kim, T. et al (2012). The Reality of an Intermediate Type Between Asthma and COPD in Practice. Respir Care 2012;57(8):1248 –1253. Available at: http://rc.rcjournal.com/content/57/8/1248.full.pdf;	
	Important for all being trained	*Thank you.*
	Helpful expansion of this section Not sure where to comment on Table 1 (which is generally very good). The comment box as written for Spirometry is confusing - 'half of people with normal spirometry' don't have asthma!? - although I know what you are trying to say.	*Thank you.* *Agree. Wording has been amended to improve clarity.*
	Good. Perhaps need to be more clear that doing spirometry in children over 5 is not always easy. it does depend on their cognitive and physical development.	*Agree. Caveat added that the developmental maturity of the child has to be taken into account and that the operator should be experienced in undertaking paediatric spirometry,*
	As above - what are busy generalists guided to do in those suspected of having asthma, who have normal spirometry in clinic/practice - suggest advise home PEF monitoring and review again in few weeks. Ref also para 3.3.2 - false negative rate of 50%! Not a great example of a 'Gold Standard diagnostic test'. Add that low FEV1 is a risk factor for asthma attacks & deaths - Table 2-2 GINA	*This approach is already suggested in section 3.3.2.* *Agreed.* *This was not within the scope of the current update.*
	Children often find it difficult to perform spirometry when they are ill or if it causes them to cough – then this is even less reliable	*Section 3.2.2 has been altered to clarify that a trained operator is needed, implying that the specific difficulties of undertaking spirometry in children are addressed.*
	page 11 mention spirometry is possible in over 5's in most settings, eludes to one large study (centered on a study population of 3- 90) However does not mention how difficult primary care to find this as they frequently do not have training to be confident and competent ... there is no evidence to support this but lots of anecdotal evidence from around the UK	*As above.*
	(Page 11-13, 3.2.2-4) Diagnostic tests - spirometry, reversibility	*Thank you.*

	testing, tests of inflammation including FeNO – are further expanded in this version of the Guideline, which can only be a good thing. (Page 14-16 Table 1). The table on individual diagnostic tests is new and should further enable HCPs to think about some of the diagnostic options available to them for establishing if asthma is present in patients. (Page 17, 3.3.1) The "initial structured clinical assessment" should be a useful concept for HCPs to actually ensure that they do not just follow QoF templates on the computer when consulting with a potential asthma patient.	*Thank you.* *Thank you.*
	The guideline encourages the use of spirometry where possible, but underlines the need for proper training in performance and interpretation of this test and the relative difficulty of carrying out spirometry in young children. It would be useful to state the age below which the FEV-1/FVC cut off of 0.7 is inaccurate in younger children.	*Thank you. These points have now been further reinforced.* *Section 3.2.2 explicitly states that the lower limit of normal and not a fixed cut-off should be used. A GPP has been added to reinforce this message.*
	It would be useful to state the age below which the FEV-1/FVC cut off of 0.7 is inaccurate in younger children. The value of exercise testing is stated but the text does not state which exercise tests can be used in everyday clinical practice (rather than in the specialist setting) (Dr. Kevin Gruffydd-Jones)	*As above.* *There is no evidence to support a statement on practical exercise tests in primary care.*
	Agree, but these emphasise the preceding comments that the diagnosis of asthma should not be based on isolated symptoms or isolated lung function tests. Many GPs and Practice nurses may find this section confusing.	*In general, comments from primary care have been supportive, perhaps because GPs are experts in handling uncertainty, using clinical assessments to formulate probabilities, and are used to the concept of diagnoses becoming apparent over time.*
	Lower and upper limits of normal important for spirometry but will need a lot of education to embed in general practice.	*Agree. The GDG are clear about the benefits of using LLN and not a fixed ratio and the recommendation has been amended to reinforce this point.*
3.2.3	Again vital and skill sets essential	*Thank you.*
	Page 11 Typo	*'Outwith' is not a typo and is in the OED.*

	Measuring lung function in children under 5 years of age is difficult and requires techniques which are not widely available outwith specialist centres;	
	Last GPP p12 - this is rather vague and it would be better if it was the same as in 13.3.1 - 'Objective diagnosis of occupational asthma should be made using serial peak flow measurements, with at least 4 readings per day'. Again in Table 1 - comment box - should be '1 in 3 people with a positive reversibility test will not have asthma'	*Agree. Amended to specify 4 readings a day.* *Agree. Corrected.*
	Good	*Thank you.*
	Page 12, Grade C rec. Strictly speaking this is a statement rather than a recommendation, and in any case it does not help in terms of saying when a challenge test should be performed. Page 12, Good Practice Point on use of PEF: This does not actually say whether, or when, PEF monitoring should be used in adults. The text in the section above suggests that this test has a role, but the GPP just advises caution when looking at results.	*Agree. Wording changed to clarify when challenge tests should be considered.* *Agree. Wording of GPPs for adults and children amended*
	12% variability PEF in patients recording diurnal readings (Reddel - referred to in GINA section on diagnosis)	*The GDG did not look at thresholds and in general adopted the levels advised by NICE.*
	Should say metacholine and histamine challenge - needs to clearer that mostly done in adults (in paediatrics but mainly done in research centres)	*The recommendation clearly states that this is in adults.*
	Peak flow monitoring – especially when an exercise challenge test is included – retains an important place in asthma diagnosis, and is the investigation of choice where occupational asthma is suspected. The value of peak flow testing in diagnosis, given its low cost, simplicity, high specificity and easy availability in primary care is not given sufficient weight in the guideline. The value of exercise testing is stated but the text does not state which exercise tests can be used in everyday clinical practice (rather than in the specialist setting).	*Agree. The advice on PEF charting has been strengthened.* *There is no evidence to support a statement on practical exercise tests in primary care.*
	Agree. We think this is important and that in adults these tests may be under-used.	*Thank you.*

	Reinforces the variability of Asthma	*Thank you.*
3.2.4	We welcome the statement that fractional exhaled nitric oxide (FeNO) 'provides supportive, but not conclusive, evidence for an asthma diagnosis' (para. 1). In reference to the 'overlap between the levels seen in normal non-asthmatic populations and in people with atopic asthma', we note the study by Lu et al (2014) which clarified that 'FeNO is typically elevated in only patients with atopic asthma'. A large study by Scott et al (2010) also found that 'FeNO behaves as a biomarker of atopy and the "allergic asthma" phenotype rather than asthma itself'. Adding this clarification could be helpful, particularly with respect to the statement on the probability of asthma. We also draw attention to the meta-analyses by Korevaar et al (2015), which found that 'FeNO, blood eosinophils, and IgE have moderate diagnostic accuracy. Their use as a single surrogate marker for airway eosinophilia in patients with asthma will lead to a substantial number of false positives or false negatives.' This could be used to strengthen the point made in paragraph 3. We agree that there is an absence of studies on the use of FeNO in primary care populations. We note the study by Price et al (2013), 'Using fractional exhaled nitric oxide (FeNO) to diagnose steroid-responsive disease and guide asthma management in routine care', which sought to identify patterns of use of FeNO assessment in routine primary care. This may be useful in informing algorithms for the use of FeNO in primary care practice. We note the differences between the BTS/SIGN guideline and the NICE draft guideline on asthma diagnosis and monitoring (January 2015) on the recommended use of FeNO. In the short term, we would encourage discussion to ensure that development of two guidelines promotes consistent, high quality asthma care rather than creating confusion. Over the long term, the development of a single guideline would give clarity to healthcare professionals and people with asthma. References Lu et al (2014). FeNO and Asthma Treatment	Thank you. The point that FeNO suggests eosinophilic inflammation and thus supports a diagnosis of atopic asthma (as opposed to providing conclusive evidence of asthma) is already made in the text. *This was not included in the NICE search (which did not include SRs) that was the basis of this section on diagnostic test accuracy; the GDG did not update these searches. In addition this SR assessed 'Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma' – so detecting eosinophilia, not asthma defined as variable airway obstruction.* *We are aware of this study which uses OPC data to identify use of FeNO in UK primary care. Although it describes how FeNO is being used, the outcomes are use of ICS. It is not a diagnostic study and does not compare FeNO with a gold standard diagnosis.* *The GDG have no wish to cause confusion but have reviewed the evidence using SIGN methodology and have come to different conclusions from NICE. The current update to the BTS/SIGN guideline builds on the approach advocated in previous editions.*

	in Children A Systematic Review and Meta-Analysis. Medicine (Baltimore). 2015 Jan; 94(4): e347. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25634163; Scott, M. et al (2010). Influence of atopy and asthma on exhaled nitric oxide in an unselected birth cohort study. Thorax. 2010 Mar; 65(3):258-62. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20335297 Korevaar, D. (2015). Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. The Lancet 2015; 3(4), 290-300. Available at: http://www.thelancet.com/journals/lanres/article/PIIS2213-2600(15)00050-8/abstract Price et al (2013). Using fractional exhaled nitric oxide (FeNO) to diagnose steroid-responsive disease and guide asthma management in routine care. Clin Transl Allergy Vol. 3. p.37. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3826517/	
	Seem good from a lay perspective	*Thank you.*
	Should the title be Tests to detect Eosinophilic Airway Inflammation or Atopy? This section is now very clear and well balanced.	*Agree. Title changed.*
	p16 Table 1. Should read for Skin prick testing "any positive test (wheal >3mm) in children." To ensure that people know it is the same as in adults	*Agreed. Changed as suggested.*
	Page 13, Grade D rec on FeNO: We're all a bit polarised about FeNO aren't we? This looks to me to be a bit biased against it, but some would say that just reflects my own bias. However, I am surprised this Rec is Graded D, as follows. Firstly, I am not sure that it is fair to say that all the studies are from secondary care. Reference 19 which supports it is from NICE, and their evidence includes more than 8 studies, a majority of which are secondary care but there is at least one community study, and a couple where the population is not stated and may well be mixed. I also wonder why the predominantly secondary care source of the data is highlighted in this recommendation but not in the many others throughout the	*We only used the studies that included 2x2 tables for diagnostic accuracy. Many of the studies in NICE were determining thresholds and we did not look at these.* *Specifically, Kostikas 2008 that screened students for asthma symptoms and Zietkowski 2006 that does not state the source of the participants were not included for this reason. All of these explicitly recruited from secondary care clinics.* *For other tests, some of the studies are from primary care.*

	guideline to which the same applies. I think this is Grade B and that the qualification about secondary care should be removed. Even if the extrapolation from secondary care is deemed appropriate, this is 2++ evidence so should be Grade C. I would suggest a recommendation in the format of the one on bronchodilator reversibility i.e. Advise use of FeNO when available, then bullet points with any pertinent caveats. Page 13, Grade D rec on skin tests etc: Typo in the Rec itself. The "%" has been omitted from "blood eosinophilia >4".	*Grade D is correct as this information is from the NICE guideline summary which is classed as level 4 evidence as it does not expressly link evidence to recommendations.* *The reference to secondary care has been removed from the recommendation.* *Corrected.*
	Suggest add that eosinophilia is a risk factor for asthma attacks and death	*This point is more relevant to section 9.1 which was not within the scope of this update.*
	FeNO - should it say that it can detect atopy? It is not clear whether you mean allergic rhinitis -	*The GDG debated the wording of this paragraph at length and concluded that the existing wording was the most appropriate.*
	The evidence for and role of FeNO testing is discussed, including the absence of evidence for its use in primary care and a recommendation (evidence level D) for its use in secondary care. TABLE 1 A useful table is provided of the sensitivity, specificity, positive and negative predictive values of the various tests and investigations.	*No response required.* *Thank you.*
	Agree. We would suggest the wording emphasising potential confounders could be stronger. Section D - (FeNO measurements) - However, a negative test does not exclude the diagnosis of asthma.	*Agree. Wording of recommendation amended.*
	Highlights the fact we lack robust diagnostic tools.	*Thank you.*
	Please could references to all the sen/ spec/ PPV, OPV in Table 1 be provided as only a few of these statements are referenced and the statements should all be supportable and fully quotable. Some statements appear to be ad hoc and not supported - such as Elevated blood eosinophil level is poorly predictive of sputum eosinophils , when there is data on the predictability of sputum eosinophils from elevated blood eosinophils (e.g Schleich et al - BMC pulmonary medicine Feb 2013; Wagener et al Thorax 2015 and others)	*The reference for all descriptions and parameters where no reference is stated is the NICE draft guidance as indicated by the footnote on table 1.* *The comments are those of the diagnostic sub-group of the GDG and have been added to aid interpretation not as supporting evidence. A footnote has been added to clarify this.*

3.3	We welcome the affirmation of the 'urgent need for diagnostic accuracy studies and implementation research to confirm, prospectively, the diagnostic accuracy of retrospectively derived algorithms and to define the optimal approach to making a diagnosis in different clinical practice settings' (Para. 2). We would encourage discussion with NICE on the algorithms presented as differences may cause confusion for healthcare professionals and impact upon people with asthma.	*Thank you.* *The GDG has no wish to cause confusion. The algorithm (Fig 1) is based on a thorough review of the evidence and, where evidence is equivocal, the expert opinion of the GDG and reflects what the GDG considered to be the best course of action.*
	Important with changes to GP practices	*Thank you.*
	Inevitably (perhaps) a bit wordy.	*This is a new section, and it was important to establish the extent of the evidence base that informed the guidance (section 3.3).* *The GDG also wanted to give very specific advice on the initial structured clinical assessment and monitored initiation of treatment. Both these are novel, and the GDG wanted to be sure they could not be misinterpreted (sections 3.3.1 and 3.3.2).* *The PCRS-UK specifically welcomed these sections and also the expanded section on alternative diagnoses.*
	Good	*Thank you.*
	Can't criticise but would say it's a very wordy section. Also use of the word pulmonologist - ? should read specialist with respiratory interest or Respiratory consultant (line 27 pg 17)	*See response to GD above.* *Term 'pulmonologist' changed to 'respiratory specialist'.*
	Section 3.3 The practical approach to diagnosis is laid out logically and the initial clinical assessment section very practical and thorough. The guideline provides a very useful pragmatic account of an approach to asthma diagnosis in adults and children, with the use of reversibility tests and carefully monitored trials of treatment in cases of intermediate probability. There is an expanded table of pointers to alternative diagnoses in adults – very useful.	*Thank you.* *Thank you.* *Thank you.*
	The practical approach to diagnosis laid out logically and the initial clinical assessment	*Thank you.*

	section very practical and thorough. The main potential problem (and it is a major problem) is that the treatment algorithm (Figure1) places a trial of therapy as a key diagnostic tool for patients with a "high probability" of asthma .This is at odds with the draft NICE Guideline and GINA Guidance which highlight the need for a positive objective test before a diagnosis of asthma is made. (unless in the urgent clinical situation where an "acute trial of therapy is recommended in the GINA Guidance) Although a trial of therapy as a diagnostic tool is practical it is not evidence–based and that is a problem for such an important recommendation in "evidenced –based guidelines." The draft Guidelines do emphasise that there should be an "objective response to therapy using validated symptom–based questionnaires, lung function and reduced peak flow variability. In order to minimise the criticism that "a trial of therapy" approach can lead to over diagnosis of asthma the criteria for what constitutes objective evidence of a positive treatment trial should be clearly emphasised. Meanwhile there is an urgent need for research to test value of "trial of therapy " as a diagnostic tool. More minor points: Figure 1. It would be useful to have a separate diagnostic algorithm for the Under 5's.	*In the context of a condition in which there is no absolute 'positive objective test', the initiation of treatment must be monitored objectively in order to confirm (or refute) the 'probable diagnosis'. Indeed, a monitored course of inhaled steroids is a reversibility test, which can establish whether or not airflow obstruction reverses to normal.* *Whilst there are no studies that have assessed the predictive value of a course of inhaled steroids, there is evidence to confirm the expected benefits of ICS in asthma (on lung function and symptom scores), and failure to achieve this should lead to reconsideration of the diagnosis.* *Table 3 now includes a definition of a 'good response' and clarification of what to do when the response is poor or equivocal (rather than poor alone).* *'* *We have included a research recommendation about defining the optimal approach to making a diagnosis in different clinical practice settings.* *Disagree that a separate algorithm is necessary but agree that greater clarity is needed about approaches in the under 5's. Footnote added to Figure 1 to clarify possible approaches in the under 5's, which are as given in the 'Suspected asthma' box of the algorithm.*
	This section is over-complicated. It should aim to emphasise that as there is no gold standard, that asthma is a variable condition and that its diagnosis can be challenging. Failure to establish the correct diagnosis is common and common pitfalls are…	*We recognise that this section is long, but we wanted to give very specific advice on the initial structured clinical assessment and monitored initiation of treatment. Both these are novel, and we wanted to be sure they could not be misinterpreted. (sections 3.3.1 and 3.3.2)* *Others have specifically welcomed these sections and also the expanded section on alternative diagnoses*

	Agree with less reliance on peak flow montoring Interesting wheeze remains a good diagnostic symptom.	*Thank you*
3.3.1	Lay person would comment on basis of knowledge	*No response required.*
	Table 2 - 2nd bullet - are you including viral associated wheeze with asthma here? (not sure you really mean to!) but If so you need to make this clear in the Diagnosis section. second heading - should it be 'Wheeze confirmed on auscultation by a doctor or nurse' - there are lots of patients with upper airway noise only. 3rd D recommendation - why have both breathlessness and dyspnoea?	*First two bullet points in Table 2 re-worded to improve clarity.* *We recognise that this is an important issue for generalists and will consider this for inclusion in the next update.* *Agree. Changed.* *This was an error; 'dyspnoea' changed to 'chest tightness'.*
	Clear	*Thank you.*
	Page 18, 3.3.1, Table 2: the first bullet under "episodic symptoms" doesn't sit very easily here. It says "A documented history of asthma attacks (but this is the initial structured assessment so how can there be a history of asthma attacks?) with symptomatic and objective improvement with treatment (again, this is initial assessment and they can't have evidence of improvement until further down the management pathway).	*The first two bullet points in Table 2 have been re-worded to improve clarity. A history of wheezy attacks, responding to asthma treatment, ideally with objective evidence of improved PEF is completely plausible and typical of the historical evidence that contributes to a diagnosis.*
	For children it would be helpful to suggest a school observation diary if doubt about symptoms from parent reports Include the importance of assessing nasal patency as part of the one airway	*There is no evidence to support use of a school observation diary.* *Nasal patency is not helpful.*
	It is a shame that BTS/SIGN have not adopted the GINA principles of assessment and management i.e the concept of optimising current control and reducing future risk. In particular the principles of assessing risk and tailoring management to reducing future risk seems to have been lost in this document.	*This point does not relate to diagnosis.* *Monitoring asthma was not within the scope of the current update. Assessing future risk will be considered for inclusion in the next update.*
	An important message that is missing here is a presentation with repeated 'lower respiratory tract infections'.	*This may be true, but there is no evidence to support the diagnostic value of repeated chest infections. However, episodic chest symptoms, and wheeze heard by a professional during the course of one or more 'chest infections' may contribute to the structured clinical assessment.*

	Spelling error - "which can produce featrues that mimic asthma". "features". Table 2 - "In adults, symptoms triggered by taking aspirin or beta blockers." Replace "aspirin" by "non-steroidal anti-inflammatory medications" (see section 7.11.5). Table 2 - "wheeze confirmed by a doctor or nurse" - change to "wheeze confirmed by a healthcare professional". Consistent with text below.	*Corrected.* *Agree. Changed* *Agree. Changed.*
	Practical but noted consensus opinion	*Thank you.*
3.3.2	We support the commencement of 'a carefully monitored initiation of treatment' in patients with a high probability of asthma (reflected in Figure 1) as a way to reduce the risk of asthma attacks, even when diagnosis remains unclear. Treatment itself is a valuable part of the diagnostic process in that it is possible to trial treatments and assess response. In a survey we conducted on GPs and Practice Nurses in 2015, 67% said they currently use trial of medication to diagnose asthma. However, we are aware that the evidence in this area is limited and an evaluation would be very useful.	*Thank you.* *This guideline has adopted the term 'monitored initiation of treatment' rather than 'trial of treatment' to emphasise the importance of monitoring response and reviewing the diagnosis and treatment accordingly.*
	As above lay perspective positive	*Thank you.*
	2nd GPP - it would be nice to mention a specific UK 'validated symptom questionnaire' or provide a reference.	*Examples now added to point 3 in Table 3. Symptom questionnaires also already covered by Table 7.*
	Clear	*Thank you.*
	Page 18, 3.3.2: The positioning of spirometry is unclear. The 1st sentence talks about "evidence of variable airflow obstruction" as a separately point from hearing wheeze, so presumably this part of the initial clinical assessment includes a measure of lung function. This should be used to establish the probability of asthma. However, the next paragraph says "Obstructive spirometry and a positive bronchodilator test provide objective evidence of variable airflow obstruction, and further increase the probability of asthma" which appears to suggest measuring spirometry again. In figure 1 the same issue occurs. Measuring FEV1/reversibility appears more than once, both before and after the "highly probable" decision point. I accept that there may be circumstances in which you might want to measure spirometry on very first	*To reflect the text in table 2, the first sentence has been amended to 'historical record of variable airflow obstruction' (eg a record of a low PEF during an attack which returns to normal after treatment, although it could be an historical spirometry result).* *Formal spirometry +/- BD reversibility (if it is obstructive and reverses) would 'further increase probability of asthma'.* *Figure 1 clarified to say 'historical record of variable PEF FEV_1 in the structured clinical assessment box.*

	presentation, and then measure it more formally afterwards with a reversibility assessment. But in the normal run of things spirometry/reversibility would only be done once, and it is not clear at what stage in the process you are recommending it	*Formal spirometry and reversibility is part of the objective tests that are required for anyone not in the 'high probability' category.*
	page 19 top of page wonder whether words "false negative" is confusing	*The GDG think this is sufficiently clear.*
	The main potential problem (and it is a major problem) is that the treatment algorithm (Figure1) places a trial of therapy as a key diagnostic tool for patients with a "high probability" of asthma .This is at odds with the draft NICE Guideline and GINA Guidance which highlight the need for a positive objective test before a diagnosis of asthma is made (unless in the urgent clinical situation where an "acute trial of therapy is recommended in the GINA Guidance). Although a trial of therapy as a diagnostic tool is practical it is not evidence–based and that is a problem for such an important recommendation in "evidenced–based guidelines." The draft Guidelines do emphasise that there should be an "objective response to therapy using validated symptom–based questionnaires, lung function and reduced peak flow variability". In order to minimise the criticism that "a trial of therapy" approach can lead to over diagnosis of asthma, the criteria for what constitutes objective evidence of a positive treatment trial should be clearly emphasised. Meanwhile there is an urgent need for research to test value of "trial of therapy" as a diagnostic tool.	*In the context of a condition in which there is no absolute 'positive objective test', the initiation of treatment must be monitored objectively in order to confirm (or refute) the 'probable diagnosis'. Indeed, a monitored course of inhaled steroids is a reversibility test, which can establish whether or not airflow obstruction reverses to normal.* *Whilst there are no studies that have assessed the predictive value of a course of inhaled steroids, there is evidence to confirm the expected benefits of ICS in asthma (on lung function and symptom scores), and failure to achieve this should lead to reconsideration of the diagnosis.* *Table 3 now includes a definition of a 'good response' and clarification of what do when the response is poor or equivocal (rather than poor alone).* *We have included a research recommendation about defining the optimal approach to making a diagnosis in different clinical practice settings*
	Agree.	*Thank you.*
	"Wheeze heard by a professional" - change to "wheeze heard by a healthcare professional" (see 3.3.1).	*Agree. Changed.*
	Use of symptom questionnaires likely to be low.	*The GDG hope that this guidance will encourage their use.*
3.3.3	As above lay perspective positive	*Thank you.*
	Table 5 - space needed 4th Clinical Clue - 'symptoms without'	*Corrected.*

	6th Clinical Clue - I think you should spell out PND (as some may not know what it is!) - although I appreciate the spacing issue. Suggest remove horizontal lines between Bronchiectasis, Inhaled foreign body, Obliterative bronchiolitis & Large airway stenosis and also between Lung Cancer and Sarcoidosis. Hyperventilation syndrome used in Table 5 and Dysfunctional breathing at the end of Table 2 - suggest consistency and use the latter throughout.	*Agreed. PND spelled out. Table amended as suggested.* *Agreed. Changed to 'dysfunctional breathing'.*
	clear	*Thank you.*
	Agree. Pertussis ought to be considered even in the absence of coughing leading to vomiting. It's sometimes referred to as the cough of 100 days and adult-onset Pertussis has recently been more commonly seen.	*Agree. Pertussis has been added to table 5 as a cause of cough without lung function abnormalities.*
	Agree with guideline	*Thank you.*
3.3.4	As above lay perspective positive	*Thank you.*
	I like Figure 1 which is different from (and much better than) NICE 2016. Perhaps Fig 1 should have a legend that says SPT = skin prick test Just wonder whether 'Poor response' should also mention review of compliance with treatment?	*Thank you.* *Now spelt out in full in algorithm.* *Table 3 gives poor adherence and poor inhaler technique as reasons for poor or equivocal response. This was omitted in figure 1 for the sake of simplicity.*
	clear	*Thank you.*
	Page 21, 3.3.4: Clarification re position of spirometry is needed in the recommendation here (see comment under 3.3.2) Section 3.3.4, page 22, 1st GPP: I think this should state what is meant by a "monitored" trial of treatment. This GPP is in the sub-section for adults and children with airflow obstruction. We know that they have airflow obstruction (i.e. we have measured it) so isn't it worth stating that the trial should involve re-measuring and looking for improvement?	*Formal spirometry and reversibility is part of the objective tests that are required for anyone not in the 'high probability' category.* *GPP re-worded - 'trial of treatment' changed to 'monitored initiation of treatment' in line with Table 3 and phrase 'assessing response to treatment by repeating lung function and objective measures of asthma control' added.*
	The guideline provides a very useful pragmatic account of an approach to asthma diagnosis in adults and children, with the use of reversibility tests and carefully monitored trials of treatment	*Thank you.*

	in cases of intermediate probability. Some commented that they liked the flexibility to use their clinical judgement. While others liked the clarity and simplicity of Fig 1 – the diagnostic algorithm. Figure 1. It would be useful to have a separate diagnostic algorithm for the Under 5's.	*See response to RCGP under section 3.3.*
	The RCGP feels that BTS/SIGN should adopt the GINA principles of assessment and management i.e the concept of optimising current control and reducing future risk. In particular the principles of assessing risk and tailoring management to reducing future risk seems to have been lost in this document. Unfortunately some the lessons learnt from the National Review of Deaths (NRAD...Royal College of Physicians London 2014) seem not to have been recognised in the Assessment part of this document e.g .the use of >12 short-acting beta-2 agonists per year as an indicator of high risk.	*This point does not relate to diagnosis.* *Monitoring asthma was not within the scope of this update.* *The monitoring asthma section was not within the scope of this update. NRAD is referred to at the beginning of section 9.*
	Agree with this table.	*Thank you.*
	Agree with guideline	*Thank you.*
3.3.5	Essential for uniformity in standards	*Thank you.*
	clear	*Thank you.*
	Please cross refer to Table 10 Emphasise the need to identify those at risk - there are a few more factors (Modifiable and non Modifiable) in Table 2-2 in GINA. Add (From NRAD) : > average of one SABA per month in last twelve months (Pro rata); and > 1 attack in last 12 months	*Section 3.3.5 relates to diagnostic reasons for referral (as opposed to management problems or severe/at risk asthma which is dealt with in chapter 9).* *We have now clarified this by revising the title of the section and table to 'Diagnostic indications for referral'.*
	It is important to know the local referral pathways for children	*This is covered in section 3.4 on 'Organisation of diagnostic services'. We have added the possible need for referral of young children for diagnostic tests.*
	Have the guideline development group (GDP) considered including some of the key recommendations from the recent National Review of Asthma Deaths (NRAD) report regarding indications for referral? For example, 'Patients with asthma must be referred to a specialist asthma service if they have required more than two courses of systemic corticosteroids, oral or injected, in the previous	*Section 3.3.5 relates to diagnostic reasons for referral (as opposed to management problems or severe/at risk asthma which is dealt with in chapter 9).*

	12 months or require management using British Thoracic Society (BTS) stepwise treatment 4 or 5 to achieve control'; 'Secondary care follow-up should be arranged after every hospital admission for asthma, and for patients who have attended the emergency department two or more times with an asthma attack in the previous 12 months'. Inclusion of the key NRAD recommendations into this guideline will help to facilitate their implementation. Apologies if this may have been covered elsewhere in the guideline/been considered already.	
	It was noted that the threshold for referral appears to have been lowered. Many of our members were positive about this in spite of the fact that it would result in more referrals, with some indicating that they were already referring in line with this new recommendation, or that this was not a bad thing. We asked members what impact this change would have on current referral patterns. They indicated that it could mean 1-2 more referrals a month, or 2 to 3, with only a handful saying that it would increase by more than 5 referrals a month The guideline now implies a need to refer for specialist assessment any child requiring more than very low inhaled steroids (more than 200mcg daily of CFC BDB equivalent) or requiring an add-one agent of any kind. This suggests a very low threshold for specialist referrals and the implications for referral rate to specialist services should be carefully considered. The adult step diagram also appears to lower the threshold for referral to specialist care.	*Section 3.3.5 relates to diagnostic reasons for referral (as opposed to management problems or severe/at risk asthma which is dealt with in chapter 9).* *The intention was to indicate that specialist referral is required if all options under 'Additional add-on therapies', as shown in Figures 2 & 3, were unsuccessful. Figures 2 & 3 have now been amended to clarify this.*
	Agree.	*Thank you.*
	Under poor response to asthma treatment should we also state all adults at step 4 and 5 all children at step 3 before initiating step 4	*Section 3.3.5 relates to diagnostic reasons for referral (as opposed to management problems or severe/at risk asthma which is dealt with in chapter 9).*
3.4	Essential	Thank you.
	Organisation of 'Diagnostic Services' is a slightly strange term/title. I appreciate that Diagnostic service is a Dutch term - but would it be better if this was entitled Organisation of Diagnostic Primary and Secondary Care Services - or is this too clunky?!	*Disagree. Title appropriate as it is.*

	clear	Thank you.
	States that sprirometry with bronchodilator reversibility is readily available in primary care. This is not our experience in paediatric population across the UK Skin prick resting in the paediatric population is also "hit and miss"	*We have now added the caveat that referral may be needed in young children.* *We already state that SPT 'are only available in some secondary care settings and a few primary care practices'.*
	As above regarding incorporation of NRAD key recommendations into the guideline.	*Monitoring section not updated (although NRAD is referred to at the beginning of chapter 9).*
	There is a brief and sensible discussion of the organisation of streamlined care pathways for the performance of tests not available in primary care.	Thank you.
	Agree.	Thank you.
	Agree with guideline	Thank you.
3.5	Previous area of uncertainties	Thank you.
	Interesting	Thank you.
	The mention of use of steroids for wheezy infants is unclear - admission to hospital of itself is not an adequate criterion for use of systemic steroids as some young infants are admitted several times over their second winter and may receive several 3 day course of prednisolone over 3 or 4 months. I think mention of other atopic features might indicate this is early onset asthma, if the child responds to bronchodilator and is admitted mainly for observation or to reassure parents then systemic steroids are not indicted	*This section was not within the scope of the current update.*
	Agree with guideline	Thank you.
Section 4		
General	Section 4 (and Table 7?) would have been much more useful for the primary care professional if it had been written in the GINA style of a Table of Points to consider to assess current control and a table of factors to consider when assessing future risk (including the use of >12 SABA).	*Section 4 was not within the scope of the current update, however, cross-references to sections 7.1.1 and 9.1.2 have been added to address the point about high use of SABA.*
4.1.2	"Using closed questions, such as "do you use your blue inhaler every day?"" - change to "Using closed questions, such as "do you use your reliever inhaler every day"". Contemporary practice is not to refer to inhalers solely by their colour but whether they are a reliever or preventer - this promotes patient understanding	*Section 4.1.2 was not within the scope of the current update.* *'blue inhaler' changed to 'reliever (blue inhaler)'.*

	of their treatment.	
4.2	Table 7: and text: Please emphasise that asthma control includes two domains: Current symptom control (3Qs, ACT, ACQ) AND Future Risk Point being that someone with good current control when assessed may still be at risk of an attack (e.g. someone who has low FEV1, someone who is pregnant, with high eosinophilia etc - See ERS/ATS Task Force (Reddel & Tailor - Mike Thomas and I were on this task force)/ Also NRAD/ and GINA Chapter 2; Table 2-2.	*Section 4.2 was not within the scope of the current update.* *Agree, and will consider for inclusion in next update.*
	"When assessing asthma control in adults use specific questions, such as “how many days a week do you use your blue inhaler?”." - change to "When assessing asthma control in adults use specific questions, such as “how many days a week do you use your reliever inhaler (or if on MART, how many additional doses of your inhaler do you use)?”. Contemporary practice is not to refer to inhalers solely by their colour but whether they are a reliever or preventer – this promotes patient understanding of their treatment. Some adult patients may be on Maintenance and Reliever Therapy (MART).	*Section 4.2 was not within the scope of the current update.* *As for section 4.1.2 above.*
4.3	Table 7: and text: Please emphasise that asthma control includes two domains: Current symptom control (3Qs, ACT, ACQ) AND Future Risk Point being that someone with good current control when assessed may still be at risk of an attack (e.g. someone who has low FEV1, someone who is pregnant, with high eosinophilia etc - See ERS/ATS Task Forse (Reddel & Tailor - Mike Thomas and I were on this task force)/ Also NRAD/ and GINA Chapter 2; Table 2-2.	*Section 4.3 was not within the scope of the current update.* *As for section 4.2 above.*
	No mention of peak flow recordings (? if know normal ? reversibity using pek flow)	*Section 4.3 was not within the scope of the current update.*
	"Bronchodilator reliance" - change to "bronchodilator reliance (or additional doses of MART)".	*Section 4.3 was not within the scope of the current update.*
	Learning and recommendations from NRAD should be incorporated into the new asthma guidelines for children in primary care.	*Section 4.3 was not within the scope of the current update. See also response to ‘General’ above.*
4.4	Table 7: and text: Please emphasise that asthma control includes two domains: Current	*Section 4.4 was not within the scope of the current update.*

	symptom control (3Qs, ACT, ACQ) AND Future Risk Point being that someone with good current control when assessed may still be at risk of an attack (e.g. someone who has low FEV1, someone who is pregnant, with high eosinophilia etc - See ERS/ATS Task Forse (Reddel & Tailor - Mike Thomas and I were on this task force)/ Also NRAD/ and GINA Chapter 2; Table 2-2.	*See also response to 'General' above.* *In the meantime, 'bronchodilator reliance' has been changed to 'bronchodilator over-use'.*
	Please can I ask if the GDP have considered providing examples of assessing 'bronchodilator reliance' which may aid assessment of control in practice? For instance, the NRAD report suggests that 'being prescribed more than 12 reliever inhalers in the previous 12 months' is a measure of risk; however this relies on having 12 months of historical data. Other options, some of which are included in ACT, ACQ, or suggested by the GINA guidelines, include asking about the number of days of reliever use over a relatively short time period (weeks), average number of reliever puffs per day over a defined period etc. Similarly, regarding underuse of preventer treatment, is the GDP able to provide a good practice point regarding thresholds of underuse that may serve as a marker of increased risk eg less than 50% ICS prescriptions requested over 12 months. Thank you.	*Section 4.4 was not within the scope of the current update.*
	Learning and recommendations from NRAD should be incorporated into the new asthma guidelines for adults in primary care.	*Section 4.4 was not within the scope of the current update.*
Section 5		
General	Need to add Health professional education somewhere here	*This is covered in the existing text and recommendation in section 5.5.*
5.3.3	There is now the option for school to hold a generic inhaler for bronchodilator and spacer to be used if a child with asthma has no personal inhaler when needed	*Although this is the case, this DoH guidance is not relevant in this section which is about self-management in schoolchildren not how to treat an asthma attack in school. However, a new sentence has been added to section 9.8.2 covering the option of schools holding a generic reliever inhaler.*
5.3.4	It should be emphasized that the bronchodilator should be accessible to the child wherever they are cared for - this may be in more than one home, more than one Nursery and other carer situations.	*Section 5.3.4 was not within the scope of the current update.*

5.3.5	Many individuals from ethnic minorities do not read translated written materials and so it may be more helpful to have a no written format for asthma education. Cultural requirements may impact on the practicalities of asthma treatments and can often be overcome if identified and incorporated into the PAAP	*Section 5.3.5 was not within the scope of the current update.* *This is covered in the existing text and recommendations in section 5.3.5.*
5.4	Is the SMART approach to self management to be encouraged?	*Section 5.3.5 was not within the scope of the current update and this approach was not reviewed.*
5.4.1	The guideline contains a new and very helpful discussion of non-adherence and the various approaches to assessing this – with key emphasis on careful sympathetic and non-judgemental clinical enquiry focussing on patient attitudes and concerns about medication. 85% of our member survey respondents found this section useful or very useful. They like the prompts for questions to ask the patients, while others said there was nothing new. A few commented that it needs to be more succinct and less wordy.	*Thank you.* *The GDG are very pleased with this endorsement.* *In the view of the GDG, all the existing text is relevant.*
	Agree. This is a significant issue and it is correct to emphasise this. Re the Necessity-Concerns Framework - This appears to be common sense. However, if referred to, it would be helpful to provide some guidance as to the commonly recognised 'disadvantages' contributing to non-adherence and suggested strategies for managing this.	*Thank you.* *In the interests of brevity (see above point from PCRS) we have not expanded this section, although the reference enables those unfamiliar with the Necessity Concerns Framework to undertake further reading. We have, however, used our understanding of the framework to guide the suggested questions in the GPP.*
	Necessity-Concerns framework - not sure how many people use or have heard of this?	*The purpose of including reference to this framework was to raise awareness of it.*
5.4.2	Very important section - well written - with excellent GPPs.	*Thank you.*
	Page 40, 5.4.2, Paragraph 2, 2nd and 4th sentences: I've read these a few times hoping the meaning will click, but they seem to contradict one another. "self-reporting typically underestimates adherence.." but "under-use is over-estimated". As under-use is a major factor in measurement of adherence, how can both be true?	*The second sentence actually states that 'self reporting typically overestimates adherence...'* *At an individual level, people try to give the acceptable answer: those who underuse medication will usually over-estimate their usage; the (minority) who overuse their*

		medication will under-estimate their usage. *For clarity, the terms over- and under-estimated have been changed to over- and under-reported.*
	Recommendation: it could mention here that the HCP should reinforce even further the importance of actually picking up the steroid prescription and not just a repeat of reliever medication. Further explain why the patient needs to know and understand the difference between reliever and preventer	*These are important points, but our aim in this section is to help clinicians open up the discussion so that they can identify poor adherence however it manifests, and address the issues raised.*
	This is helpful. However, measurement of the serum eosinophil level has been omitted; this is easily available and usually suppressed by effective treatment. Section D is very helpful.	*There is no evidence that measuring serum eosinophils is a marker of adherence.* *Thank you (we assume this refers to the 'D' grade recommendation and GPP).*
	Interesting consensus opinion for asking about adherence evidence base.	*Thank you.*
5.4.3	We welcome the reference to innovative IT-based ways to support adherence. We note the recent study of the Propeller Health sensor - a small device that attaches to the top of an existing inhaler and notifies patients (or family members) if they miss a scheduled dose. A randomised controlled trial of 495 patients assessing the Propeller Health Asthma Platform for reliever inhaler monitoring found that over a 12-month period reliever use was reduced, reliever-free days were increased, and asthma control was improved (Merchant et al, 2016). Additionally, a randomised controlled trial of 220 patients who used smart inhalers with an audio-visual reminder found significant improvements in adherence to preventer medication in school-aged children with asthma (Chan, 2015). We also draw attention to the study by D'Arcy et al. (2014), 'A Method to Assess Adherence in Inhaler Use through Analysis of Acoustic Recordings of Inhaler Events'. Though a small study, the results demonstrate how the use of a smart inhaler to objectively assess how errors in both time and technique of inhaler use could impact clinical outcomes. Such technologies could help people to better self-manage by dynamically responding to changing triggers to reduce their risk of an asthma attack, and enable healthcare	*Thank you.* *We refer to electronic monitoring as the 'gold standard' and highlight some of these papers in the adherence section and also in the telehealthcare section (a cross-reference to section 14.4.1 has been added).* *The more recent papers were published since our searches were undertaken and have therefore not been included in this review.*

	professionals to identify those people at higher risk of an attack. Further trials to demonstrate proof of concept for new technologies improve asthma management should be encouraged. Mobile apps - We acknowledge the limited evidence in the field of self-management mobile apps, which is insufficient to advise clinicians (Belisario, 2013). Huckvale et al. (2015) note the need for 'coordinated quality assurance processes that can adapt to changing clinical and information governance-related risks, ensure compliance with the evidence base and reflect local variations in clinical practice'. Until the use of more advanced mobile apps is proven, we would advise that the guideline recommends digital delivery of clinically approved information. Under 'Initiatives to promote adherence to regular treatment', we recommend that consideration should be given, in the first instance, to whether information for patients can be delivered in a digital format, with an electronic copy of a personal asthma action plan offered to patients. References Merchant R. et al (2016). Effectiveness of Population Health Management Using the Propeller Health Asthma Platform: A Randomized Clinical Trial. J Allergy Clin Immunol Pract. 2016 Jan 8. pii: S2213-2198(15)00665-0. Available at: http://www.sciencedirect.com/science/article/pii/S2213219815006650 Chan A. et al (2015). The effect of an inhaler with ringtones on asthma control and school attendance in children. Lancet Respir Med. 2015 Mar;3(3):210-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25617215 D'Arcy et al. (2014). A Method to Assess Adherence in Inhaler Use through Analysis of Acoustic Recordings of Inhaler Events. PLoS One. 2014 Jun 6;9(6). Available at: http://www.ncbi.nlm.nih.gov/pubmed/24905012 Belisario, M. et al (2015). Smartphone and tablet self management apps for asthma (Review). Cochrane Database Syst Rev. 2013 Nov 27;11:CD010013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24282112 Huckvale, K. et al (2015). The evolution of	

	mobile apps for asthma: an updated systematic assessment of content and tools. BMC Med. 2015 Mar 23;13:58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25857569	
	Please may I check if this important trial has been reviewed by the GDP: ' The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial' Amy Chan et al, Lancet Respiratory Medicine 3, 3, 210-219	*The evidence review for this section was limited to systematic reviews which it was felt provided sufficient evidence. See also response to A UK above.*
	Agree next generation of inhalers should have electronic dose counters. We may also need media campaigns to actually convince people inhalers are medication and not cheap.	*This aspect was not reviewed. Current evidence is, however, inconsistent with some positive but some showing improved adherence but not improved control.*
Section 6		
6.1.8	New obesity paras and the 2 new GPPs are good additions	*Thank you.*
	Page 46, 6.1.8: there are 3 grouped recommendations here about obesity. The first one is from the existing 2014 guideline and hedges its bets about the relationship between obesity and asthma, correctly so in my view. I think the new Recs should do the same e.g. “Obese and overweight children should be offered weight-loss programmes to reduce the likelihood of respiratory symptoms suggestive of asthma”	*Agree. Second recommendation re-worded as suggested. The third recommendation has been deleted and replaced by a statement about there being no direct evidence that reducing maternal obesity reduces the likelihood of subsequent asthma in children.*
	RCPE would strongly agree with the promotion of weight reduction. It is also important to obtain good control to facilitate exercise to promote weight loss, and to avoid Prednisolone rescue therapy which may counteract weight loss.	*Thank you.*
6.1.10	Add more on diesel fume effects.	*Section 6.1.10 was not within the scope of the current update.*
	Although this section should address avoidance of “other air pollutants” there is no mention on what advice to give during short-term increases in air pollution. Clinicians must be provided with the tools to discuss what actions patients/parents may use to mitigate exposure on high pollution days. For example; http://uk-air.defra.gov.uk/air-pollution/daqi.	*Section 6.1.10 was not within the scope of the current update.* *Sentence and DEFRA website address added to section 6.2.4.*
6.2.4	Our experts note that the statement on prevalence of asthma in non-metropolitan areas should be removed since there is now	*Agree. Statement deleted.* *Section 6.2.4 was not within the scope of the current update.*

	clear evidence that locally-generated air pollution both causes asthma and exacerbates asthma. We recommend that the guidelines advocate more research into advice that reduces long-term exposure. For example, encouraging patients to travel actively using lower pollution exposure routes (eg planned by the Walkit app https://walkit.com).	*However, a sentence and DEFRA website address have been added to section 6.2.4.*
	The statement on prevalence of asthma in non-metropolitan areas is not relevant since there is now clear evidence that locally-generated air pollution both causes asthma and exacerbates asthma. We recommend that this sentence is removed and this section includes a sentence on "the need for more research into long-term exposure mitigation advice. For example, encouraging active travel using lower pollution exposure routes".	*Section 6.2.4 was not within the scope of the current update.*
6.2.8	Typo - remove 'in' before interactions 3rd sentence 2nd para Useful additional paras & recommendation	*Disagree. Text is correct as written.* *Thank you.*
	New evidence is presented on the value of weight loss interventions in overweight patients with asthma – this is considered helpful.	*Thank you.*
Section 7		
General	AstraZeneca acknowledges some of the issues surrounding the use of beclomethasone dipropionate (BDP) equivalence as a means of comparing the relative potency of inhaled corticosteroids but considers is remains the best method of comparing relative potency in spite of its flaws. Omission of BDP equivalence has the potential for inappropriate/earlier prescribing of potent ICS containing products especially when the labelled dose appears very low. In addition historically inhaled corticosteroid doses have been expressed in terms of BDP equivalents and this is reflected in the literature and other references on the subject. AstraZeneca therefore considers completely moving away from the use of BDP equivalents is a retrograde step and would welcome the retention of this relative potency measure	*Disagree. BDP is no longer available*
	AstraZeneca welcomes the clarity that Table 9 (Doses of inhaled corticosteroids) brings to BDP equivalence. Inclusion of this table avoids the necessity of healthcare professionals having to calculate this for themselves with the possibility for errors, but	

	would recommend that the BDP equivalence of the four dose columns is also included; see below for how this could be accomplished. In addition, and in line with section 7.10: Stepping Down which recommends that patients should be maintained at the lowest possible dose of ICS, AstraZeneca would suggest that the adult doses in Figure 2 extend across all four dose ranges as illustrated below. As part of the Symbicort Maintenance And Reliever Therapy development program AstraZeneca conducted one study with a treatment arm of budesonide/formoterol 100/6 one dose twice daily as maintenance plus as needed compared to budesonide 400 mcg one dose twice daily.[O'Byrne] The lower ICS maintenance dose was shown to be superior in terms of severe exacerbations. *(See Table A at the end of this report)* AstraZeneca is concerned that some of the entries in the table are inaccurate, potentially confusing and very different to the current BTS/SIGN 2014 guidelines, for example: • Budesonide in a Turbohaler device (Pulmicort) is included as a very low dose, low dose and medium dose ICS option at twice the dose of the corresponding Symbicort (budesonide/formoterol) entry in the table. • The option for Symbicort Turbohaler at a medium dose is only given as 100/6 two doses twice a day (400 mcg BDP) whereas the 200/6 at one dose twice a day (400 mcg BDP) provides the same ICS dose without increasing the formoterol dose if this is not necessary. • The range of ICS/LABA products positioned as low dose options have a range of BDP equivalence from 200 mcg daily (Symbicort) to 1,000 mcg (Relvar). AstraZeneca considers it inappropriate to present treatment options with a five-fold difference in ICS BDP dose as representing a similar safety profile for patients. Such a wide BDP dosage range should not be presented within a single low dose bucket. Similarly, there are wide BDP equivalence ranges at the medium and high dose columns. For the AstraZeneca products mentioned in Table 9, budesonide Turbohaler and Symbicort Turbohaler, AstraZeneca considers the data below to be accurate, on-label and in line with	*Evidence for use of formoterol as reliever was not reviewed for this update of the guideline* *Comment on figure 2 appears to relate to Table 9 which has now been revised and split into adult and paediatric tables.* *Agree. Table 9 has been revised to take account of these and subsequent comments.*

	currently accepted guidelines, including the current BTS/SIGN 2014 guidance. *(See Table B at the end of this report).*	
	As the marketing authorisations for many inhaled therapies have differences for paediatric dosing compared to adult doses AstraZeneca believes it would be beneficial to the final reader to have paediatric licensed products and dosing in a separate table.	*Agree. Table 9 has now been split to show adult and paediatric doses separately.*
	Figure 2: summary of management of asthma This figure is extremely important as it likely to be the most utilised aspect of the new SIGN guidelines, as a quick reference guide to the treatment pathway, and as such AstraZeneca considers that it needs to be able to "stand alone". On first glance, the pathway looks similar to the existing BTS/SIGN guideline but there are some fundamental changes and there is the potential for confusion. The absence of labelling the steps of the treatment pathway is one of the fundamental changes and AstraZeneca considers this to be a retrograde step as in clinical discussions the current step 1 to step 5 is extremely useful to healthcare professionals in understanding severity of disease. The removal of this easy reference language may make communication more difficult and possibly lead to mis-interpretation. Consideration of labelling the steps should be made, perhaps on an alphabetical basis rather than numerical to differentiate the new guideline from the current guideline.	*The GDG considered this new approach very carefully and agreed that it was imperative to remove the term 'step' because the content of the bars in the new Figures 2 & 3 does not equate to the content of the 'steps' in the old Figures 4, 5 & 6 and retaining the term 'step' and the numbering could therefore cause confusion amongst healthcare professionals. The rationale is that removing the term 'step' will encourage HCPs to look at the new figures closely and not assume that the bars are the same as the previous 'steps'*
	Inclusion of the BDP equivalence for the four ICS dosage ranges should also be considered; see comments and suggestion above.	*Disagree. BDP is no longer available.*
	AstraZeneca welcomes the early introduction of ICS as part of the diagnostic section (2.1.1) alongside objective spirometry testing and a full clinical history. These later two aspects should be included in the treatment pathway presented in Figure 2 to avoid the misinterpretation that a trial of ICS is the sole diagnostic element.	*Disagree. Figure 2 amended to show that first bar is a monitored initiation of treatment with low dose ICS as described in Table 3.*
	The mild intermittent asthma (including exercise induced asthma) is unclear as to which patients are likely to fit this particular	*Agree that there is a lack of clarity. The text in the figure has been changed to 'Infrequent, short-lived*

	part of the treatment pathway. It would also appear to be at odds to Section 7.11.2 which clearly states: *For most patients, exercise induced asthma is an expression of poorly controlled asthma and regular treatment including inhaled corticosteroids should be reviewed.* AstraZeneca believes further clarity on patients for whom a SABA alone is recommended within Figure 2 to avoid the risk of appropriate patients not being prescribed an ICS and the continuing over reliance of SABA in patients as highlighted in the 2014 National Review of Asthma Deaths confidential enquiry.[NRAD]	*wheeze'*
	AstraZeneca also supports the earlier introduction of ICS/LABA ahead of increasing the ICS dose, as there is evidence of a synergistic effect with the combination, as well as the earlier referral to specialist care.	*Thank you.*
	As stated before Wide range and efficacy described	*Thank you.*
	Typo on 53 There are differences in how the doses of ICS are expressed (ex-valve - labelled or ex-actuator - delivered) so it is increasingly difficult to cover all the possible does (I think should be DOSES) in the text.	*No change required.* *Corrected*
	It is noted that reference to BDP equivalence is no longer mentioned here/or in table 9 of inhaled corticosteroids. We would recommend making it clear which inhaler brands (QVAR and Fostair) contain extrafine beclometasone given the MHRA drug safety warning. https://www.gov.uk/drug-safety-update/inhaled-medicines-containing-corticosteroid#different-potencies-of-cfc-free-beclometasone-inhalers Please be clear that ex-valve - labelled doses of inhalers have been used in table 9. However the dose for Relvar has been quoted as the ex-actuator - delivered dose. We would suggest that for consistency the ex-valve - labelled dose is used here (100/25 and 200/25). Relvar SPC. https://www.medicines.org.uk/emc/medicine/28496 https://www.medicines.org.uk/emc/medicine/28495	*Table 9 has been revised and now includes reference to extrafine beclometasone.* *The doses given in Table 9 are the ones actually prescribed to patients and are quoted in the literature and the SPC. Changing them as suggested here could cause confusion.*
	Typo p53 - Para after 2nd GPP - 2nd sentence at the end should be 'doses'	*Corrected.*

	Not sure where to comment on the Step Diagrams Figs 2&3 - I note changes which are fine but it would be good to add Step 1,2,3&4 somewhere - this is the short hand we all use.	*The GDG considered this new approach very carefully and agreed that it was imperative to remove the term 'step' because the content of the bars in the new Figures 2 & 3 does not equate to the content of the 'steps' in the old Figures 4, 5 & 6 and retaining the term 'step' and the numbering could therefore cause confusion amongst healthcare professionals. The rationale is that removing the term 'step' will encourage HCPs to look at the new figures closely and not assume that the bars are the same as the previous 'steps'.*
	Until May 2009 all doses of ICS in this section were referenced against beclometasone dipropionate (BDP) given via chlorofluorocarbon metered dose inhalers (CFC-MDIs). BDP-CFC is now unavailable. There are differences in how the doses of ICS are expressed (ex-valve - labelled or ex-actuator - delivered) so it is increasingly difficult to cover all the possible doses in the text. The doses of ICS are therefore expressed as very low (generally paediatric doses), low (generally starting dose for adults), medium and high (see Table 9)". This move away from BDP equivalence to categories of very low, low, medium and high dose ICS is fully supported by GSK as you will know from our previous dialogue with BTS. It may, however, be useful for readers to understand the rationale for why this change has been made in more detail.	*Thank you.* *The GDG consider that the information provided is sufficient.*
	P57: Table 9 Doses of inhaled corticosteroids *Fluticasone propionate* GSK believes that there is inconsistency in how the Fluticasone propionate (FP) Accuhaler has been categorised in Table 9 'Doses of inhaled corticosteroids' compared with the FP Evohaler: • FP Evohaler (50 mcg one puff twice a day) is categorised as a 'Very low dose' ICS • FP Accuhaler (50 mcg one dose twice a day) is categorised as a 'Low dose' ICS Whilst BTS/SIGN is moving away from BDP equivalence for expressing the ICS dose of different medicines it is recognised that "Fluticasone propionate provides equal clinical activity to BDP and budesonide at half the dosage" (P56: 7.2.4 Comparison of inhaled corticosteroids). Non-proprietary BDP 50 mcg	*Table 9 has been updated.*

	two puffs twice a day is categorised as a 'Very low dose' ICS in Table 9 therefore FP 50 mcg one puff twice a day should also be categorised as a 'Very low dose' ICS. This applies to the FP Evohaler (currently correctly positioned in Table 9) and the FP Accuhaler (currently incorrectly positioned within Table 9 as a 'Low dose' as opposed to a 'Very low dose' ICS). Following on from this all doses of the FP Accuhaler within Table 9 need to be shifted to the left: • 50mcg one dose twice a day Incorrectly placed in the low dose as opposed to the very low dose column • 100mcg one dose twice a day - Incorrectly placed in the medium dose as opposed to the low dose column • 250mcg one dose twice a day - Incorrectly placed in the high dose as opposed to the medium dose column • 500mcg one dose twice a day - Currently not included, should be in the high dose column Please note that the maximum licensed dose of FP for the treatment of asthma in children is 200 mcg twice a day as per the Flixotide Evohaler SPC https://www.medicines.org.uk/emc/medicine/2913 and the Flixotide Accuhaler SPC https://www.medicines.org.uk/emc/medicine/86 *Seretide* Please note that the maximum licensed dose of fluticasone propionate delivered by a Seretide inhaler in children is 100 microgram twice daily as per the Seretide Evohaler SPC https://www.medicines.org.uk/emc/medicine/2914 and the Seretide Accuhaler SPC https://www.medicines.org.uk/emc/medicine/2317/SPC/Seretide+100,+250,+500+Accuhaler	*Table 9 includes 200 micrograms of FP because this is the dose available in the Accuhaler. Prescribers should check licensed does for children in the BNF or SPC.*
	Relvar GSK supports the classification of Relvar 92/22 mcg as a low-medium dose ICS and 184/22 mcg as a high dose ICS in Table 9 'Doses of inhaled corticosteroids' as per the Relvar Ellipta SPC (4.2 Posology and method of administration) https://www.medicines.org.uk/emc/medicine/28495 '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. If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control.' 'Relvar Ellipta 184/22 micrograms should be considered for adults and adolescents 12 years and over who require a higher dose of inhaled corticosteroid in combination with a long-acting beta2-agonist.'	
	Page 53, highlighted section: Typo - "does" should be "doses"	*Corrected.*
	One of the main changes in this section of the guideline was of the removal of the "step" terminology when describing the different treatment levels that can be used to control asthma. Some specialist asthma healthcare professionals we have spoken to have expressed concern that this new concept may be confusing to end-users; general practitioners and nurses. We would recommend that any change to the terminology is accompanied by an education resource for HCPs.	*The GDG considered this new approach very carefully and agreed that it was imperative to remove the term 'step' because the content of the bars in the new Figures 2 & 3 does not equate to the content of the 'steps' in the old Figures 4, 5 & 6 and retaining the term 'step' and the numbering could therefore cause confusion amongst healthcare professionals. The rationale is that removing the term 'step' will encourage HCPs to look at the new figures closely and not assume that the bars are the same as the previous 'steps'.* *The GDG agrees that there is a need to bring these changes to the attention of HCP and is considering possible approaches to this.*
	Typo – page 53 – says "does" instead of "dose"	*Corrected.*
	It is a shame that BTS/SIGN have not adopted the GINA principles of assessment and management i.e the concept of optimising current control and reducing future risk. In particular the principles of assessing risk and tailoring management to reducing future risk seems to have been lost in this document. *Banding of ICS vs BDP as reference product* In general our members were positive about the shift to referring to inhaled steroids in bands according to their strength - 66% felt the bands were clear or very clear. This was felt to be a pragmatic and useful classification of inhaled steroid dosages – very low dose, low dose, medium dose and high dose. Whether this will make the task of explaining the complex and important issues of inhaled	*Reiteration of point made in relation to section 3.* *Assessing future risk is important but comes under monitoring which was not within the scope of the current update, but will be considered for inclusion in the next update.* *The GDG are pleased that this change is considered positive by a majority of primary care HCPs responding to the survey.*

	steroids dose ranges to health professionals remains to be seen. Some said that the banding might avoid some of the high dose use of steroids that happens currently. Views were mixed on the merits of losing BDP as a reference point. Some argued that comparisons with BDP were now redundant, while others felt it could be problematic to lose BDP as a reference point. 38% of our member survey responders considered the loss of BDP would be no problem, whereas 33% did see difficulties and 28% were unsure. One member commented that it made clear that moving from ICS to combinations increases the ICS and there is not a low dose ICS possibility once a patient is moved onto a combination.	*This change was considered necessary as BDP is no longer available.*
	A few spotted inconsistencies in the table, e.g. identical doses of 800mcg BDP referred to sometimes as high dose and sometimes as medium. Some disputed where Symbicort and fluticasone should sit. It might be deemed contentious that Fluticasone furorate/vilanterol 92 mcg/22mcg od/ Relvar is considered "low dose". For example: "...described as puffs and some are as doses. This should be standardised to one or the other. Secondly, I see many categorisation inconsistencies and this may be down to how the low, medium and high dose groups are classified. But even despite that, it seems that certain inhalers are inconsistently categorised. For example, non pproprietary Beclometasone at 800mcg is classified as "High dose". However, teh following inhalers are classified as "Medium dose" but contain 1000mcg of BDP equivalent: Fluticasone Evohaler 125, Flutiform 125, Seretide 125 evohaler, Seretide 250 accuhaler – all of these contain BDP equivalent 1000mcg but have been placed in the "Medium" dose category. Either these all need to be re-categorised as high dose or Non proprietary Beclometasone needs to be re-categorised as medium dose. If non proprietary Beclometasone at 800mcg will be re-categoirsed to medium, then Symbicort will also need to be reclassified to medium dose. Finally, there are low dose inconsistencies too. Fluticasone accuhaler 50 at 1 puff twice daily is classified as "Low dose" but it provides BDP	*Agree. For inhalers, the term 'puffs' has been used as this is the terminology used by the BNF.* *Table 9 has been revised.*

	equivalent of only 200 mcg so should be “Very low dose”, similarily the Fluticasone accuhaler 100 should be downgraded from medium to low as it only provides BDP equivalent 400mcg.” “On the surface there appear to be omissions or misleading divisions of dose. Eg noveliser is available in 400. FP accuhaler 1pbd would equate to very low dose. Easyhaler is spelt with a ‘Y’. Turbohaler 400 2pbd would be high dose but not included. Mometasone is usually OD dosing. Beclometasone DP is not included. Symbicort 100/6 2pbd would be low dose and preferable to 200/6 1pbd which would give insufficient LABA. Fostair now available in 200/6 for high dose. Relvar 92/22? better placed at medium rather than low dose as many do not see it as an adult starting dose of ICS.	
	In summary - The problems with the new approach are: a) (as one of our respondents pointed out) one really needs the list of ICS to hand at all times to remind you which drug and dosage comes into which category. This is a significant issue for the large numbers of GPs and practice nurses who are managing asthma yet do not have a particular interest in asthma. What dissemination and education is planned by SIGN/BTS? b) division of the various drugs into "Low dose", High dose" etc. has to be accurate and based on explicit, transparent criteria. i.e at present there is no background information /appendix making it clear on what basis a drug is put into which category. c) as new drugs come along who is going to decide, and when into which category the ICS lies?	*The need for education about the new approach is recognised and will be taken into account as part of the publication process.* *The introduction to section 7 briefly explains the rationale for this approach. The table will be updated as necessary during each biennial revision of the guideline.*
	We recommend that this table is subjected to considerable scrutiny prior to publication. If the bandings are to be useful it is important that they are accurate. One pointed out that if the recommendation is to prescribe by brand, then the brand names should be dominant in Table 9.	*Agree. The table will be checked again by a pharmacist as part of the editorial process.*
	There is also inconsistency in describing medication – sometimes ‘puffs’ and sometimes ‘doses’. This needs tidying up for clarity.	*Agree. Term ‘puffs’ now used in Table 9 (in line with BNF terminology).*
	No numbered steps	*Thank you, this is helpful feedback*

	This iteration has abandoned the numbering of the treatment stages and our members were evenly divided as to whether this is a positive step or not. 47% felt there would be no problem, while 47% felt it was likely to be problematic. Some commented that using verbal descriptions for the steps could lead to confusion with mild/moderate/ severe descriptions. Numbers were felt to be less ambiguous. It was considered that to abandon the numbered steps was to lose a sense of sequence.	*and reflects discussions within the GDG*
	Others liked the descriptive labels, considered them to be clearer than the numbers and felt it was just a question of getting used to them. So it is not clear whether or not this will detract from the clarity of the message about treatment steps.	*The GDG hope that the descriptive labels will become medical parlance.*
	In terms of the additional step being added – current step 3 being divided into 'initial add on' and 'additional add on therapies' – 71% in our member survey were positive about this. It seems to formalise the thinking clinicians were already doing at that step, and clarifies the sequence of medications.	*Thank you. The splitting of this step is a key change in the diagram.*
	Essential Still not convinced people with asthma believe in their inhalers as medicine. Non adherence appears to be at the root of many people with asthmas problems	*No response needed.*
7.1	Interesting but concern for patients and their compliance	*No response needed.*
	Agree, although there is an argument for early introduction of inhaled steroid therapy in what is an inflammatory condition in which it is well known that patients under-estimate their symptoms.	*This is covered by a monitored initiation of treatment (Table 3) at diagnosis stage and by section 7.2 post-diagnosis.*
	I hoped this would be removed altogether.	*This section has been revised to improve clarity.*
7.1.1	Section 7.1.1 is this now quite high given what control is should this not be lower. 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. Recommendation: There are single steroid inhalers that also have a once daily license that can be utilised for low dose usage in	*Unclear what point is being made*

	patients, instead of pMDi usage or moving to combination too quickly	*as this section relates to use of SABA.*
	This seems like a significant omission given the guidance that emerged from the National Review of Asthma Deaths. Clarity about the level of SABA use that represents poor control would be very useful.	*Although not updated this section is compliant with NRAD as >1 SABA a month equals >12 SABA a year. This is also now covered in section 9.1.2*
7.2	Reference to section 7.2.6 made (other preventor therapies) should be 7.2.7	*Corrected.*
	(Page 57 Table 9) In the pharmacological treatment section, it is not that clear as to find the classification of inhaled steroids into very low dose, low dose, medium dose, and high dose Recommendation: This could be made clearer that the "steps" are being replaced with the very low, low, medium and high dose ICS classification Typo: Easyhaler is spelt incorrectly here and this could also potentially say once daily license also If turbohaler can be in at very low dose with the below, then easyhaler should be as well? What is the rationale for only including some products here and not all?	*Unclear what point is being made here.* *This is not the case. The 'steps' have not been replaced with the ICS dose categories shown in Table 9.* *Spelling of 'Easihaler' corrected to 'Easyhaler'.* *Table 9 has been revised.* *Table 9 has been revised.*
	The evidence regarding intermittent use of LABA/ICS in mild asthma does not appear to have been considered	*Correct. This was not within the scope of the current update of the guideline.*
	The evidence regarding intermittent use of LABA/ICS in mild asthma does not appear to have been considered.	*As above.*
7.2.1	Napp suggests that to aid adherence it may be possible to simplify patient treatment regimens by using the same inhaler type for rescue and prevention, and when stepping up and down through treatment doses to gain better control. The challenges with inhaler technique education would therefore be minimised by introducing only 1 technique to a patient rather than 2 different techniques for 2 different inhaler types.	*See section 8.4 Prescribing Devices.*
	The guideline now implies a need to refer for specialist assessment any child requiring more than very low inhaled steroids (more than 200mcg daily of CFC BDB equivalent) or requiring and add-one agent of any kind. This suggests a very low threshold for specialist	*Figure 3 has been amended and now shows that referral to specialist care should occur at the 'High-dose therapies' and 'Continuous use of oral steroids' stages.*

	referrals and the implications for referral rate to specialist services should be carefully considered. The adult step diagram also appears to lower the threshold for referral to specialist care. The valuable option of short term quintupling inhaled steroid doses to reduce the severity of exacerbations is mentioned for the first time – for adults. The studies to investigate the effectiveness of this in children remain to be done and the guideline could usefully identify this as a research priority.	*That is correct.* *Unclear what this point relates to as this approach is not mentioned here.*
7.2.2	Very lose dose, low dose, medium dose and high dose are good explanations, but this should all be made much clearer in the guideline that we are moving away from the "steps" approach. This is not clear and only can be seen if you really look at the guideline	*These dose categories are not a replacement for the 'steps' but are a new way of presenting the data in table 9 on ICS doses.*
	Under the diagnostic section for children it does not state what dose of ICS should be used for small children (under 5). Many paediatricians advocate a "low dose" of 400mcg per day BDP not the lower dose of 200 mcg per day stated here. This is not addressed at all in the document which says one can use "lower dose" or "very low doses". More clarity would be useful here.	*No dosage information is given in the diagnosis section.* *Second GPP amended to clarify that 'very low dose' is a reasonable starting dose for children of any age.*
	There is a typo here says does not dose	*Corrected.*
7.2.3	Please make it clear that not all products are licensed for OD use	*Evidence for once-daily use of ICS was not reviewed for this update.*
7.2.4	"Fluticasone provides equal clinical activity to BDP and budesonide at half the dosage". Please kindly clarify that this statement refers to Fluticasone propionate and not to Fluticasone furoate	*Agreed. Text changed.*
	?need a stronger statement about the difficulty in determining the potency of fluticasone fourate	*Disagree. Existing statement is clear.*
	Relvar and its potency….how can this be classed in the low to medium category when one dose of Relvar would give equivalent to 1000 of BDP or Budesonide? What is the rationale for this in terms of calculation?	*This point relates to Table 9 which has now been revised.*
	The change from exact doses of Inhaled steroids at different treatment steps to the concept of "low dose", medium dose" and "high dose" is generally welcome and in line with GINA Guidance. Table 9 should feature prominently in any shortened guideline and	*Thank you.* *Agree. Table 9 has not previously been included in the Quick Reference Guide, but will be included this time.*

	presented in a form which can be laminated and placed on a clinical room wall.	
	The change from exact doses of Inhaled steroids at different treatment steps to the concept of "low dose", medium dose" and "high dose" is generally welcome and in line with GINA Guidance. Table 9 should feature prominently in any shortened guideline and presented in a form which can be laminated and placed on a clinical room wall. It might be deemed contentious that Fluticasone furorate/vilanterol 92 mcg/22mcg od is considered "low dose".	*As above.* *Table 9 has been revised.*
	"Fluticasone provides equal clinical activity to BDP and budesonide at half the dosage." change to "Fluticasone propionate provides equal clinical activity to BDP and budesonide at half the dosage." "It is difficult to establish the exact equipotent dose of fluticasone furoate." Whilst that statement is correct it would also be helpful to make reference to the guidance in Relvar's SPC. The SPC states: "patients with asthma, fluticasone furoate (FF) 100 micrograms once daily is approximately equivalent to fluticasone propionate (FP) 250 micrograms twice daily, " Should reference be made to extra-fine BDP? (100 micrograms of beclometasone dipropionate extrafine in Fostair are equivalent to 250 micrograms of beclometasone dipropionate in a non-extrafine formulation).	*Agree. Text changed.* *Agree. See revised Table 9.*
	There is lots of evidence that 1.5-2.0 : 1.0 is closer to old MDI BDP, not least because turbohaler delivers twice as much drug FDP MDI and spacer delivers a lot more than Accuhaler! Definitely not 1:1 based on adrenal suppression stud	*Table 9 has been revised.*
7.2.5	Table 9: Spelling error here. This should read Clenil Modulite. Table 9: Combination inhalers- Please consider adding the generic name (ICS/LABA) of each combination inhaler as it is misleading at present as only the ICS is stated. Table 9: Please add "extrafine beclometasone" to Fostair, and an explanation of what this means as a footnote. This would also apply to QVAR. Table 9: Combination inhalers- Fostair-	*Spelling corrected.* *Agree. Added to Table 9.* *Agree. sub-heading of Table 9 amended to include 'extrafine'; QVAR also annotated to show 'extrafine'.*

	Consider adding the available devices here i.e. pMDI and NEXThaler- to make it clear that these two devices have different posology (in terms of the Fostair pMDI 100/6 MART-maintenance and reliever therapy indication which should be mentioned in Section 7.3.4) (As below both Seretide Evohaler and Accuhaler are listed demonstrating the differences in dosing). Table 9- Combination inhalers- Fostair- Please include in the "high dose" section- Fostair 200/6- two puffs twice daily. Fostair 200/6 was licensed for adult asthma on the 14th August 2015.	*Agree. Added to Table 9.* *Agree. Added to Table 9.*
	Table 9 is very useful – well done.	*Thank you.*
	The new table (9) does not accurately reflect the dosing info in the SPC. It classes budesonide 800mcg daily as medium dose and then puts Symbicort 800mcg daily as high dose (these contain the same drug). According to the SPC symbicort 100 is not equivalent to fostair 100 or fluticasone 125. In the SPC for Relvar the 192/22 dose is compared to 250mcg twice daily (as stated earlier in the SIGN guideline this is accepted to be equivalent to 2000mcg "traditional BDP"). At half the dose the lower strength of Relvar should therefore be equivalent to 1000mcg BDP. When comparing this with the other inhalers in the table this is not LOW dose. I would have thought >800mcg traditional BDP should be considered as high dose. Although CFC containing BDP is no longer available I still think it is widely accepted as a valid comparison. It could be called "traditional BDP" and as long as it is compared with for example Clenil then it would be clear. I understand the debate around Relvar but I think it is valid to use the SPC until more information is produced. This table is not consistent with the rest of the table.	*Table 9 has been revised.*
	The statement on use of High Dose Inhaled Corticosteroid Card seems unduly negative. Perhaps it should be caveated by the point that the MHRA recommend that patients on high dose ICS should be given a steroid card. The blue steroid card was not designed for use with high dose ICS, so a more respiratory specific card has been developed. Whilst I don't disagree that the benefits and possible disadvantages remain to be established, if the MHRA advise HCPs to issue a steroid card as	*Section 7.2.5 was not within the scope of the current update.*

	a safety measure, then perhaps the guidance should make this clear and that the high dose ICS safety card is a more respiratory patient friendly way of doing this.	
	Table 9 clenil modulite typo and ? high dose correct (250 2 puffs BD= 1000VFP 250 2 puff bd -= 2000) ? is this a typo Need a comment on the importance of plotting children's growth on centiles as this is poorly understood and not always done in GP surgery.	*Spelling of 'Clenil modulate' corrected to 'Clenil Modulite'.* *Table 9 has been amended.* *This is covered by the first GPP in section 7.2.5.*
	There are inconsistenices in table 9 Budesonide 400 is moderate here and high for Symbicort below - i.e. not consistent I would not consider Relvar low dose despite serum cortisol. I would still go with NICE the lower strength delivers fluticason furoate 92mcgms once daily (mapporximatelt equivalent to FP 250mcgsa twice daily). Because a lower strength is not available, the ability to step down treatment is limited. I also think the licensing for these drugs should be on the table	*Table 9 has been revised.*
	Page 65/193 (57 as a numbered page): Table 9: Doses of inhaled corticosteroids; here, ciclesonide is indicated for 12 and above. The way it is presented is confusing as it is not clear on whether or not ciclesonide is indicated for paediatrics and for which age group.	*Table 9 has been revised and split into adult and paediatric sections to improve clarity.*
	There are a number of errors in the table in this section - e.g. should be Modulite and Easyhaler - and a number of omissions of products that have been launched since the previous version - such as DuoResp Spiromax, Fostair NEXThaler. All should be included for completeness for comparison in particular due to the guidance to not prescribe generically (and therefore to prescribe by brand). In addition for example - there are no non proprietary inhalers with beclometasone MDI and there is already DH guidance to prescribe beclometasone MDIs by brand from 8th August 2006. This table should reflect all brands and only those generics that are available as at the end of this consultation period as a minimum, and be accurate and complete. In addition, we note the inclusion of Relvar in the low dose category - despite the fact that the Relvar SmPC in section 4.2 states	*Spelling corrected.* *Agree. Specified products added to Table 9.* *Table 9 revised.*

	that "100mcg of fluticasone furoate is equivalent to 250mcg twice daily of fluticasone propionate" (500mcg daily) = 1000mcg daily of beclometasone dipropionate equivalent, yet the same low dose column in this table in the guidance refers to equivalent lower doses of fluticasone propionate and beclometasone dipropionate. Fluticasone low dose is detailed as 200mcg equivalent and beclometasone (suggest add standard particle to differentiate from extra fine particle in Qvar) is detailed at 400mcg daily equivalent. Relvar included as low dose is therefore not reflective of their SmPC and is confusing and not equivalent to others in the same column. This equivalent of 500mcg fluticasone propionate (= 1000mcg beclometasone dipropionate standard particle) is an in appropriate starting dose for adults and should not be considered low dose as referred to in this table and could cause significant patients safety issues if it is recommend as so. Correct equivalents for very low, low, medium and high should be detailed.	
	Table 9- fluticasone propionate accuhaler 50mcg one dose b.d and symbicort 100/6 one dose bd are under low dose but are equivalent to 200mcg BDP equiv- ? should be very low dose. mometasone twisthaler 200mcg one dose twice daily is equivalent to 800mcg of BDP equiv- ? should this be medium dose not low dose. Relvar 92/22 one dose once daily is equivalent to 1000mcg of BDP equiv- ? should be high dose not low dose. Fluticasone 125 mcg two puffs b.d is equivalent to 1000mcg of BDP equiv- ? Should this be high dose Fluticasone 100 mcg one puff b.d and symbicort 100/6 two doses bd are equivalent to 400 mcg of BDP equiv- ? Should they be low dose Flutiform 125/5 2 puffs b.d, seretide accuhaler 250 one dose b.d and seretide evohaler 125 two puffs b.d are all equiv to 1000 mcg of BDP equiv- ? should be high dose not medium Symbicort 200/6 two doses b.d and symbicort 400/12 one dose b.d are equiv to 800mcg BDP equiv- ? should this be high dose? mometasone twisthaler 400mcg one dose	*Table 9 has been revised.*

	twice daily is equivalent to 1600mcg of BDP equiv- ? should this be high dose not medium dose. Fostair 100/6 two puffs bd is equivalent to 1000mcg of BDP equiv- ? should this be high dose and not medium	
7.2.6	Agree. This is an important message.	*Thank you.*
	Bud 400 is moderate here and high for Symbicort below - i.e. not consistent	*Table 9 has been revised.*
7.2.7	Bud 400 is moderate here and high for Symbicort below - i.e. not consistent	*Table 9 has been revised.*
7.3	Figure 2 states 'SABA as required - consider moving up if using 3 doses a week or more'; is a dose defined as a puff of SABA, or is a dose considered a day on which SABA is used (regardless of the number of puffs used that day)? Would it be helpful to include the option of SIT to the figure (eg for patients with severe exacerbations) or a footnote added? For patients on SIT, the use of SABA as a guide to step up is not applicable, because their reliever use is ICS/LABA - does the figure need to take account of this? Finally, SABA/reliever use is only one factor with which step up/down decisions are made - other factors are symptoms (eg awakenings, activity limitation), lung function plus risk of future adverse events. Should this be included in the figure (eg by advocating use of RCP3/ACT/ACQ/spirometry, as per the text?) Thank you.	*Although these are valid points, consideration of SABA and use of other reliever medications was outwith the scope of the current update but will be considered for inclusion in the next update.*
7.3.2	"In children, options for initial add-on therapy are limited to LABA and LTRA, with evidence to support both individually, but insufficient evidence to support use of one over the other (see section 7.4.2). LABA are not licensed for use in children under 5 years of age and evidence for use of LTRA in this age group is limited to studies comparing LTRA with ICS or placebo (see section 7.2.7)." Seretide (FP and salmeterol) is licensed for use in Children 4 years and older and is indicated for the regular treatment of asthma where use of a combination product (long-acting β2 agonist and inhaled corticosteroid) is appropriate as per the Seretide Evohaler SPC https://www.medicines.org.uk/emc/medicine/2914 and the Seretide Accuhaler SPC https://www.medicines.org.uk/emc/medicine/2317/SPC/Seretide+100,+250,+500+Accuhaler	*Agree. Age changed to <4. Wording of recommendation changed to ≥5. The GDG does not feel that there is enough evidence to make a recommendation for use in the <5's*

	The evidence base for recommending the move to additional agents (SABA or LTRA) before increasing inhaled steroids to low dose (400mcg of BDP-CFC equivalent) in children remains unclear.	*Agree.*
	Agree.	*Thank you.*
7.3.4	AstraZeneca welcomes increased guidance around the use of a single inhaler for both maintenance and reliever therapy in Section 7.3. However, AstraZeneca considers that some of the new additions require revision to accurately reflect the references used and to ensure clarity of the guideline: • Section 7.3.4 currently covers both fixed dose ICS/LABA combination inhalers as well as a single inhaler for both maintenance and reliever use. As currently presented there is potential for confusion over the recommendations for ICS/LABA fixed dose combinations and those for maintenance and reliever therapy. AstraZeneca therefore propose that maintenance and reliever therapy should be given its own subsection. • AstraZeneca believes that the wording "single inhaler therapy" alone in reference to ICS/LABA used as maintenance and reliever therapy is unclear as it is possible for some asthmatics to be prescribed only a single inhaler e.g. mild intermittent asthmatics using a SABA. The term "single inhaler therapy" does not adequately convey that it is maintenance and reliever in one inhaler. Therefore, AstraZeneca proposes that it is referred to as maintenance and reliever therapy, consistent with wording in the relevant product licences.[Symbicort, DuoResp, Fostair SPCs]	*Thank you.* *Agree. a separate subsection (7.3.5) covering Maintenance and Reliever Therapy has been created.*
	With reference to the statement "*Single inhaler therapy (combining maintenance and reliever therapy) in patients already on ICS/LABA combinations reduces the number of asthma attacks requiring oral steroids or hospitalisation but may increase the number of adverse events*": AstraZeneca disagrees with the wording "may increase the number of adverse events." The reference used[Kew] demonstrates a non-significant <u>decrease</u> in adverse events when using maintenance and reliever therapy (see table below). AstraZeneca would therefore propose rewording the statement to more accurately reflect the reference used: "*Maintenance and reliever therapy in patients*	*Agree. This section has been revised.*

	already on ICS/LABA combinations reduces the number of asthma attacks requiring oral steroids or hospitalisation, with no change in the number of adverse events." (See Fig 3) "*Compared with current best practice, single inhaler therapy did not lead to significant reductions in hospital admissions and increased the number of adverse drug reactions*". AstraZeneca disagrees with this statement in its entirety as current best practice is not a defined treatment strategy and in the reference cited was ICS maintenance plus SABA as needed. Additionally the reference[Cates] also shows that maintenance and reliever therapy shows a significant reduction in the incidence of exacerbations requiring OCS use in comparison to ICS alone (see table below). It is important to consider the phenotype of asthma patients who are on maintenance ICS with no add on therapy. Typically, these patients have mild to moderate asthma and are not normally considered to be frequent exacerbators. It is therefore not surprising that no difference in hospitalisations was noted in this meta-analysis. AstraZeneca would therefore propose that the statement is reworded to read: "*Compared with ICS alone, maintenance and reliever therapy did lead to significant reductions in exacerbations requiring OCS use although there was not a significant reduction in hospital admissions, with no change in the number of adverse drug reactions*" In light of this change, AstraZeneca would also recommend that the removal of recommendation "Single inhaler therapy should not be used as a step-up therapy for patients on inhaled corticosteroids only" (See Fig 4) AstraZeneca also disagrees with the two statements regarding maintenance and reliever therapy at the end of this section: *In adults over the age of 18, single inhaler therapy can be used for patients who are stable on combined therapy and a short-acting β2 agonist.* *Single inhaler therapy should not be used as a step-up therapy for patients on inhaled corticosteroids only.*	*As above.* *Agree. Second recommendation deleted.* *This recommendation has been revised.* *This recommendation has been deleted.*

	The randomised clinical trials supporting Symbicort maintenance and reliever therapy were not in stable asthma patients but in patients who had experienced an exacerbation of their condition in the previous 12 months. Approximately 50% of patients were receiving ICS and LABA prior to study entry supporting the positioning of this treatment option in patients not currently controlled on a combined product and a short-acting β2 agonist.[Kuna, Rabe] Additionally the study by O'Byrne recruited patients who were on ICS plus SABA with a history of one or more asthma exacerbation in the last year. The study compared Symbicort maintenance and reliever therapy at a maintenance dose of 100/6 twice daily to an ICS dose of budesonide 400 mcg twice daily. The study demonstrated a lower exacerbation rate and a prolonged time to exacerbation for Symbicort maintenance and reliever therapy compared to the 4-fold higher budesonide study arm. The median average use of Symbicort as a reliever medication was 0.5 inhalations per day.	
	Fostair 100/6 (beclometasone dipropionate/ formoterol) pMDI is also licensed for maintenance and reliever therapy (MART). For this indication patients would take their Fostair 100/6 as both maintenance (one inhalation twice daily), and as a reliever in response to symptoms (one additional inhalation as needed). Maximum of 8 inhalations daily. Please note that the Fostair NEXThaler 100/6 and the Fostair NEXThaler and pMDI 200/6 do not have a licence for MART.	*This is now covered in the new section 7.3.5.*
	Page 60, section 7.3.4: I am not a major enthusiast for Single Inhaler Regimens, but can see that they have a place and I think the highlighted, newly added parts of this section are rather slanted against SIT. Reference 463 does not demonstrate an increase in adverse events; I appreciate that the authors of the review use the same wording as you in their abstract, but this was actually a neutral result, if anything the odds ratio favoured SIT, and one could equally well state that a benefit of SIT on adverse events was not excluded. And while I agree with the statements from reference 464, why pick out these two results from this review? Why not point out that SIT reduced the need for those exacerbations requiring oral steroids? However, the most important issue is the wording of the 1st recommendation. In one	*Section 7.3.4 has been split and now includes a separate sub-section on Maintenance and reliever Therapy (7.3.5). The text has also been revised.*

	sense it is correct in that patients may prefer SIT purely for convenience if stable (i.e. well-controlled) on ICS/LABA plus SABA. However, in the bulk of the studies that comprise the evidence here, the patients were not particularly stable. They had a measurable need for SABA in the study run-up, and FEV1 tended to be low. I therefore think the word stable in the recommendation is (a) misleading and (b) does not capture all the possibilities of SIT. SIT may also be an option to try in patients who have had some benefit from adding a LABA but whose control remains imperfect on ICS/LABA plus SABA, as an alternative to adding a separate drug.	
	A warning should be added here regarding the dose of ICS prescribed when initiating LABA/ICS combination therapy. We have replicated the Covvey study published in Thorax looking at dose of ICS prescribed when LABA/ICS combination was started and found the same results (even worse) that patients were moved to high dose ICS by prescribers when a combination inhaler was started. This was not deliberate, it is just prescribers don't know what the equivalent doses of ICS are.	*This is covered by the revised Table 9.*
	I have a number of questions about this section please. 1. I believe that paragraph 3 in this section (under the GPP 'tick'), refers to the wording in the prior version of the guideline. As I understand it, single inhaler therapy (SIT) with budesonide/formoterol may be used in selected adult patients on ICS or ICS/LABA, who have poor control (eg with recent prior severe asthma exacerbations), because SIT is associated with a reduction in severe exacerbations compared to the same dose of budesonide/formoterol used for maintenance treatment with additional SABA use for relief. This is predominantly drawn from the Rabe (ref 460) and O'Byrne (ref 459) studies, with the proviso that these studies had some methodological limitations which limited their generalisability (hence the caution to not reduce maintenance ICS dose when prescribing SIT to patients with poor control). However, the Grade A recommendations in this section advise that SIT can be used for 'stable patients already on combined therapy'; this is misleading, because the Rabe and O'Byrne trials were conducted in patients with recent poor control or ongoing current symptoms during run-in - the word 'stable' in the recommendations implies that the GDG are advocating SIT use in patients who have	*Section 7.3.4 has been revised and a new section (7.3.5) on Maintenance and Reliever Therapy added.*

	not had recent poor control. 2. In addition, paragraph 3 states that SIT can be considered in patients on ICS alone who have poor control, yet the recommendations in this section suggest that only patients already on combination therapy are eligible. This seems at odds with the text and the evidence base. 3. The recommendations in this section state 'Single inhaler therapy should not be used as a step-up therapy for patients on inhaled corticosteroids only'. However, what is the evidence for this? Both paragraph 3 in this section and the Rabe and O'Byrne studies included patients on ICS alone. SIT may be considered in poorly controlled patients on ICS alone or ICS/LABA. 4. In paragraph 4 of this section (the new highlighted section), there is mention of increased risk of 'adverse events' with SIT. Please could you specify what these are and consider including details in the text, to aid clinicians in their decision making regarding use of SIT and also to aid patient counselling when prescribing SIT. 5. There is further evidence regarding the benefit of SIT in reducing severe exacerbations in patients at risk of poor control/with recent poor control from the recent Papi paper 'Beclometasone–formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial' (Lancet respiratory medicine 2013 1, 1, 23-31); there has also been a non-commercial study undertaken (please note my declarations, because I have undertaken non-commercial research on SIT) . Taken together, in patients at risk of severe exacerbations, SIT may be considered to be superior to the same maintenance dose of ICS/LABA with SABA for relief in terms of reducing severe exacerbations, and with comparable outcomes for other measures. However, this message does not come across in this section ie that SIT is potentially a valuable treatment option in reducing the burden of exacerbations in 'at risk' patients [with the caveats that patients need an asthma plan, counselling about when to seek medical review in the setting of worsening asthma, and other general asthma care such as inhaler technique checks]. Might the GDG consider inserting a table/checklist to aid clinicians in terms of helping to select the patient groups in whom SIT can be considered particularly beneficial, as well as highlighting	

	key adverse effects/issues that need to be considered when prescribing SIT (eg not to reduce maintenance ICS dose). Thank you 6. Given that a specific combination of ICS/LABA (budesonide/formoterol) is mentioned in paragraph 3 in this section, consideration should be given to including a statement that other formulations are also approved for use with SIT (eg beclomethasone/formoterol).	
	The recommendation that “single inhaler LABA/ICS maintenance and reliever therapy should not be used as a step up from ICS alone“ may not apply to all patients. If the concept of future risk is considered then patients with a history of exacerbations may respond more favourably to single LABA/ICS therapy. (GINA Guidelines and referenced studies).	*This recommendation has been removed.*
	The recommendation that " single inhaler LABA/ICS maintenance and reliever therapy should not be used as a step up from ICS alone " may not apply to all patients. If the concept of future risk is considered then patients with a history of exacerbations may respond more favourably to single LABA/ICS therapy. (GINA Guidelines and referenced studies).	*This recommendation has been removed.*
	Evidences suggest use of LABA without ICS increases the mortality risk in asthmatics. In order to improve compliance and to avoid use of LABA on its own, LABA + ICS combination should be used as add on therapy. This should be clearly reflected on the figure 2 in the summary of asthma guidelines for adults.	*Agree. Figure 2 amended.*
7.4	Tiotropium (Spiriva Respimat) is the only LAMA currently indicated for use in asthma. The SPC states that it can be used ''as an add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥800 µg budesonide/day or equivalent) and long-acting β2 agonists and who experienced one or more severe exacerbations in the previous year''. Consequently use as outlined in Section 7.4 is considered off label use and as such tiotropium is not accepted by SMC for use at this stage of the treatment pathway.	*Agree. Text in section 7.4 amended to clarify that tiotropium is currently the only LAMA licensed for use in asthma.* *Agree. Text amended to clarify that ICS plus tiotropium is an off-label combination. No recommendation is made for use of tiotropium at this treatment stage although it is identified as an option when other approaches have proved inadequate.*
	The new text seems fair.	*Thank you.*
	I would suggest to remove use of Beta agonists oral tablets from the asthma guideline	*Disagree. Oral tablets are still available and remain an option in*

	as this should not be the case in this 21st century when we instead use high dose nebulised beta agonist.	*adults if other options have failed.*
	Agree.	*Thank you.*
	"If no improvement when a LABA is added, stop the LABA and try a LAMA."- Tiotropium respimat is only licensed if patient is also on a LAMA. Also SMC advice states must be on a LABA. Also not clear that this advice is for adults only.	*Agree. See response to ND above.* *Also 'Additional add-on therapies' box of Figure 2 altered to reflect fact that LAMA can be considered in addition to ICS and LABA if control is still inadequate on this combination.* *Paragraph 7.4.3 clearly states that evidence relates only to adults.*
7.4.1	I think the title should be inhaled corticosteroids rather than just ICS	*Agree. Changed.*
	The new text seems fair.	*Thank you.*
	The valuable option of short term quintupling inhaled steroid doses to reduce the severity of exacerbations is mentioned for the first time – for adults. The studies to investigate the effectiveness of this in children remain to be done and the guideline could usefully identify this as a research priority.	*Unclear to what this refers. It may be a reference to 7.11.1 (increasing ICS as part of a PAAP) which was outwith the scope of this update. However, the statement there still stands – including the need for research.*
	Agree.	*Thank you.*
7.4.2	usefulness if concurrent rhinitis include mention of need to explain potential adverse effects on children's emotional health	*This was not within the scope of this update.*
	Agree.	*Thank you.*
7.4.3	It is important to highlight to relevant parties that all the studies discussed in this section either directly or indirectly (through referenced RCT review papers) are all regarding tiotropium. The use of the "LAMA" term may mislead HCP's reading this guideline into assuming that this discussed evidence is applicable to all LAMA medications and that there are other LAMA's with an indication in asthma. It is important to highlight that currently tiotropium specifically in the Spiriva Respimat soft mist formulation is the only LAMA with a licensed indication in asthma in the UK. This section relies heavily upon the recent 2016 Cochrane review (Kew KM, Dahri K. 2016.) in interpreting the evidence for adding	*Agree. 'LAMA' changed to 'tiotropium' in title and text.* *Now specified in section title.* *The review results are based almost exclusively on these two trials; other trial data do not change*

	tiotropium treatment in addition to baseline ics/laba. This review paper was a post hoc analysis of only 3 studies, two of which were the key registration Primotina twin studies for tiotropium (Kerstjens HAM, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al.. N Engl J Med. 2012; 367:1198–1207. PMID:22938706) and the other was the Cadentina (Ohta et al. PLOS ONE | DOI:10.1371/journal.pone.0124109 April 20, 2015) study. It would be more prudent to use the Primotina twin studies alone when discussing the evidence for this. Primotina was designed specifically to look at symptomatic asthmatic patients at step 4 who were still having at least 1 exacerbation in the past year despite high dose ics/laba. Cadentina was very different in terms of patient population and background treatment, for example only 56.8% of the Cadentina patient populations were on a LABA medication and therefore the appropriateness of pooling this data with the Primotina data for a review of the evidence for adding an LAMA to ICS/LABA should be questioned. The phrase that “evidence relating to serious adverse effects was inconclusive” should be elaborated on so as not to give the impression to HCP’s that a safety signal may have been raised. The frequencies of patients who were reported with serious adverse events were similar between the treatment groups in the PrimoTinA-asthma® trials (tiotropium Respimat® 5 µg: 8.1%, placebo: 8.8%). Also the RCT review paper also states that “people taking tiotropium add-on were less likely to have adverse events than those taking ICS/LABA alone (OR 0.7 95% CI 0.52-0.94)” (Kew KM, Dahri K. 2016). The phrase “There is insufficient evidence to suggest that addition of LAMA to ICS in patients inadequately controlled on ICS alone has any benefit over addition of LABA to ICS” does not accurately reflect the Cochrane RCT review paper summary. A more accurate statement would be that currently there is no evidence to demonstrate that LABA has any superiority over LAMA as an add-on therapy-however given that the evidence base for LABA + ICS is currently much larger, the authors do not feel that the evidence is strong enough to recommend that LAMA can be substituted for LABA at present. Further Comments	*the result.* *The review paper states that there were fewer “...non-serious adverse events...” but “...the benefit of tiotropium add-on on the frequency of hospital admission is still unknown...”. Sentence revised to reflect this.* *Disagree. The GDG consider that the statement is appropriate as written.*

	We believe that it is extremely relevant to HCP's to include some discussion relating to the potential emerging role of Tiotropium in treating paediatric asthma. Although it should be clearly stated that there is currently no licensed indication for the use of tiotropium in children for the UK, it is recognized that there is growing evidence for the use of of tiotropium in paediatric patient subsets (Hamelmann M et al Journal of Allergy and Clinical Immunology doi:10.1016/j.jaci.2016.01.011) + (Vogel C, Curr Opin Pulm Med 2016, 22:74–79). The new GINA 2016 guidelines recognize that "Add-on tiotropium by mist inhaler improves lung function and increases the time to severe exacerbation" and as such they have updated their guidelines to now recommend that "tiotropium (long-acting muscarinic antagonist) by mist inhaler may be used as add-on therapy for adult or adolescent patients with a history of exacerbations" at step 4 or 5.	*Evidence for use of tiotropium in paediatric asthma was not reviewed.* *The GDG did not feel that the evidence was strong enough to support a recommendation for use of tiotropium at the 'additional add-on therapy' stage of treatment.*
	Not sure what you mean by (although results were inconclusive) - mid long 1st sentence! - ?explain.	*According to the review paper, "...the confidence intervals did not rule out that there was no difference..." therefore the results were inconclusive.*
	As per the point highlighted in section 7.4 while no recommendation is made the text should reflect that this is off label use and as such it has not been accepted for routine use at this stage of the treatment pathway.	*Agreed. Text amended.*
	I do not think the evidence supports the use of LAMAs in asthma as the draft guideline has placed it. The referenced Cochrane reviews do not support it as a clear alternative when there is no response to addition of LABA. The licensed indication for tiotropium in asthma is for pts on 800mcg ICS and a LABA and have had one or more severe exacerbations. The evidence supporting this license only included people with fixed airways obstruction. Therefore it should only be used by specialists for patients in this category. This draft guideline has placed it in an unlicensed position. There is a theoretical safety concern if patients are given a long acting bronchodilator (LAMA) separate to an ICS, therefore I think the use of LAMAs in asthma at present should be restricted at present. I think placing it in the steps alongside LRTA will encourage use in primary care outwith license and without the evidence to support it.	*The GL does not make a recommendation for use of LAMA at the 'additional add-on therapy' stage. However the GDG consider that use of LAMA as an additional treatment in patients inadequately controlled on ICS plus LABA, is a possible option. The wording in Figure 2 has been altered to clarify that a trial of this option can be 'considered'.* *Use of ICS+LAMA as an alternative to ICS+LABA if the latter is ineffective is mentioned in 7.4 as a possible option, but again no recommendation is made and this option is not included in Figure 2 reflecting the lack of evidence to support this approach rather than increasing the dose of ICS. A statement has been added to 7.4 to clarify that this would be 'off-label' use.*

	The guideline presents the evidence for the possible use of LAMA at stage 3 and beyond in asthma treatment in adults.	*No response needed.*
	Agree.	*Thank you.*
	There needs to be a clear indications and criteria to use LAMA. -A further clarification is required whether there is any evidence in favour of other available LAMA apart from tiotropium	*Agree. Text amended to reflect that evidence refers only to tiotropium.*
	"the addition of LAMA to ICS is a possible alternative"- Should also be on a LABA- See comment for 7.4.	*Text amended to show that ICS+LAMA is 'off-label' use.*
7.4.4	When should GORD be investigated in difficult asthma?	*Not relevant to this section. GORD not within the scope of this review.*
	This section could perhaps also draw attention to unpredictable metabolism in smokers and the potential for some antibiotics to alter therapeutic levels.	*Smoking and ICS covered in 7.2.6; antibiotics in 7.7.3.*
7.5	In this section it states that "In adults, the addition of a LAMA to high-dose ICS plus LABA may confer some additional benefit although results are currently inconclusive (see section 7.4.3) and further research is needed to confirm… " ,which I do not believe reflects current evidence. The Primotina clinical trials were large (n=912) double blinded, RCT twin studies which demonstrated that tiotropium added to at least ICS+LABA background treatment in this patient cohort demonstrated statistically significant improvements in lung function and delayed time to first severe asthma exacerbation vs the control group.	*Caveat removed from here as section 7.4.3 (as cross-referenced) explains this further.*
	2nd para - slightly clumsy repetitive sentence - suggest end sentence after 'and further research is needed'. Recommendation 4th bullet - Does anyone still prescribe slow release beta-2 agonist tablets? - particularly as every patient is already receiving a LABA - this is a carry over from guidelines circa 1990 (!!) - ?remove	*Sentence split, rather than truncated as need for research refers to different doses of ICS/LABA not just 'high-dose ICS plus LABA'.* *Disagree. Tablets are still available so it is appropriate to include them as an option.*
	Agree.	*Thank you.*
	Should there also be an indication here for referral.	*The second GPP specifies the need for referral to specialist care before proceeding to continuous or*

		frequent use of oral steroid therapy.
	Safe ICS dosage should be mentioned as foot note at the bottom of the summary of the asthma guidelines for both adults as well children	*ICS dosage covered by revised Table 9.*
	"add a LAMA"- does not say not for children	*This is already stated in the text. Bullet point in recommendation amended to clarify this.*
7.6	There should be a clear mention of continuous oral steroids should never be used apart from certain indications like proven Bronchopulmonary aspergillosis!	*Disagree. This option is widely used and the need for specific monitoring is covered in section 7.6.1.*
7.6.1	We would suggest that there is a really important absence in screening in adults for cataracts or glaucoma if they have had multiple courses of OCS	*Agree. Glaucoma added to final bullet point.*
7.7.1	Just a comment, but there is always a disproportionate amount on Omalizumab. Is Mepo licensed yet? - if so ?add as another recommendation	*This reflects the evidence and the number of things to take into account if considering its use.* *Mepolizumab covered under new section 7.7.2.*
	In the current draft BTS/SIGN guidelines, mepolizumab is discussed under the 'ANTI-IgE MONOCLONAL ANTIBODY' subheading. This is incorrect as mepolizumab is an anti-IL5 monoclonal antibody. Furthermore, it mainly references a systematic review published in July 2015. Mepolizumab received a European license as an add-on treatment for severe refractory eosinophilic asthma in adult patients at a recommended dose of 100mg SC once every 4 weeks in December 2015 (1). Thus, the systematic review does not take into account mepolizumab's licensed severe asthma population, dose and route of administration. We recommend inclusion of literature relevant to mepolizumab's license as outlined below. We would also like to bring to your attention the recently updated GINA 2016 guidelines, where mepolizumab received guidance in a severe refractory eosinophilic asthma population for uncontrolled step 4 and step 5 of the treatment algorithm (2). The systematic review that is currently referenced included clinical trials from earlier studies, which have shown that mepolizumab is not efficacious in the whole asthma population (3), however identified mepolizumab's efficacy in a severe asthma	*Agree. New sub-section (7.7.2) and heading 'Anti-IL-5 monoclonal antibody' added to cover mepolizumab.* *The GDG consider that the existing text adequately identifies the populations in whom this treatment might be beneficial. A review of evidence of steroid-sparing effects of treatments was not within the scope of this update.* *Reference 3 cited here is the Powell 2015 review cited in the guideline; references 4-9 are all included in the Powell review, references 10-12 are outwith the*

	population (4-6). The following 3 pivotal phase IIb and III clinical trials, have formed the basis of the population, dose and dosing regimen of mepolizumab's licence and are referenced in mepolizumab's SmPC. Two exacerbation studies, DREAM and MENSA, and one oral corticosteroid sparing study, SIRIUS, showed mepolizumab's efficacy in reducing exacerbation rates, reducing dependency on OCS, improving quality of life and improving asthma control in a severe refractory eosinophilic asthma population (7-9). Mepolizumab's dose and route of administration was established through a comprehensive clinical research programme which established the subcutaneous absolute bioavailability for mepolizumab to be 74%. A dose-response analysis identified the 75 mg IV dose (i.e., 100 mg SC) as the pharmacologic effective dose achieving 90% of the maximum effect. The phase III trial program confirmed similar efficacy in the 75mg IV and the licensed 100mg SC route in severe refractory eosinophilic asthma patients (7, 8, 10). This is reflected in mepolizumab's licensed fixed dosing regimen of 100mg SC at 4 weekly intervals (1). Therefore the evidence considered should be relevant in terms of disease severity (severe refractory eosinophilic asthma) as well as the indicated route and dose of administration. In summary, (i) mepolizumab should have a separate subheading: 'Anti-IL5 monoclonal antibody'; (ii) the systematic review in the current BTS/SIGN guidance was published before mepolizumab's licence (July 2015) (3), therefore does not take into account the above mentioned points, and is thus out of date. We suggest inclusion of a summary of the key studies relevant to mepolizumab's licence in the guidance. We have summarised these studies, with a list of relevant references, for your convenience below: Mepolizumab is a monoclonal antibody which targets interleukin-5 (IL-5). IL-5 is a cytokine responsible for growth, differentiation, recruitment, activation and survival of eosinophils (11). Mepolizumab inhibits the bioactivity of IL-5 by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils. In adults, it is licensed in the UK with the following indication: as an add-on treatment for severe refractory eosinophilic	*scope of this update.*

	asthma in adult patients. Mepolizumab should be prescribed by physicians experienced in the diagnosis and treatment of adult severe refractory eosinophilic asthma. The recommended dose is 100 mg administered subcutaneously once every 4 weeks (1). There were 3 randomised, double-blind, parallel-group clinical studies of between 24-52 weeks duration. These patients either remained uncontrolled (at least two severe exacerbations in the previous 12 months) on their current standard of care, including at least high doses of inhaled corticosteroids (ICS) plus an additional maintenance treatment(s), or were dependent on systemic corticosteroids (7-9). Although the clinical trial data contains both 75mg IV and 100mg SC data, a pharmacodynamic and pharmacokinetic study (MEA114092) was also carried out in adult asthmatic patients with elevated blood eosinophil levels, which demonstrated that there was bioequivalence between these two doses (10). This was further confirmed in the clinical trials.	
	Two exacerbation studies, DREAM and MENSA, enrolled a total of 1192 patients. There was a requirement for patients to have a history of two or more asthma exacerbations and a record of high-dose ICS use in the 12 months prior to screening plus an additional maintenance treatment(s). In DREAM, the inclusion criteria were based on patients having airway inflammation that was likely to be eosinophilic in nature identified by one or more criteria at study entry or in the previous year: blood eosinophil count, sputum eosinophil count, exhaled nitric oxide and response to OCS treatment. Based on exploratory multivariate modelling, a blood eosinophil count of 300 cells/µL in the previous 12 months or 150 cells/µL at baseline was considered an appropriate marker of response and taken forward as inclusion criteria in the phase III trials (MENSA and SIRIUS). Patients continued to receive their existing asthma medicine during the studies. The proportion of patients on maintenance OCS was 31% and 24% in DREAM and MENSA, respectively (8, 9). The primary efficacy endpoint in both DREAM and MENSA was the rate of clinically significant exacerbations. This was defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalisation and/or emergency department visits. Mepolizumab showed consistent efficacy	

	vs. placebo across both trials, with a reduction in rate of clinically significant exacerbations of 48%, 47% and 53% (p<0.001) in the 75mg IV treatment in DREAM, and MENSA 75mg IV and 100mg SC, respectively. Results of the meta-analyses of the two exacerbation studies supported the individual study results by demonstrating similar reductions on the rate of clinically significant exacerbations (47% to 56%, p<0.001 all doses of mepolizumab). Mepolizumab also achieved improvements in blood eosinophil levels, lung function, asthma control, quality of life and overall response to therapy (8, 9, 12).	
	In the oral corticosteroid-sparing study, SIRIUS, a total of 135 patients were enrolled, who were being treated daily with OCS (5-35mg per day), in addition to optimised standard of care (i.e. high-dose ICS plus an additional maintenance treatment[s]). SIRIUS was designed to evaluate if add-on treatment with mepolizumab, as a 100mg SC injection, enabled reduction in maintenance OCS from baseline following OCS dose optimisation, while maintaining asthma control in comparison with placebo. The primary efficacy endpoint for this study was the number of subjects in each category of percent reduction of OCS dose (90% to 100%, 75% to <90%, 50% to <75%, >0% to <50%, no decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment) at Weeks 20-24 compared with the baseline dose. The results of this study demonstrated that with the addition of mepolizumab to standard of care, patients were significantly more likely to achieve greater reductions in their maintenance OCS doses, while maintaining asthma control, compared with subjects receiving placebo (odds ratio: 2.39, p=0.008). It should also be considered that although this study was powered to reduce maintenance OCS doses, the patients within this study also achieved a clinically meaningful reduction in the rate of clinically significant exacerbations (32%, p=0.042) as well improvement in quality of life and asthma control (7). In the clinical studies, in patients with severe refractory eosinophilic asthma, the most commonly reported adverse reactions during treatment were headache, injection site reactions and back pain. Acute and delayed systemic reactions, including hypersensitivity reactions (e.g. urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of mepolizumab. These reactions generally occur within hours	

	of administration, but in some instances have a delayed onset (i.e., typically within several days). These reactions may occur for the first time after a long duration of treatment. The incidence of local injection site reactions with mepolizumab 100mg SC and placebo was 8% and 3%, respectively, and were non-serious events. There were no cases of anaphylaxis in the mepolizumab clinical trial program, and all patients were observed for 1 hour post administration of mepolizumab (1).	
	References 1. Nucala, Summary of Product Characteristics 2015. Available from: http://www.medicines.org.uk/emc/medicine/31388. 2. Global Initiative For Asthma (GINA) 2016. Available from: http://ginasthma.org/. 3. C P. Mepolizumab versus placebo for asthma (Review). Cochrane Library. 2015. 4. Flood-Page P, Swenson C, Faiferman I, Matthews J, Williams M, Brannick L, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. American Journal of Respiratory and Critical Care Medicine. 2007;176(11):1062-71. 5. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. New England Journal of Medicine. 2009;360(10):973-84. 6. Nair P, Pizzichini MMM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. New England Journal of Medicine. 2009;360(10):985-93. 7. Bel EH, Ortega HG, Pavord ID. Glucocorticoids and mepolizumab in eosinophilic asthma. The New England journal of medicine. 2014;371(25):2434. 8. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. New England Journal of Medicine. 2014;371(13):1198-207. 9. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): A	

	multicentre, double-blind, placebo-controlled trial. The Lancet. 2012;380(9842):651-9. 10. Pouliquen IJ, Kornmann O, Barton SV, Price JA, Ortega HG. Characterization of the relationship between dose and blood eosinophil response following subcutaneous administration of Mepolizumab. International Journal of Clinical Pharmacology and Therapeutics. 2015;53(12):1015-27. 11. Garcia G, Taillé C, Laveneziana P, Bourdin A, Chanez P, Humbert M. Anti-interleukin-5 therapy in severe asthma. European Respiratory Review. 2013;22(129):251-7. 12. Yancey SW. Exacerbation Reduction in Severe Eosinophilic Asthma Based on Eosinophil Thresholds. Journal of Allergy Clinical Immunology. 2016	
	Page 64, section 7.7.1: The recommendation on omalizumab repeats itself a bit. Is it necessary to say “to reduce the steroid burden for the patient”? Page 64, section 7.7.1: Should the paragraph on mepolizumab be here, or should the section title be changed? The section is currently entitled “Anti-IgE monoclonal antibody” and mepolizumab is not.	*Agree. Recommendation amended as suggested.* *Agree. New sub-heading ‘Anti-IL-5 monoclonal antibody’ added to cover mepolizumab.*
	Page 71/193 (63 as a numbered page): • Typographical error: "Anti-IgE monocolonal antibodies..."; this should be "monoclonal" Page 72 /193 (64 as a numbered page) • The information on mepolizumab should be removed from the anti-IgE section of the guideline, as this should relate to omalizumab, • The guideline states: "Omalizumab given by subcutaneous injection may be considered in patients with a high steroid burden to reduce the steroid burden for the patient." This should be in line with the current NICE TAG 278 recommendations: "Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE mediated asthma as an add on to optimised standard therapy in people aged 6 years and older: who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year)" NICE TAG 278 recommendation: Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133	*Corrected.* *Agree. New sub-heading ‘Anti-IL-5 monoclonal antibody’ added to cover mepolizumab.* *Disagree. The guideline is based on an independent review of the literature and recommendations reflect the evidence and the overall view of the GDG.*

	and 201) Available online: https://www.nice.org.uk/guidance/ta278/resources/costing-statement-425321245 [Last accessed: April 2016] Page 72/193 (64 as a numbered page) • While the comment to reference 483 is fair, Powell et al. state that "It is not possible to draw firm conclusions from this review with respect to the role of mepolizumab in patients with asthma" and that "At the present time, larger studies using licensed treatment regimens are required to establish the role of mepolizumab in the treatment of severe asthma." We believe this should be incorporated into the BTS/SIGN guidelines to accurately reflect the current body of evidence. Powell C et al. (2015) Mepolizumab versus placebo for asthma. Cochrane Database of Systematic Reviews. Available online: http://www.cochrane.org/CD010834/AIRWAYS_mepolizumab-opposed-placebo-asthma [Last accessed: April 2016].	*Disagree. The GDG consider that the current wording is appropriate.*
	This section also includes a paragraph on mepolizumab, whereas the rest of the text refers to omalizumab...is this intentional?	*New sub-heading 'Anti-IL-5 monoclonal antibody' added to cover mepolizumab.*
	Agree.	*Thank you.*
	The title should reflect biologic therapy for asthma, not just anti-IgE. Anti-IgE and Anti-IL-5 should be subheadings in the section. We would also request that the Castro paper (and results be included for a more complete section on anti-IL5 treatments) along with other publications in this area. Citation: Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials Castro, Mario et al.The Lancet Respiratory Medicine , Volume 3 , Issue 5 , 355 – 3	*Agree. New sub-heading 'Anti-IL-5 monoclonal antibody' added to cover mepolizumab.*
7.7.2	There is only limited mention of the newer biological agents, of which mepolizumab is one. These have shown advantages in reducing severe exacerbations in selected patients. Does the GDG consider that the addition of a section on these newer biologic agents may be helpful, given that they are on the horizon in terms of being used in clinically?	*Omalizumab and Mepolizumab were covered in section 7.7.1 (now 7.7.1 and 7.7.2, respectively).*
7.8	The evidence presented suggests that	*Section 7.8 was not within the*

	subcutaneous immunotherapy is effective but has a high risk of side effects. It would be clearer if the reason for not recommending subcutaneous immunotherapy were made clear….presumably because of the risk of side effects. Are there some patients in whom it would be recommended?	*scope of the current update.*
	The evidence presented suggests that subcutaneous immunotherapy is effective but has a high risk of side effects. It would be clearer if the reason for not recommending subcutaneous immunotherapy were made clear....presumably because of the risk of side effects. Are there some patients in whom it would be recommended? Figures 2 and 3. These are generally clear and continue to emphasise the concept of step – down as well as step –up. However the advice to check compliance, inhaler technique etc. before "stepping up" is lost in the header and should be highlighted more. (obviously a colour version of the Figure will help). (	*Section 7.8 was not within the scope of the current update.* *Agree. Points to check are now listed as bullet points rather than a list.*
7.9	Page 75 and 76 /193 (67 and 68 as numbered pages) • To keep in line with GINA 2016 guidelines, "monoclonal treatments" or "biologics" should be mentioned at Step 5 instead of stating "other treatments" in the context of: "Consider other treatments to minimize use of steroid tablets". • We would also like to raise the lack of information in the step-wise diagram: This diagram is widely used by primary care healthcare professionals, which is often their only reference document. Whilst it gives positive encouragement for earlier referral it does not highlight the benefits of a referral e.g. IgE, biologics, bronchial thermoplasty, etc. Given that many primary care healthcare professionals aren't aware of treatment options after continuous OCS this seems a missed opportunity. By highlighting the role of monoclonal treatments/biologics, it would also streamline BTS/SIGN with GINA guidance, ultimately ensuring patients receive the most appropriate treatment in a timely manner.	*Disagree. Figures 2 and 3 cover the main options at each treatment stage; they are not designed to capture all possible options.*
	tables on page 67 and 68 need more clarity	*Unclear as to what this relates.*

	between steps	
7.10	When stepping up and down a therapy we recommend that patients remain on the same steroid and the same type of device until asthma control is stabilised. By changing more than one treatment parameter (e.g. dose, steroid, inhaler type) when stepping up or down, if lack of control occurs the true reason for this may be masked. Asthma patients experience periods of adequate control and exacerbations. We recommend due to this changeable nature of asthma, the choice of treatment should take in to consideration the availability of flexible range of dosing. Therefore, this will allow step up and step down with the same inhaler type and /or the same combination where appropriate. Though unfortunately we expect it will not be published in time to inform this revision of the guideline, Napp have a study nearing completion which looks at a step down methodology, and may be able to inform this section further in future.	*This is covered in section 8.* *Section 7.10 was not within the scope of the current update.*
	Needs clearer is should a patient who is well controlled but had an attack a month ago be stepped down)	*Section 7.10 was not within the scope of the current update.*
	Figures 2 and 3. These are generally clear and continue to emphasise the concept of step –down as well as step –up. However the advice to check compliance, inhaler technique etc. before "stepping up" is lost in the header and should be highlighted more. (obviously a colour version of the Figure Most of those responding to our member survey were happy with the single chart (Figure 3) for children, with the age specific information embedded within.	*Agree. Points to check are now listed as bullet points rather than a list.* *Thank you.*
7.11.7	The guidance in the BNF was updated a few years ago "beta-blockers can precipitate bronchospasm and should therefore usually be avoided in patients with a history of asthma. When there is no suitable alternative, it may be necessary for a patient with well-controlled asthma to receive treatment with a beta-blocker for a co-existing condition (e.g. heart failure or following myocardial infarction). In this situation, a cardioselective beta-blocker should be selected and initiated at a low dose by a specialist; the patient should be closely monitored for adverse effects".	*Section 7.11.7 was not within the scope of the current update.* *However, a statement has been added referring readers to the BNF for current guidance.*

Section 8		
8.1	There is still no standardised delivery of training on inhaler technique and still a lot of misunderstanding about how devices are different.	*Section 8.1 was not within the scope of the current update.*
8.2.1	This is confusing. Severe without life-threatening features is different to life-threatening. This needs clarifying.	*Agree. Text changed to 'acute severe or life-threatening asthma' in line with Table 11.*
8.2.2	Please ensure that the text in bold reflects the text above. Is the word spacer missing from:In children aged 5–12 there is no significant difference between pMDI (**+ spacer**)and DPI. Is the text "+/-" spacer missing from:In adults there is no significant difference between pMDI + spacer and DPI	*Agree. Text amended to match recommendation.*
8.3	Please note that the Pulvinal beclometasone and Pulvinal Salbutamol inhalers have now been permanently discontinued as of 26th November 2015. Please make this clear or remove reference to the product.	*Agreed. Pulvinal removed from text.*
8.4	Section 2.5 and 8.4: "Generic prescribing of inhalers should be avoided as this might lead to people with asthma being given an unfamiliar inhaler device which they are not able to use properly" AstraZeneca welcomes the move by SIGN to recognise the importance of prescribing by brand name linking to patient adherence and safety. The inhaler market is increasingly complex, and with the entry of an increasing number of branded generics in different inhaler devices, there is a need for highly respected organisations such as SIGN to provide this guidance. When a patient is inadvertently switched at community pharmacy level, there is a risk they will not receive counselling from their healthcare provider about the new medication and device: this may result in poor inhalation technique.[Schulte] In addition, two different devices albeit containing the same molecules may have differences in their licenses. For example, the combination of budesonide and formoterol is available in both the Turbohaler and the Spiromax device, however they differ in licensed age range and method of operation of the inhaler.	*Thank you.*

	Therefore, whilst we welcome this addition to the guidance, due to the seriousness of the potential consequences of generic prescribing of inhalers in terms of patient safety and unlicensed prescribing, we urge SIGN to provide stronger guidance around this point. AstraZeneca suggests: "*Branded prescribing of inhalers is recommended whenever possible as this will ensure the patient receives the device that they have been trained to use. Generic prescribing may lead to patients being given an unfamiliar inhaler device which they are not able to use properly, which may have an impact on their adherence and outcomes*". AstraZeneca would like to thank SIGN again for the opportunity to provide feedback on the draft asthma guidelines and hope that the comments and considerations presented in this response are helpful in finalising the guidance.	*Disagree. The GDG consider that the existing wording of the GPP is appropriate. This is also implicit in the recommendation.*
	The guideline advises the avoidance of generic prescribing of inhalers so as to avoid the confusion resulting from the supply of confusingly different inhaler devices. We welcome this but it needs to be implemented via GP computer systems if it is to happen in practice.	*Thank you.* *This is beyond the remit of the guideline.*
	Agree inhalers should not be generically prescribed.	*Thank you.*
8.5	Suggest that the word "compatible with" is changed to "licensed with". We would also recommend that the following statement is added in: "Spacer devices should not be considered interchangeable." Reference: Levy ML et al. Inhaler technique: facts and fantasies. A view from the Aerosol Drug Management Improvement Team (ADMIT). NPJ Prim Care Respir Med. 2016; 26: 1601	*Disagree. The GDG agree that the current wording is appropriate.* *Wording of first bullet point has been expanded.*
	Very useful.	*Thank you.*
	The value and importance of using spacers to improve lung deposition, improve clinical effectiveness and reduced adverse effects of inhaled medication remains underemphasised in the guideline. This should receive greater emphasis in section 8.4	*Section 8.5 was not within the scope of the current update.*
	As set out earlier in the document, prescribing branded inhalers can be equally fraught with	*No response needed.*

	problems.	
Section 9		
9.1	Useful.	*Thank you.*
9.1.4	Is this thought due to environmental temperature or allergen load or viral infection association??	*Section 9.1.4 was not within the scope of the current update.*
9.3.1	I note the important addition to the end of 2nd sentence 1st para based on NZ study: Perrin et al Thorax 2011 66 937-41- but as it stands it needs some explanation. ?Another sentence 106 pts randomised to 8 litres/min O2 (high) or titrated to 93-95% SpO2 (as per O2 guidelines) (low) - with pCO2>8mmHg as outcome. I think this should be added.	*Disagree. Adding additional unnecessary information may reduce the clarity of the guidance given.*
	Agree. As mentioned earlier when using the term controlled oxygen, it is important to be clear that this is not completely synonymous with COPD and a high PaC02 is not necessarily an indication to reduce oxygen concentration.	*An additional statement regarding hypoxia and over-oxygenation has been added to the 3rd paragraph.*
	' taking care to avoid over-oxygenation which may be detrimental' hardly definitive for many generalists. Should advocate pulse oximtery and tritration.	*Unclear what is meant here. The term 'titrated' has been added to the recommendation.*
9.3.2	These are seldom used in UK, but it is acceptable to include them in the guideline. This is not controversial, although many patients when acutely unwell cannot manage their inhalers.	*Thank you.*
	"without life-threatening features" should be in bold. What should be used in those with life-threatening features needs stating	*Disagree. Bold text is reserved for headings and recommendations. GPP covers life-threatening asthma.* *Annex 2 covers detailed approach to take in life-threatening (and other levels of severity) of asthma and is cross-referenced from the start of the section (9.2).*
9.3.3	Bottom of p81 - last sentence - I think 'Do not stop inhaled corticosteroids during prescription of oral corticosteroids' deserves to be a GPP - we should have done this several editions ago!	*Agree. GPP added.*
	Agree. This is an important message.	*Thank you.*
	"For convenience, steroid tablets may be given as 2 x 25 mg tablets daily rather than 8–10 x 5 mg tablets." There is now a 20mg	*This text has now been deleted.*

	prednisolone available in the UK (Pevanti); this is cheaper than 25mg tablets and reduces the steroid burden. In light of this, I would be interested to know whether the committee wishes to change the recommended dose to 40mg daily (rather than 40-50mg daily).	
9.3.12	1st sentence 1st para - should be 'and' a poor response rather than with. Exactly the same in 9.9.5	*Agree. Changed.*
	Need to include 'High Normal pCO2' in 9.3.12 (NRAD) as indication for urgent referral to ICU team	*The GDG consider that hypercapnia is adequately covered by the existing text.*
	We would endorse this. The use of Ketamine can be associated with significant psychological side-effects, so the downside of therapy can easily out-weigh the unproven benefit. This section could suggest this treatment should be avoided outside of the context of further RCTs.	*Thank you.* *No change required as uncertainty of benefit is already highlighted in the text as is the need for critical care teams to be involved at this stage.*
9.3.13	Yes, usually airway pressures in asthma is too high. NIV is likely to be ineffective and distressing to a patient already in a distressed and anxious state.	*Thank you.*
9.6	This needs to include SIGN QS 25: 10% of NRAD deaths were within 28 days of discharge from hospital following Rx for acute asthma.	*Section 9.6 was not within the scope of the current update.*
9.6.1	Should have been in view of NRAD and the case of Tamara Mills which resulted in a regulation 28 statement. See https://endasthmadeaths.wordpress.com/category/asthma-deaths-cases/ The guideline needs to be responsive to major new information and something like this can't wait another 3 years for change (GINA is updated twice a year!)	*Section 9.6 was not within the scope of the current update.*
9.6.3	Should have been in view of NRAD and the case of Tamara Mills which resulted in a regulation 28 statement. See https://endasthmadeaths.wordpress.com/category/asthma-deaths-cases/ The guideline, needs to be responsive to major new information and something like this can't wait another 3 years for change (GINA is updated twice a year!)	*Section 9.6 was not within the scope of the current update.*
9.7	Should have been in view of NRAD and the case of Tamara Mills which resulted in a regulation 28 statement. see	*Section 9.6 was not within the scope of the current update.*

	https://endasthmadeaths.wordpress.com/category/asthma-deaths-cases/ The guideline needs to be responsive to major new information and something like this can't wait another 3 years for change (GINA is updated twice a year!)	*The guideline is updated biennially.*
	need to use appropriate size probe	*Section 9.6 was not within the scope of the current update.*
9.7.3	Often distresses the child, causes cough	*Section 9.7.3 was not within the scope of the current update.*
9.8.1	humidify if high flow rates	*Section 9.7.3 was not within the scope of the current update.*
9.8.4	We note the absence of prednisolone oral solutions in this section. Asthma UK regularly hears from people with asthma about the difficulty for children in swallowing prednisolone tablets due to the very bitter taste, with many reporting children vomiting. Though we note vomiting remains a possible side effect of prednisolone oral solution, studies have suggested it can be an effective, well-tolerated and cheap alternative to tablets (see Lucas-Bouwman et al, 2000). References Lucas-Bouwman, M.E. (2000). Crushed prednisolone tablets or oral solution for acute asthma?. Arch Dis Child 2001;Vol. 84:p.347-348. Available at: http://adc.bmj.com/content/84/4/347.abstract	*First sentence after recommendations has been deleted.*
	"A soluble preparation dissolved in 5ml of water is preferable in those unable to swallow tablets." Oral solutions of prednisolone are now available, and are now used in preference to soluble tablets due to their lower cost.	*First sentence after recommendations has been deleted.*
9.9	Please describe high dependency care rather than a high dependency unit as this may indicate the need to transfer the child to a different hospital with added potential risk.	*Agree. Final sentence of first paragraph amended.*
9.9.1	Glad to see this is back	*This section has not been updated.*
9.9.5	In 9.3.13 it is NIV - while in 9.9.5 it is NIPPV. Shouldn't it be NIV throughout?	*Agree. NIPPV changed to NIV throughout.*
9.9.6	New short para under the bullet points. I am again confused (as in Table 2) whether we are including viral associated wheeze in these guidelines - is this really a different disorder? -	*No change required. This is a diagnostic difficulty. New sentence added referring readers to the BTS Care Bundle which covers this issue.*

	over to the paediatricians!	
	Section 9.9.6 describes discharge planning. The discussion of hospital management of acute severe wheezing in children should include a warning about care in diagnostic labelling in this context. Young children with episodic viral wheezing are frequently sent home from hospital with an insufficiently substantiated diagnosis of asthma. The guideline could usefully discuss this.	*Agree. New bullet point about diagnosis added as first in list.*
Section 10		
10.1	Essential to improve outcomes for patients	*Thank you.*
	Would add "despite adherence to high ICS" and ideally involving an assessment of home environment (Bracken et al 2009, Archives of Disease in Children)	*Section 10.1 was not within the scope of the current update.*
10.2.1	The more information and ownership given to patients about the implications of non adherence and support for concerns the better	*No response required.*
	The 2 new paras are excellent - suggest remove last sentence 1st para since you could easily say there is no evidence for 50% of this whole guideline!!	*Agree. Final sentence deleted as previous sentence states that this is a theory not a fact.*
	Page 96: agree with new text on difficult asthma and adherence	*Thank you.*
	? mention mart monitoring and home assessment as above	*MART is covered in new section 7.3.5.*
	Agree. As mentioned above this is very important.	*Thank you.*
	Increasingly I am convinced this is fundamental to poor levels of control and behind much ' difficult' asthma	*Thank you.*
10.2.3	?physion assessment should be part of the MDT assessment	*Section 10.2.3 was not within the scope of the current update.*
10.2.4	Information about allergen exposure at home (again Bracken as above)	*Section 10.2.4 was not within the scope of the current update.*
Section 11		
11.3	I suggest that issues such as the hormonal changes of adolescence may affect previously well controlled asthma and further reduce the confidence of the young person in their self management	*Section 11.3 was not within the scope of the current update.*

11.3.1	Many adolescent girls reduce their participation in exercise and this may mask worsening asthma as fewer signs are obvious	*Section 11.3.1 was not within the scope of the current update.*
11.3.4	Regular monitoring of patients via Spirometry at least annually is of benefit. Them did not happen for me.	*Section 11.3.4 was not within the scope of the current update.*
11.4	Other types of smoking than simply tobacco should be specified as further risks for adolescents with asthma - both active and passive exposure to forms of smoking	*Section 11.4 was not within the scope of the current update.*
11.4.4	Worse when the pool environment is warm - usually worse later in the day, this section should include advice about sport rules on use of asthma treatment for competitive athletes as this can be of real importance for adolescents.	*Section 11.4.4 was not within the scope of the current update.*
11.5.1	More study into anxiety is needed, and its affects whilst having Asthma attacks.	*Section 11.5.1 was not within the scope of the current update.*
11.5.3	What investigations and when should these be recommended for individuals with asthma or directly to therapeutic trial of treatment.	*Section 11.5.3 was not within the scope of the current update.*
11.6	Clinician to be able to recommend ?refer to career advisors	*Section 11.6 was not within the scope of the current update.*
	NHS111 need to know that people on nebulizer Sambutamol which is not working, need emergency treatment.	*Section 11.6 was not within the scope of the current update.*
11.7	Advice should offered to school career advisers via educational health for career planning	*Section 11.7 was not within the scope of the current update.*
11.10	Supervision of ICS considered (consider DOT in paediatrics, no evidence anecdotal evidence from across the UK)	*Section 11.10 was not within the scope of the current update.*
11.11.2	School nursing and medical services should have asthma training and a role in supporting both young people and staff in supporting their needs	*Section 11.11.2 was not within the scope of the current update.*
11.11.3	Suggest that young people are offered orientation to the adult acute ward environment to reduce their anxiety about the unknown future.	*Section 11.11.3 was not within the scope of the current update.*
11.11.4	Adolescents may prefer to attend clinic with a friend rather than alone or with a parent and this can facilitate peer learning and support	*Section 11.11.4 was not within the scope of the current update.*
Section 14		

14.3.1	"In primary care, people with asthma should be reviewed regularly by a nurse or doctor with appropriate training in asthma management. Review should incorporate a written action plan." Pharmacists also run asthma clinics.	*Section 14.3.1 was not within the scope of the current update.*
14.4	Practical issues can stand in the way of delivering the high quality asthma care outlined in the BTS/SIGN guideline. The guideline should advise on how reviews could be delivered more dynamically, in line with the desire and needs of both patients and health care professionals – for example, using informatics to transmit monitoring information remotely, communicating with patients via telephone and video conferencing. Asthma UK asked healthcare professionals which tools they thought could be used to communicate with people about their asthma and found a positive response to the use of new technologies. The use of personalised action plans that are accessible on a smart phone was strongly supported, as was the use of SMS text messaging to broadcast asthma advice, and personalised SMS messages. Such technologies could help people with asthma and healthcare professionals to remain vigilant with respect to the symptoms of an asthma attack. Healthcare professionals were divided on whether an asthma review could be achieved over the telephone. A key concern raised was the importance of making sure inhalers are being used correctly by their patients. People with asthma also gave a mixed response regarding preference for face-to-face versus telephone reviews. This appeared to be dependent upon individual experiences of the face-to-face reviews. We note that people with asthma can have vastly different expressions of their symptoms and needs and the use of a range of options for the delivery of care – including telehealthcare – could enable more people to be reached. Further research into the barriers that need to be overcome to deliver healthcare remotely should be explored.	*These issues were all explored by the GDG and are covered in sections 14.4.1-14.4.3 as far as available evidence allows.* *Personalised asthma plans are covered in section 5.2.2.*
	Good additional para - needs end bracket after 'school-based' and refs 2nd sentence	*Thank you. Closing bracket added.*
	The guideline contains a new discussion of the evidence base for telehealthcare, remote consulting, computerised decision support -	*Thank you.*

	with suitably cautious recommendations given the limited evidence base for safety and effectiveness.	
	Important section as we are pushed more and more along this route of care – on limited evidence.	*Thank you.*
14.4.1	The term 'Telehealthcare' used to me (at least to me) seeing and talking to patients via a TV link - does telehealthcare now include texting, emailing etc? If so the recommendation is confusing - but this is generally a good addition.	*Agree that terminology is confusing and evolving. Telehealthcare (or sometimes telehealth as opposed to social telecare) is often used as an over-arching term.* *Introductory paragraph added to 14.4 to explain this.* *Existing introductory paragraph moved to section 14.4.1 as it is about self-management.*
	Pages 118-119, section 14.4.1: The section on telehealthcare starts off by saying this is a means of supporting self-management, and this is reflected in the bulk of the evidence. However, the recommendation says that it can be used "for delivering asthma care". That is a much broader concept than supporting self-management, and I don't think the recommendation should stand as it is.	*Introductory paragraph added to 14.4 to explain use of term 'telehealthcare'.* *Existing introductory paragraph moved to section 14.4.1 as it is about self-management.* *Agree. Wording of recommendation changed.*
	Pulmonary Rehab for severe asthmatics.	*Unclear as to what this comment relates.*
14.4.2	I am confused by the terminology - perhaps the terms Telehealthcare & Remote consulting and Synchronous and Asynchronous consulting and Telemonitoring (which you have defined) need more definition and clearer example.	*See response to GD in 14.4.1 above.* *Asynchronous and synchronous remote consulting are defined in the first sentence in 14.4.2.*
14.4.3	Good additional para & recommendation	*Thank you.*
Section 15		
15.1.1	Please amend the text on Asthma UK to read: Asthma UK, 18 Mansell Street, London E1 8AA Tel: 0300 222 5800 Asthma UK's Helpline nurses: 0300 222 5800 (9am-5pm; Mon-Fri) – nurses provide advice for people with asthma and for healthcare professionals www.asthma.org.uk	*Corrected.*

	General enquiries: info@asthma.org.uk Asthma UK is the charity dedicated to improving the health and well-being of people with who are affected by asthma. The charity provides a wide range of information and resources on their website, including downloadable asthma action plans. Printed information booklets and other resources are available on request, and bulk copies are available for purchase by healthcare professionals.	
	Essential and organisation's involvement useful	*Thank you.*
15.1.2	Support groups in local areas and GP practices useful	*Thank you.*
Section 16		
16.1	Noted and supported	*Thank you.*
16.2	As above	*Thank you.*
Annexes		
	Useful particularly graphic presentations	*Thank you.*
	As mentioned in relevant sections	*No response required.*

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Figures and references as indicated in report.

Section 7

Table A

	Very Low dose	Low dose	Medium dose	High dose
	Paediatric doses ←——→ Adult doses ←——→			
	200 mcg BDP	400-500 mcg BDP	800-1,000 mcg BDP	1,600-2,000 mcg BDP

Table B

	Very Low dose	Low dose	Medium dose	High dose
	Paediatric doses ←——→ Adult doses ←——→			
	200 mcg BDP	400-500 mcg BDP	800-1,000 mcg BDP	1,600-2,000 mcg BDP
Budesonide (Turbohaler)[SPC]	100 mcg one dose twice a day	100 mcg two doses twice a day 200 mcg one dose twice a day	200 mcg two doses twice a day 400 mcg one dose twice a day	400 mcg two doses twice a day
Symbicort (Turbohaler)[SPC]	100/6 one dose twice a day (not licensed at this dose < 12 years)	100/6 two doses twice a day 200/6 one dose twice a day	200/6 two doses twice a day 400/12 one dose twice a day	400/12 two doses twice a day

Section 7.3.4

Table C

Outcome	Relative effect (95% CI) MART vs ICS/LABA
Patients with severe exacerbations (requiring hospitalisation or ER visit)	OR 0.72 (0.57 to 0.90)
Patients with exacerbations requiring oral steroids	OR 0.75 (0.65 to 0.87)
Patients with serious adverse events	OR 0.92 (0.74 to 1.13)

Table D

Outcome	Relative effect (95% CI) MART vs ICS
Patients with exacerbations causing hospitalisation.	OR 0.56 (0.28 to 1.09)
Patients with exacerbations treated with oral steroids.	OR 0.54 (0.45 to 0.64)
Patients with serious adverse events (non-fatal)	OR 0.97 (0.74 to 1.29)
Patients with serious adverse events (fatal)	OR 0.37 (0.05 to 2.62)

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