Diagnosis and management of stable COPD
(Version 5.0)

Sandwell & West Birmingham CCG

Revision History

<table>
<thead>
<tr>
<th>Guideline Author:</th>
<th>Alice Turner in conjunction with pan-Birmingham Respiratory Network</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline Sponsor:</td>
<td>Raj Ramachandran</td>
</tr>
<tr>
<td>Date of Approval:</td>
<td>22nd October 2015</td>
</tr>
<tr>
<td>Approved by:</td>
<td>Respiratory network</td>
</tr>
<tr>
<td>Date of CSC Ratification:</td>
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<td>October 2016</td>
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<tr>
<td>Related Policies / Topic / Driver</td>
<td>NICE guidance 2010</td>
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<table>
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<tr>
<th>Version No</th>
<th>Date of Issue</th>
<th>Author</th>
<th>Reason for Issue</th>
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</thead>
<tbody>
<tr>
<td>3.0</td>
<td>13.05.15</td>
<td>Alice Turner</td>
<td>First sign off by RCN Membership</td>
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<tr>
<td>4.0</td>
<td>23.07.15</td>
<td>Alice Turner</td>
<td>Second sign off RCN Membership</td>
</tr>
<tr>
<td>5.0</td>
<td>22.10.15</td>
<td>Alice Turner</td>
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Clinical Director: Signed…………………………
Name………………………………
Date………………………………
Guideline Readership

This guideline may be used by all staff in primary and secondary care across the Birmingham and Solihull region to aid their diagnosis and management of patients with suspected and confirmed COPD.

Guideline Objectives

There are 2 main reasons behind this guideline
- To ensure that the diagnosis of COPD is made correctly
- To ensure rational prescribing in diagnosed COPD patients. We also wish to raise pulmonary rehabilitation referral rates, as this is an underused, evidence based treatment, and to make savings on COPD prescribing by using the most cost effective treatment.

Other Guidance

NICE guideline, which is also the BTS guideline
BTS quality standards
ATS/ERS guidelines

This guideline does not differ markedly from the NICE guidance, except that it is more specific on which drug classes to use, and includes some of the trial data issued post NICE which has revealed that use of inhaled corticosteroids may not be required as much as NICE suggested.
Flow Chart for diagnosis of COPD

Consider a diagnosis of COPD in patients
- Aged over 35 **and** smoker or ex-smoker **and**
- Who have any of
  - exertional breathlessness
  - chronic cough
  - regular sputum production
  - frequent winter 'bronchitis'
  - wheeze
- **AND** do not have clinical features of asthma:
  - chronic unproductive cough
  - significantly variable breathlessness
  - night-time wakening with breathlessness and/or wheeze
  - significant diurnal or day-to-day variability of symptoms

**COPD clinically likely**

- Post-bronchodilator spirometry
- Severity assessment = spirometry, MRC & CAT scores
- Chest X-ray to exclude other diagnoses
- Full blood count to identify anaemia or polycythaemia
- Body mass index (BMI) calculation

**Interpreting spirometry**

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Is it airflow obstruction?</th>
<th>Spirometric severity assessment</th>
<th>Make sure it isn't asthma*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 blows with FEV1 values within 100ml of one another</td>
<td>FEV1/FVC&lt;0.7 and &lt;lower limit of normal</td>
<td>FEV1 ≥80%</td>
<td>Mild</td>
</tr>
<tr>
<td>FVC obtained after blowing out &gt;= 6 seconds</td>
<td></td>
<td>50-79%</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30-49%</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;30%</td>
<td>Very severe</td>
</tr>
</tbody>
</table>

*Overlap between asthma and COPD can occur; In general there should therefore be a lower threshold for use of ICS if there is definite overlap of COPD with asthma, however if the diagnosis is not clear we would advocate use of the guideline for the condition most prominent in the patient (i.e. patients with COPD who exhibit reversibility to bronchodilators should be treated using the COPD guideline and those with lifelong asthma, with fixed airflow obstruction, should be treated using the asthma guideline). Please see Appendix 3, Section 12 for more detail.
2. Executive Summary & Overview

This guideline is intended for use to aid diagnosis in patients with a suspected diagnosis of a chronic obstructive pulmonary disease (COPD), and in patients with a confirmed diagnosis of COPD. In the latter group it is intended to direct management including prescribing. It is aimed primarily at cost-effective management, and will be reviewed annually as evidence is rapidly emerging in this field.

2.1 Summary of management guidance
After making a diagnosis of COPD as per the flowchart above management should be:

1. Stop smoking, check inhaler technique
2. Start SABA
3. Refer to pulmonary rehabilitation if indicated
4. If still symptomatic start LAMA

Thereafter if symptoms still occur it will depend on spirometry results as to what inhalers the patient should be prescribed. In general those with an FEV1 > 50% predicted should be on a LAMA/LABA combination inhaler, and those with an FEV1 < 50% may need the addition of an inhaled steroid by moving to a combination of 2 inhalers (LABA/ICS + LAMA) if they have frequent exacerbations. If they do not then they should be managed with bronchodilation alone.

2.2 Reasoning and principles behind the guideline
The diagnosis of COPD is based on standard criteria, and mimics NICE guidance in most respects. We have used the fixed ratio of 0.7 as our main criterion for airflow obstruction, but (unlike NICE) have also noted the importance of the lower limit of normal (LLN). This is because use of the fixed ratio without reference to the LLN can lead to overdiagnosis in older patients.

Drug choices within the guideline are based on clinical evidence as well as cost and have been designed to ensure that patients do not get too many different types of inhaler to use. The common steps up in treatment will be from LAMA to LABA/LAMA and from LAMA to LAMA + LABA/ICS. The device for each LAMA is different, and whilst we have designed our guideline to allow prescribers to step up to a LABA/LAMA in the same device, this is not possible in all cases for the addition of LABA/ICS combinations. For example, if a patient is on glycopyrronium (which comes in the Breezhaler device) and requires addition of a LABA/ICS there are no available compounds yet in the this device, so you will need to assess technique with either an MDI (Fostair), Turbuhaler (Symbicort) or Accuhaler (Seretide 500). Seretide 250 Evohaler (MDI) is not licensed for COPD and is much more expensive than all of our recommended products. As such if a patient is unable to use any device apart from an MDI, Fostair should be prescribed, as it has a COPD license.

Oxygen is a drug and should not be prescribed long term (LTOT) without assessment by a home oxygen service (HOS-AR). The evidence for efficacy of ambulatory oxygen is weak and it should not be prescribed without assessment by the HOS-AR. There is no evidence that short burst oxygen therapy (SBOT) works; therefore it
should not be prescribed. If pO2 at the end of an exacerbation meets LTOT criteria it is preferable to wait until 6 weeks after this event to prescribe it, when the levels can be rechecked to ensure that it represents their stable state level. All of the benefits of LTOT occur long term, hence waiting this period is safe; it is also preferable to the awkward situation of having to remove oxygen at a later date.

3. Body of Guideline

For all patients in whom diagnosis is confirmed

- Offer/refer to smoking cessation if appropriate (e.g. BCHC stop smoking service)
- Start salbutamol (SABA) prn
- Check inhaler technique
- Ensure have had flu and pneumonia vaccine and are on recall list for flu vaccine
- Ensure that the patient has a COPD self-management plan which details recognition of exacerbations, who their primary point of contact for advice is (e.g. COPD nurse, GP) and information on managing stable COPD.
- Assess whether they have any commonly recognised co-morbidities of COPD, such as ischaemic heart disease, heart failure, anxiety or depression, osteoporosis, diabetes, and manage them appropriately

Table 1: Drug class abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full name</th>
<th>Examples of drugs in class</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABA</td>
<td>Short acting beta agonist</td>
<td>Salbutamol</td>
</tr>
<tr>
<td>LABA</td>
<td>Long acting beta agonist</td>
<td>Formoterol, Indacaterol</td>
</tr>
<tr>
<td>LAMA</td>
<td>Long acting muscarinic antagonist</td>
<td>Glycopyrronium, Tiotropium</td>
</tr>
<tr>
<td>LABA/LAMA</td>
<td>Combination of LABA and LAMA</td>
<td>Ultibro, Duakir</td>
</tr>
<tr>
<td>LABA/ICS</td>
<td>Combination of ICS and LABA</td>
<td>Symbicort, Fostair</td>
</tr>
<tr>
<td>LTOT</td>
<td>Long term oxygen therapy</td>
<td>Oxygen used for more than 12 hours/day</td>
</tr>
</tbody>
</table>

Assess response to treatment

This should include an assessment of symptoms and how activities of daily life have changed post treatment. Quality of life scores such as CAT (www.cattestonline.co.uk) may be useful here, but neither this nor a checklist approach to questioning the patient is advocated as the sole way of checking response; an individualised approach is more likely to engage the patient with treatment.

If still symptomatic on SABA

- If walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace refer to pulmonary rehabilitation. Table 2 shows referral routes for various local providers; forms may be obtained from the provider. If no form is mentioned in the table then referral may be made simply by providing clinical details by phone/email/letter (as shown)
- Start LAMA unless contraindicated, in which case use LABA
  - See Table 3 for prescribing guidance.
  - Ensure inhaler technique is taught.
Use Aclidinium if eGFR <30 mL/min/1.73m²
• Do not start multiple drugs at this assessment

Table 2: Pulmonary rehabilitation providers in pan-Birmingham region

<table>
<thead>
<tr>
<th>Provider</th>
<th>Areas served</th>
<th>Location of classes</th>
<th>How to refer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birmingham Community Healthcare (BCHC)</td>
<td>Old HOB PCT (parts of South Central, Cross City and Sandwell CCGs)</td>
<td>Pannell Croft village, Newtown; St Johns Church Hall, Sparkhill</td>
<td>Fax or email form to: 0121 245 5711 <a href="mailto:bchnt.bchrespiratory@nhs.net">bchnt.bchrespiratory@nhs.net</a></td>
</tr>
<tr>
<td>Heart of England NHS Foundation Trust</td>
<td>All local CCGs, HEFT inpatients</td>
<td>Heartlands, Solihull and Good Hope Hospitals</td>
<td><a href="mailto:bhs-tr.pulmonary-rehab@nhs.net">bhs-tr.pulmonary-rehab@nhs.net</a></td>
</tr>
<tr>
<td>South Doc</td>
<td>Cross City &amp; South Central CCGs</td>
<td>Moseley Hall Hospital, West Heath Medical Centre, Northfield; River Brook Surgery, Stirchley; Kenrick Centre, Quinton.</td>
<td>Fax or email form to: 0121 483 2127 <a href="mailto:southdocservices@nhs.net">southdocservices@nhs.net</a></td>
</tr>
<tr>
<td>Sandwell and West Birmingham NHS Trust</td>
<td>Sandwell CCG</td>
<td>Sandwell Hospital Gym Hurst Road Community Centre Tipton Leisure Centre</td>
<td>Fax form to 0121 507 3026 Tel: 0121 507 2664, Option 4 <a href="mailto:swbh.respiratoryservice@nhs.net">swbh.respiratoryservice@nhs.net</a></td>
</tr>
<tr>
<td>Solihull Community Respiratory Team</td>
<td>Solihull CCG</td>
<td>Chelmsley Wood Leisure Centre, Dorridge Community Hall</td>
<td>Tel: 0121-424-4766</td>
</tr>
</tbody>
</table>
Table 3: Drug choices for new starters in stable COPD

<table>
<thead>
<tr>
<th>Device</th>
<th>LAMA</th>
<th>LABA</th>
<th>LABA/LAMA**</th>
<th>LABA/ICS**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breezhaler</td>
<td>1.Glycopyrronium 44mcg OD</td>
<td>-</td>
<td>Ultibro 1 puff OD</td>
<td>-</td>
</tr>
<tr>
<td>Genuair</td>
<td>1.Aclidinium 322mcg BD Use if eGFR &lt;30</td>
<td>-</td>
<td>Duaklir 1 puff BD</td>
<td>-</td>
</tr>
<tr>
<td>Handihaler</td>
<td>Tiotropium 18mcg OD</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Respimat</td>
<td>Tiotropium 5mcg OD</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Turbohaler</td>
<td>-</td>
<td>Formoterol **12mcg BD</td>
<td>-</td>
<td>1. **Symbicort 400/12 1 puff BD</td>
</tr>
<tr>
<td>Accuhaler</td>
<td>-</td>
<td>Salmeterol 50mcg BD</td>
<td>-</td>
<td>Seretide Accuhaler 500 one puff BD</td>
</tr>
<tr>
<td>MDI</td>
<td>-</td>
<td>Salmeterol 50mcg BD Formoterol 12mcg BD</td>
<td>-</td>
<td>1. Fostair 100/6 2 puffs BD</td>
</tr>
</tbody>
</table>

# The combination drugs are indicated by brand name for ease of presentation in the table, however we would recommend prescribing by brand to ensure that device consistency is maintained once generic products are on the market. Ultibro = Indacaterol + Glycopyrronium, Duaklir = Aclidinium + Formoterol, Symbicort = Budesonide + Formoterol, Seretide = Salmeterol + Fluticasone, Fostair = Beclometasone + Formoterol.

** Formoterol and Budesonide/Formoterol are available in several devices; please ensure that you prescribe the brand which comes in the device the patient can use best.

1. Patients should only be prescribed an inhaler that they can use effectively – the number "1" denotes first choice inhaler devices in a given class – for LAMAs these are Glycopyrronium and Aclidinium as these can be stepped up to the same device in a LABA/LAMA combination if necessary; for LABA/ICS combinations these are Symbicort and Fostair because the steroid component represents a lower Beclometasone-equivalent dose.

If your patient is already on, or requires, Relvar, Anoro or Incruse due to their inhaler technique we do not advocate switching. Please note that these devices are NOT included within the APC- approved formulary. These compounds are of similar efficacy to others in the same class, albeit with slight differences in cost.
If still symptomatic at this point follow the flow chart to select treatment:

**FEV1 >50% predicted**
- Persistent breathlessness or exacerbations
  - Step up to LABA/LAMA
  - Check inhaler technique again & maintain device if good

**FEV1 <50% predicted**
- Persistent breathlessness alone
  - Exacerbations +/- persistent breathlessness
  - Add LABA/ICS
  - Check inhaler technique first & select accordingly

We do not advocate stepping up to LABA/LAMA/ICS if FEV1>50% predicted – please consider the guidance below and discussion with a respiratory specialist

If still breathless at this point
- Check oxygen saturations and refer to local HOS-AR if <92% on at least 2 occasions when clinically stable. Table 4 shows local providers and referral routes. Forms may be obtained from the provider.
- Trial of theophylline 200mg BD for 6 weeks; if beneficial continue.
  - Remember to check for drug interactions prior to prescribing, and to check levels if patient has significant side effects or fails to respond. The therapeutic window is fairly narrow and dose adjustments may be required.
  - Effects are reduced in smokers and increased in the elderly, those with liver disease and cardiac failure, amongst others.
  - Routine monitoring should include a check of level 5 days after starting the drug (4-6 hours post dose) and after any dose adjustment. Regular levels are not required if the patient is well and has not had any other drugs altered that could affect theophyllines. Dose adjustment will be required if given acute prescriptions of interacting drugs such as quinolones or macrolides.

Table 4: Home Oxygen Assessment and Review (HOS-AR) providers

<table>
<thead>
<tr>
<th>Provider</th>
<th>Areas served</th>
<th>Location of clinics</th>
<th>How to refer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart of England NHS Foundation Trust</td>
<td>All local CCGs</td>
<td>Heartlands, Solihull and Good Hope Hospitals</td>
<td>Letter, as for normal OPD referral</td>
</tr>
<tr>
<td>Sandwell/West Bham NHS Trust</td>
<td>Sandwell CCG</td>
<td>Lyng Centre for Health and Social Care and Birmingham Treatment Centre</td>
<td>Letter or Fax form to: 0121 507 3026</td>
</tr>
<tr>
<td>Solihull Community Respiratory Team</td>
<td>Solihull CCG</td>
<td>Community &amp; Solihull Hospital</td>
<td>Tel: 0121 424 4766</td>
</tr>
<tr>
<td>University Hospitals Birmingham</td>
<td>All local CCGs</td>
<td>Queen Elizabeth Hospital</td>
<td>Fax form to 0121 460 5822</td>
</tr>
</tbody>
</table>
If sputum is a problem
- Add carbocisteine 750mg tds for a trial (at least 6 weeks), and maintain at an appropriate maintenance dose if beneficial.
- Consider whether bronchiectasis is a possibility. If yes and you have direct access, please request high resolution CT thorax (HRCT)
- Send sputum MCS and AFB x 3

A full description of the evidence base for all the above pharmacological and non-pharmacological management starts in section 4.

What if my patient is on ICS and these are not indicated?
It is quite common when reviewing COPD treatment, especially in the context of this new guideline, to find changes you wish to make to a patient's management. We anticipate that there may be many patients in whom ICS are no longer indicated. However if the patient is on high dose ICS it would not be advisable to stop these suddenly as there is a risk of adrenal suppression. Please see Appendix 1 for general advice on use of ICS, and Appendix 2 for suitable step-down regimes.

Rescue packs
These are unlikely to be appropriate when a diagnosis has just been made.
Consider providing a rescue pack for patients who exacerbate frequently (at least twice/year), in the context of a self-management plan, if you are confident that the patient understands the principles of self-management. Prednisolone at 30mg OD for 5-7 days with Doxycycline 200mg on day 1 and 100mg for 6 further days (assuming no contraindications), is an appropriate choice of treatment for the pack, however this should be guided by the individual (e.g. sputum culture results, frequency of infective v non-infective exacerbations). For all patients they should contact their respiratory nurse, case manager or GP on every occasion that they use a rescue pack, and no more than 3 should be issued without medical review.

Osteoprotection
If patients require 3 or more courses of steroids/year for exacerbations please prescribe a suitable bisphosphonate as prophylaxis against osteoporosis if they are aged 65 or over (+/- Calcium and Vitamin D supplementation). If aged less than 65 arrange a DEXA scan and prescribe similarly if osteoporosis is present.

If still having problems at this point consider referral to community respiratory service or respiratory physician.

Available community respiratory services include:
- BCHC ➔ some parts of Cross City
- Sandwell and West Birmingham Community Respiratory Team ➔ Sandwell CCG
- Solihull Community Respiratory Team ➔ Solihull CCG

Other community services:
- Some COPD patients, particularly those regularly admitted to hospital, may benefit from referral to their local community matron. The services provided by community matrons may be a very useful complement or alternative to a community respiratory service.

NB An extensive review of the evidence base for the guideline is provided in Appendix 3.
4. Reason for Development of the Guideline

This guideline has been developed in part due to NICE guidance, and in part due to the national COPD quality standards released in 2011. It is also driven by the fact that there are an increasing number of COPD inhalers available and patients being diagnosed, hence there is a greater public health need for rational prescribing. National audits also show relatively low referral rates for pulmonary rehabilitation, which we wish to improve by highlighting within a guideline.

5. Methodology

This guideline was developed by the HEFT COPD lead (Dr Alice Turner) in conjunction with the pan-Birmingham respiratory network and refined after discussion with respiratory directorates at HEFT, UHB and Sandwell, local CCGs respiratory leads, the joint medicines management team and other interested parties linked to the network. An extensive review of the evidence base is provided in Appendix 3.

6. Implementation

This is intended for general use by all staff. The guideline will be promoted via a series of events in primary care, for which funding from a pharma-alliance has been agreed. Within secondary care Trusts each will have their own precise mechanism for promotion, which may include departmental teaching sessions to junior doctors, emails to medical consultants, promotion via grand rounds and discussion with staff in other key departments (such as acute medicine). Inhaler technique education sessions run in local CCGs for non-medical staff will also be used as an opportunity to distribute and promote the guideline; again funding for this has been sought from the pharma-alliance.

7. Monitoring

Each CCG and NHS Trust have different systems for monitoring their guidelines. Examples of the data to be collected and potential targets within a typical secondary care Trust are shown in table 9. In primary care QOF data and prescribing rates will be the more practical elements to collect. In both cases National COPD audits spanning primary and secondary care will be utilised to gather relevant data when they occur (secondary care audit occurred in 2014, primary care will be in 2015, and on average every 3 years thereafter. Standards relevant to this guideline are as follows

Table 9: Possible audit standards in secondary care

<table>
<thead>
<tr>
<th>Standard</th>
<th>Target</th>
<th>National achievement 2010</th>
<th>National achievement 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease confirmed by spirometry</td>
<td>90%</td>
<td>54%</td>
<td>46%</td>
</tr>
<tr>
<td>Smoking cessation advice if applicable</td>
<td>90%</td>
<td>27%</td>
<td>58%</td>
</tr>
<tr>
<td>Inhaler technique &amp; medications reviewed</td>
<td>100%</td>
<td>55%</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary rehabilitation referral if eligible</td>
<td>70%</td>
<td>41%</td>
<td>40%</td>
</tr>
<tr>
<td>Inpatients: seen by respiratory specialist/CNS</td>
<td>90%</td>
<td>-</td>
<td>79%</td>
</tr>
</tbody>
</table>
8. Application of the Guideline

The guideline applies to all COPD patients, at all HEFT, Sandwell and UHB secondary care sites, and to Cross-City, Sandwell/West Birmingham, Solihull and South Central CCGs. Key beneficiaries will be patients, local CCGs and respiratory departments, as this is where cost savings and efficiency gains will be most apparent. Implementation should be by all staff seeing patients with the diagnosis; however we recognise that it relies heavily on the respiratory team, including the CNS for some aspects (e.g. oxygen, inhaler technique).

9. Launch and Implementation Plan for Clinical Guidelines

To be completed and attached to any document which guides practice when submitted to the appropriate committee for consideration and approval.

<table>
<thead>
<tr>
<th>Action</th>
<th>Who</th>
<th>When</th>
<th>How</th>
</tr>
</thead>
<tbody>
<tr>
<td>If previous document is in use: proposed action to retrieve out-of-date copies of the document (electronic and/or paper)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communicate new guideline/changes to guideline</td>
<td>Alice Turner or designated support staff</td>
<td>Ongoing over next 12 months</td>
<td>Meetings with GPs and nurses in primary care, training sessions and talks to junior doctors and colleagues in secondary care locations</td>
</tr>
<tr>
<td>Offer awareness training/incorporate within existing training programmes</td>
<td>Individual Trust and CCG leads</td>
<td>Ongoing over next 12 months</td>
<td>Foundation programme training and CMT training, as well as Grand Rounds within Trusts are suitable secondary care routes. In primary care PLT and VTS trainee sessions may be most suitable</td>
</tr>
<tr>
<td>Circulation of document(paper)</td>
<td>Carol Watson</td>
<td>By Sept 2015</td>
<td>To GP practices</td>
</tr>
<tr>
<td>Circulation of document(electronic)</td>
<td>Carol Watson</td>
<td>By June 2015</td>
<td>Via email to directorate leads in respiratory at all sites and all GP practices</td>
</tr>
</tbody>
</table>


Appendix 1: Inhaled Corticosteroids in Adults: Prescribing Guidance for Healthcare Professionals

1. Inhaled corticosteroids (ICS) are generally considered safe when used in low doses. However, when higher doses are used over long periods, there is a risk of systemic side effects. All clinical guidelines stress the importance of ensuring that the lowest effective dose of inhaled corticosteroids is used.

2. The systemic side effects of corticosteroids are well known. High doses of inhaled corticosteroids are associated with clinically detectable adrenal suppression (Arch Intern Med 1999;159:941-55), increased risk of non-fatal pneumonia in patients with COPD (Arch Intern Med 2009;169:219-29), increased risk of type II diabetes (Am J Med 2010;123:1001-6), and may increase the risk of fractures (Thorax 2011;66:699-708). It is strongly recommended that all patients on higher doses of ICS (>1000 micrograms Beclometasone dipropionate (BDP) equivalent per day, or Step 4 or above of BTS/SIGN Asthma guidelines) should be made aware of the potential risks and given an inhaled corticosteroid safety warning card about adrenal suppression.

3. Patients taking nasal corticosteroids in addition to inhaled corticosteroids should be assessed for their potential total daily dose of corticosteroid. For those patients on doses of inhaled corticosteroids between 800-1000 micrograms of BDP equivalent per day, a corticosteroid safety card is recommended, especially if additional corticosteroids are taken.

4. Clinical trials of combination therapy in COPD show that both Symbicort 400 1 inhalation twice a day (Eur Respir J 2003; 22:912-19, Eur Respir J 2003; 21:74-81) and Seretide 500 Accuhaler 1 inhalation twice a day (N Engl J Med 2007; 356:775-89, Am J Respir Crit Care Med 2008;177:19-26) (Seretide 250 evohaler is not licensed for use in COPD) are equally effective in reducing the frequency of exacerbations and statistical improvements in quality of life in those with severe or very severe COPD and who have 2 or more exacerbations a year. However, the recommended BDP equivalent dose of Seretide is more than twice that of Symbicort. This may have an effect on the long term risk of corticosteroid side effects. The choice of which to use should be discussed with your patient.

5. At equipotent doses, there is no difference in the safety profile of different inhaled corticosteroids. Budesonide and ciclesonide are roughly equipotent to BDP. Fluticasone, mometasone and the newer ultrafine particle BDP HFA inhalers (QVAR and Fostair) are roughly twice as potent as standard BDP inhalers – see the BDP dose equivalence chart.

Before increasing the dose of inhaled corticosteroid:

6. Check inhaler technique. Poor inhaler technique, especially with aerosol inhalers is very common, and will contribute to treatment failure. Improving delivery of ICS to the lungs may be more effective than increasing the dose. Thus it is imperative that inhaler technique is checked at all times and appropriate changes made. All ICS MDIs (other than the newer ultrafine Beclometasone-HFA) should be used, and use taught, with a spacer (Volumatic or Aerochamber). The use of a large volume spacer may double drug delivery to the lungs (Br J
Clin Pharmacol 1998; 46:45-8, Clin Pharmacokinet 2004; 43:349-60). It is important to
prescribe a spacer that is compatible with the MDI device.

7. Although it is recommended in clinical asthma guidelines, there is limited evidence that
increasing the dose of inhaled corticosteroid over 800 micrograms BDP equivalent/day is
effective in improving asthma control. Even in acute exacerbations, there is little evidence
that doubling the dose of inhaled corticosteroid is effective as self-management (Cochrane
Review CD007524). In asthma, add on therapy with long acting beta agonists should be tried
before increasing the dose of inhaled corticosteroid above 800 micrograms BDP
 equivalent/day (step 3 of BTS/SIGN Asthma Guidelines).

8. MHRA guidance on the prescribing of fluticasone states that because of the risk of
systemic side effects, doses between 250-500 micrograms twice daily should only be
prescribed for moderate to severe asthma. Doses above this level should only be prescribed
by a specialist in asthma (consultant or GP) where additional benefit is expected or
demonstrated, or by the ability to reduce oral corticosteroid use.

9. Where there is dose equivalence, consider prescribing the lowest cost inhaler that the
patient can use effectively and if prescribing an MDI, prescribe with a spacer if appropriate.
Appendix 2 includes the costs of each inhaler per month at commonly used dosages.

10. Once a patient has achieved good asthma control on higher doses of inhaled
corticosteroid for a period of time (e.g. 3 months), consider stepping down the dose of
inhaled corticosteroid by 25 % (adapted from London resp team)
Appendix 2: Inhaled Corticosteroid (ICS) COPD Step-Down Inhaler Dose Guide

This guide may be used by GPs to review patients diagnosed with COPD with a percentage of predicted FEV₁ of >50% with no history of asthma and no acute exacerbations 12 months before commencing ICS. Step down should occur no more frequently than every 4 weeks after a face to face review and assessment of symptoms. Patients who have been stepped down need to be followed up 2 weeks after step down or sooner if symptoms necessitate, and periodically thereafter as clinically needed. Please note that ICS monotherapy in COPD is NOT indicated.

Symbicort Turbetadata® 400/12
- Symbicort 400/12 Turbetadata® 1 puff bd (£38.00)
  (800mcg BDP* equivalent/day + 24mcg formoterol/day)
- Symbicort 100/6 Turbetadata® 2 puffs bd (£33.00)
  (400mcg BDP* equivalent/day + 24mcg formoterol/day)

Symbicort Turbetadata® 200/6
- Symbicort 200/6 Turbetadata® 2 puffs bd (£38.00)
  (600mcg BDP* equivalent/day + 24mcg formoterol/day)
- Symbicort 100/6 Turbetadata® 2 puffs bd (£33.00)
  (400mcg BDP* equivalent/day + 24mcg formoterol/day)

Symbicort Turbetadata® 100/6
- Symbicort 200/6 Turbetadata® 1 puff bd (£19.00)
  (400mcg BDP* equivalent/day + 12mcg formoterol/day)
- Symbicort 100/6 Turbetadata® 2 puffs bd (£33.00)
  (400mcg BDP* equivalent/day + 24mcg formoterol/day)

This step down document should be used as a guide and step down individualised for each patient. It is important to ensure the dose of long acting bronchodilator is maintained and not stepped down at the same time. Costs are listed as 28 day cost without spacer (MIMS June 14). *total daily dose inhaled corticosteroid in terms of beclometasone dipropionate (BDP CFC) equivalent (standard particle size). **denotes unlicensed use of inhaler.

Oridonol Easyhaler®
12 micrograms inhalation powder.
One puff twice daily (£11.08)

OR
Formoterol MDI 12micrograms.
One puff twice daily (£16.83)

OR
Formoterol Turbetadata® 12micrograms.
One puff twice daily (£23.15)
Appendix 3: Detailed summary of evidence base

This part of the guideline includes the full evidence base for the treatments discussed. It is very detailed and only needs consideration if you wish to learn all of the major trials in COPD.

1. Pulmonary rehabilitation

Pulmonary rehabilitation has been supported by grade A evidence for many years; the Cochrane review in 2006 noted that it improved dyspnoea, fatigue, emotional function and self-efficacy. A subsequent review of rehabilitation performed after a hospital admission demonstrated that it reduces admissions and mortality, as well as improving quality of life (QOL). There is a strong evidence base for use of pulmonary rehabilitation, mostly in those with mMRC of at least 2. The course involves attending twice weekly for approximately 6-8 weeks for classes which involve tailored exercise and education about COPD; this usually includes how to expectorate sputum, how to take inhalers and how to manage exacerbations and panic attacks. This is not an exhaustive list. Patients on LTOT and with co-morbidity are not excluded, although those unable to stand/walk for reasons other than their COPD (e.g. due to severe OA/RA, not due to breathlessness) may get less out of the class. Patients don’t necessarily need to see a chest physician prior to being referred. Please explain what the classes involve prior to referral; motivated patients will get more from them. The exact composition of rehabilitation programmes varies across the various sites in Birmingham, but in general will involve a combination of the above exercises and education.

2. SABA

Although many patients with COPD do not have reversible airflow obstruction many have noted symptomatic improvement with the use of short acting beta2 agonists; SABAs. SABAs are used both in acute and chronic management of COPD, the most commonly used being salbutamol. The most recent Cochrane review showed that use of SABAs for at least seven days improved post bronchodilator lung function in patients with moderate to severe COPD. Patients were also less dyspnoeic and more likely to comply with treatment.

3. LAMA

Short acting anti muscarinic inhalers (SAMA e.g. ipratropium) should generally be avoided in preference to LAMAs. Head to head comparison demonstrated that tiotropium was superior, thus current guidance places LAMA ahead of SAMA for maintenance therapy.

Until relatively recently there was only one LAMA on the market (tiotropium), but many other products have recently been licensed. The Cochrane review of LABA v LAMA was only able to consider trials using tiotropium (due to their search dates) and concluded that its effects were superior to LABAs in terms of preventing exacerbations and disease related hospitalisation. Few head to head trials of LAMAs have been carried out, with the notable exception of GLOW2 (tiotropium v glycopyrronium) which concluded that the products were equivalent in terms of trough FEV1, dyspnoea score and exacerbation reduction. Aclidinium has been studied alongside tiotropium, but this trial was a small study of crossover design; a larger definitive study would be preferable. A summary of clinical effects, as demonstrated by the various LAMA trials, is shown in table 5. Two meta-analyses with indirect comparison shows that effects appear to be roughly equivalent between all
LAMAs\textsuperscript{9, 10}. Although these were undertaken prior to licensing of Umeclidinium there is some evidence of equivalence to tiotropium, at least in terms of bronchodilation\textsuperscript{11}; trials for Umeclidinium have not been long enough to date to report on exacerbation reduction robustly.

**Table 5: Summary of major LAMA trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration</th>
<th>Outcome</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acclidinium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jones et al 2011 (ACCLAIM I &amp; II)\textsuperscript{12}</td>
<td>1 year</td>
<td>↑ trough FEV1</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ HRQoL</td>
<td></td>
</tr>
<tr>
<td>Jones et al 2011 (ATTAIN)\textsuperscript{13}</td>
<td>6 months</td>
<td>↑ FEV1</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ HRQoL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ dyspnoea (TDI)</td>
<td></td>
</tr>
<tr>
<td>Kerwin et al 2012 (ACCORD)\textsuperscript{14}</td>
<td>12 weeks</td>
<td>↑ FEV1</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ HRQoL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ dyspnoea (TDI)</td>
<td></td>
</tr>
<tr>
<td>Fuhr et al 2012\textsuperscript{15}</td>
<td>15 days per treatment</td>
<td>Similar to ACCORD v placebo</td>
<td>Placebo, tiotropium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ morning FEV1 v tiotropium</td>
<td></td>
</tr>
<tr>
<td><strong>Glycopyrronium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D’Urzo et al 2011 (GLOW1)\textsuperscript{15}</td>
<td>26 weeks</td>
<td>↑ trough FEV1</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ HRQoL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ dyspnoea (TDI score)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ exacerbations</td>
<td></td>
</tr>
<tr>
<td>Kerwin et al 2012 (GLOW2)\textsuperscript{17}</td>
<td>1 year</td>
<td>Similar to GLOW1 v placebo</td>
<td>Placebo, tiotropium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ bronchodilation on Day1 &amp; week 26 v tiotropium</td>
<td></td>
</tr>
<tr>
<td>Beeh et al 2012 (GLOW3)\textsuperscript{18}</td>
<td>8 weeks</td>
<td>↑ endurance time</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ inspiratory capacity</td>
<td></td>
</tr>
<tr>
<td><strong>Tiotropium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brusasco et al 2003\textsuperscript{17}</td>
<td>26 weeks</td>
<td>↓ exacerbations</td>
<td>Placebo, salmeterol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ HRQoL</td>
<td></td>
</tr>
<tr>
<td>Briggs et al 2005\textsuperscript{18}</td>
<td>12 weeks</td>
<td>↑ FEV1</td>
<td>Salmeterol</td>
</tr>
<tr>
<td>Tashkin et al 2008 (UPLIFT)\textsuperscript{19}</td>
<td>4 years</td>
<td>↓ exacerbations</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ HRQoL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ FEV1</td>
<td></td>
</tr>
<tr>
<td>Vogelmeier et al 2011 (POET)\textsuperscript{20}</td>
<td>1 year</td>
<td>↓ exacerbations</td>
<td>Salmeterol</td>
</tr>
<tr>
<td><strong>Umeclidinium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donohue et al 2013\textsuperscript{21}</td>
<td>26 weeks</td>
<td>↑ FEV1</td>
<td>Placebo, Umeclidinium/vilanterol, Vilanterol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ HRQoL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ dyspnoea (TDI score)</td>
<td></td>
</tr>
<tr>
<td>Trivedi et al 2014\textsuperscript{22}</td>
<td>12 weeks</td>
<td>↑ FEV1</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ HRQoL</td>
<td></td>
</tr>
</tbody>
</table>
Although tiotropium has the largest evidence base, due to the duration of its license, most of its competitors are more cost-effective, since they are cheaper per month but have equivalent effects. Anyone already on tiotropium, who has good inhaler technique, and does not requires LABA/LAMA, may be maintained on it.

3.1 Safety 
The adverse effects encountered with LAMAs are largely those attributed to its anti-cholinergic activity with dry mouth being one of the most commonly reported side effects. Clinical trials involving all drugs have reported similar adverse event rates with the active intervention compared with placebo. The most common events reported in the aclidinium and glycopyrronium trials over placebo were nasopharyngitis. In the 4 year UPLIFT study of tiotropium the most commonly encountered adverse events were due to lower respiratory causes however this was similar in the placebo arm. 

A study prior to the publication of UPLIFT had suggested that use of tiotropium increased cardiovascular morbidity and mortality; data from UPLIFT refuted this demonstrating a non-significant reduction in all cause cardiovascular mortality. It is of note that UPLIFT used the Handihaler device, and excluded those with cardiovascular co-morbidity. Later indirect analyses of trial data using the Respimat device (not licensed in the USA, but available in at least 55 countries worldwide, including the UK) still suggested an adverse cardiovascular mortality effect with tiotropium in the Respimat device. Much debate ensued after this, but a head to head trial of Respimat v Handihaler (TIOSPIR) showed that Handihaler and Respimat were equal in respiratory efficacy and had no difference in cardiovascular event rate. Thus the effect from the meta-analyses was not borne out in an adequately powered prospective study, and it may be prescribed if this is the best device for the patient.

4. LABAs
This class of drug has been reviewed and compared to a LAMA by the Cochrane collaboration, although significant trial heterogeneity precluded meta-analysis, primarily due to the fact that one of the LABAs (indacaterol) had a better effect on health related quality of life (HRQoL) than the other drugs in the class. A subsequent network meta-analysis also confirmed that indacaterol may be superior to other LABAs. Most of the primary studies of LABAs did not have exacerbation frequency as a primary outcome measure, although meta-analysis of their data has been carried out; in general there is a class effect showing reduction in exacerbations against placebo. However since head to head comparison of both indacaterol and salmeterol against tiotropium, show LAMAs to be better in this regard, LABAs remain our second choice long acting bronchodilator.

Salmeterol and formoterol are LABAs with extended duration of action maintained 12hrs after inhalation of a single dose which has led to their twice daily dosing. Formoterol's potency and speed of action make it effective in both quick relief and for prolonged effect. Clinical trials pertaining to the efficacy of formoterol, salmeterol and indacaterol are shown in table 6. Whilst no head to head trials have been done, indirect comparison within a Cochrane review suggests that many effects are largely the same but indacaterol has some evidence of superiority. It is also cost- effective, as both head to head comparison against salmeterol and real-life UK data showed that long term gains were present in cost terms, despite higher cost/inhaler. Thus it is not within our formulary but remains an evidence based choice, if inhaler technique were to mandate it. Salmeterol only has a step up option in the
same device if the accuhaler is used.

Table 6: Summary of major LABA trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration</th>
<th>Outcome</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formoterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dahl et al 2001(^{32})</td>
<td>12 weeks</td>
<td>↑ FEV1 ↓ symptom scores</td>
<td>Placebo, ipratropium</td>
</tr>
<tr>
<td>De Rossi et al 2002(^{33})</td>
<td>1 year</td>
<td>↑ FEV1</td>
<td>Placebo, theophylline</td>
</tr>
<tr>
<td>Calverley et al 2003(^{34})</td>
<td>1 year</td>
<td>↔ FEV1</td>
<td>Placebo, budesonide, budesonide/formoterol</td>
</tr>
<tr>
<td>Szafranski et al 2003(^{35})</td>
<td>1 year</td>
<td>↔ FEV1</td>
<td>Placebo, budesonide, budesonide/formoterol</td>
</tr>
<tr>
<td><strong>Indacaterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feldman et al 2010(^{36})</td>
<td>12 weeks</td>
<td>↑ FEV1</td>
<td>Placebo</td>
</tr>
<tr>
<td>Donohue et al 2010(^{37})</td>
<td>26 weeks</td>
<td>↑ FEV1 ↑ HRQoL ↓ exacerbations</td>
<td>Placebo Comparisons to tiotropium showed equivalence on all measures</td>
</tr>
<tr>
<td>Dahl et al 2010(^{38})</td>
<td>1 year</td>
<td>↑ FEV1 ↓ symptom scores</td>
<td>Placebo, formoterol</td>
</tr>
<tr>
<td>Kornmann et al 2011(^{39})</td>
<td>26 weeks</td>
<td>↑ FEV1</td>
<td>Placebo, salmeterol</td>
</tr>
<tr>
<td>Chapman et al 2011(^{40})</td>
<td>1 year</td>
<td>↑ FEV1 ↑ HRQoL ↓ exacerbations</td>
<td>Placebo</td>
</tr>
<tr>
<td>Decramer et al 2013(^{28})</td>
<td>1 year</td>
<td>↔ FEV1 ↑ HRQoL ↑ exacerbations</td>
<td>Tiotropium</td>
</tr>
<tr>
<td><strong>Salmeterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boyd G et al 1997(^{41})</td>
<td>16 weeks</td>
<td>↑ FEV1</td>
<td>Placebo</td>
</tr>
<tr>
<td>Mahler et al 1999(^{52})</td>
<td>12 weeks</td>
<td>↑ FEV1</td>
<td>Placebo, ipratropium*</td>
</tr>
<tr>
<td>Rennard et al 2001(^{43})</td>
<td>12 weeks</td>
<td>↑ FEV1</td>
<td>Placebo</td>
</tr>
<tr>
<td>Calverley et al 2003(^{34}) (TRISTAN)</td>
<td>1 year</td>
<td>↑ FEV1 ↓ exacerbations ↑ HRQoL</td>
<td>Placebo, fluticasone, fluticasone/salmeter</td>
</tr>
<tr>
<td>Calverley et al 2007(^{45}) (TORCH)</td>
<td>3 years</td>
<td>↑ FEV1 ↓ exacerbations ↑ HRQoL</td>
<td>Placebo, fluticasone, salmeterol/fluticasone</td>
</tr>
</tbody>
</table>
4.1 Safety
In general both SABAs and LABAs are well tolerated apart from the occasional episode of tachycardia and tremor. There has been some concern with regard to cardiovascular safety and use of B2 agonists. Salpeter et al\(^\text{46}\) suggested increased cardiovascular risk with LABAs compared with placebo, a fact hotly debated but disproven in subsequent meta-analyses in COPD\(^\text{47}\). It has also been suggested that tolerance/tachyphylaxis would render LABAs less efficacious over time. Data from Szafranski et al\(^\text{45}\) and TORCH\(^\text{45}\) has refuted this by demonstrating that the bronchodilator effect of LABA therapy is maintained at 1 and 3 years respectively.

5. LABA/LAMA
The combination of LAMA and LABA in the same device improves convenience for patients, and there are no new pharmacology or safety issues to consider, since they are composites of the individual agents discussed above. In general this class of inhaler improves breathlessness, HRQoL and exacerbations. Most trials have been against active components rather than placebo, due to the known efficacy of LAMA and LABA. The key licensed agents are summarised in table 7. Although there are class effects across LAMA and (with the exception of indacaterol) across LABA, it was apparent that Ultibro had stronger clinical efficacy evidence than its competitors. All of the LAMAs within table 3 can be stepped up to a LABA/LAMA in the same device, although tiotropium’s combination product with olodaterol in the Respimat device is not on our formulary at present, as it was not licensed at the time of our evidence review. Since we wish to make device consistency a key principle of our guideline we have not ranked Ultibro higher than its competitors in our guidance table (table 3), as patients who were best able to use an alternative device at the LAMA alone stage are likely to gain more benefit from continuing a device they can use well than switching.

No combination inhalers are planned in the Handihaler device.

| Table 7: Summary of major LABA/LAMA drug trials |
|-----------------|----------|-----------------|-----------------|
| **Trial**       | **Duration** | **Outcome**       | **Comparator**            |
| Formoterol/acldinium - Duaklr |           |                 |                             |
| Singh et al 2014\(^\text{48}\) | 24 weeks | ↑ FEV1           | Placebo, aclidinium, formoterol |
| Indacaterol/glycopyrronium - Ultibro |       |                 |                             |
| Vogelmeier et al 2013 (ILLUMINATE)\(^\text{49}\) | 1 year | ↑ FEV1           | Salmeterol/fluticasone     |
| Wedzica et al 2013 (SPARK)\(^\text{50}\) | 1 year | ↑ FEV1           | Glycopyrronium, tiotropium  |
| Mahler et al 2014 (BLAZE)\(^\text{51}\) | 6 weeks | ↑ FEV1           | Placebo, tiotropium        |
| Vilanterol/Umeclidinium - Anoro |           |                 |                             |
| Donohue et al 2013\(^\text{52}\) | 26 weeks | ↑ FEV1           | Placebo, Umeclidinium, Vilanterol |
|                             |           | ↑ HRQoL         |                             |
|                             |           | ↓ dyspnoea (TDI score) |                             |
6. LABA/ICS

This drug class is used in part to reduce breathlessness via bronchodilation and partly to reduce exacerbations; both features may improve HRQoL. The ICS component has little effect on breathlessness so we favour reserving use for those patients in whom exacerbations are a problem, as shown in the flow diagram on page 3. ICS should not be used alone in COPD, instead they are only licensed in combination with LABA; currently licensed combinations are beclomethasone/formoterol (Fostair), budesonide/formoterol (Symbicort or Duoresp), fluticasone furoate/vilanterol (Relvar) and fluticasone/salmeterol (Seretide). All trials with Seretide have been carried out using the Accuhaler device which is a DPI. The MDI is not licensed in COPD, and is considerably more expensive. In general effects seen in this drug class are the same between agents, as demonstrated by indirect comparisons in the Cochrane review\(^5\); this was carried out prior to the licensing of Fostair or Relvar for COPD, so we have considered the primary evidence when assessing the placement of these drugs in our guideline. A recent study (WISDOM) has shown that withdrawal of ICS from patients with severe disease currently using LABA/ICS resulted in no difference in exacerbation frequency or lung function, although some patients had a slight increase in FEV1 decline\(^52\). Further research regarding the role of ICS in COPD is ongoing.

It is clear that ICS reduce airway inflammation, airflow limitation, and symptoms in asthma and are the mainstay of treatment\(^53\). In COPD, however, the role of ICS is more controversial, predominantly because the pattern of inflammation differs. The inflammation in COPD is dominated by neutrophilic infiltration with increased numbers of macrophages and CD8 T lymphocytes which is not as responsive to steroids as the eosinophilic inflammation seen in asthma\(^54\). Despite this ICS were used in COPD before any real evidence of efficacy was known. The Cochrane collaboration have reviewed ICS use in COPD and concluded that although use of ICS is associated with a reduction in exacerbation rates and possibly a reduced rate of decline in FEV1, these benefits need to be weighed against increased pneumonia risks \(^55\). There is growing evidence that patient selection for ICS may be appropriate; for instance several studies have shown that patients with eosinophilic airways inflammation tend to respond to steroids (oral or ICS) whereas non-eosinophilic ones do not \(^56-58\).

The two components of LABA/ICS may have an additive or synergistic effect; there is greater evidence of synergy in allergic inflammation than in COPD patients\(^59\). Animal studies suggest that the combination of ICS plus LABA behaves synergistically\(^60\), as ICS may regulate the coupling of β receptors to G proteins and hence cAMP activation, and overall response to LABA. Exposure to exogenous LABA (or SABA) leads to uncoupling by phosphorylation of the receptor via various pathways, which theoretically can lead to drug tolerance. Exposure to corticosteroids restores receptors to their previously sensitised state\(^61\). Chronic LABA or SABA exposure will also lead to reduced β receptor numbers, as they are internalized and degraded; ICS reverse this effect because the activation of GRE causes gene transcription and hence synthesis of these receptors\(^62\).
The main RCTS for LABA/ICS inhalers are shown in table 8.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration</th>
<th>Outcome</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beclomethasone/formoterol – Fostair MDI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calverley et al 2010(^{34})</td>
<td>1 year</td>
<td>↔ FEV1, HRQoL to b</td>
<td>Formoterol, Budesonide/formoterol</td>
</tr>
<tr>
<td>Singh et al 2014(^{44})</td>
<td>12 weeks</td>
<td>Equivalent in all outcomes except ↑ FEV1</td>
<td>Salmeterol/fluticasone</td>
</tr>
<tr>
<td>Wedzicha et al 2014 (FORWARD)(^{65})</td>
<td>48 weeks</td>
<td>↓ exacerbations, ↑ HRQoL</td>
<td>Formoterol</td>
</tr>
<tr>
<td><strong>Budesonide/formoterol – all Symbicort</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calverley et al 2003(^{34})</td>
<td>1 year</td>
<td>↓ exacerbations v P &amp; F, ↔ FEV1 v all, ↑ HRQoL v all</td>
<td>Placebo, formoterol, budesonide</td>
</tr>
<tr>
<td>Szafranski et al 2003(^{35})</td>
<td>1 year</td>
<td>↓ exacerbations v P &amp; F, ↔ FEV1 v P &amp; B, ↑ HRQoL v P &amp; B</td>
<td>Placebo, formoterol, budesonide</td>
</tr>
<tr>
<td><strong>Fluticasone furoate/vilanterol - Relvar</strong></td>
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</tr>
<tr>
<td>Dransfield et al 2013(^{66})</td>
<td>1 year</td>
<td>↑ FEV1, ↓ exacerbations, ↑ HRQoL</td>
<td>Placebo, Vilanterol</td>
</tr>
<tr>
<td>Agusti et al 2014</td>
<td>12 weeks</td>
<td>Equivalent in all parameters</td>
<td>Fluticasone/salmeterol</td>
</tr>
<tr>
<td><strong>Fluticasone/Salmeterol – Seretide accuhaler</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calverley et al 2003 (TRISTAN) (^{44})</td>
<td>1 year</td>
<td>↑ FEV1 v all, ↑ HRQoL v all, ↓ exacerbations v P</td>
<td>Placebo, salmeterol, fluticasone</td>
</tr>
<tr>
<td>Calverley et al 2007 (TORCH) (^{45})</td>
<td>3 years</td>
<td>↓ exacerbations v all, ↑ HRQoL v P</td>
<td>Placebo, salmeterol, fluticasone</td>
</tr>
<tr>
<td>Wedzicha et al 2007 (INSPIRE) (^{67})</td>
<td>2 years</td>
<td>↔ exacerbations, ↑ HRQoL, ↓ mortality, ↑ pneumonia</td>
<td>Tiotropium</td>
</tr>
</tbody>
</table>

The table shows all results for the selected LABA/ICS trials and uses the following abbreviations; P=placebo, F=formoterol, S=salmeterol, B=budesonide. See also table 6.

A number of secondary analyses of TORCH data have also been published, detailing determinants of change in health status\(^{68}\), beneficial effects on FEV1 decline\(^{69}\) and stratifying analysis for disease stage\(^{70}\). In a large observational study Symbicort was superior to Seretide in 'real-life' patients, for reducing exacerbations and hospitalizations, and was therefore more cost effective\(^{71}\). We recognize that it is likely most benefits are class effects, and as such inhaler technique should be the main driver.
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of choice. The ones we chose to appear in table 3 are those which are more cost-effective, due to lower cost/month for the drug, together with evidence of clinical equivalence. Relvar would meet these criteria, but has not been approved by our local formulary. It is notable that the European Medicines Agency has approved DuoResp Spiromax (budesonide/formoterol) for use in COPD patients, deeming it equivalent to Symbicort, on the basis of pharmacokinetic studies showing equivalence. No primary COPD studies have been carried out, and the device is not one in which any other COPD medications are available at present, however there is no reason not to use it if the device is one suitable for the patient. Care must be taken when prescribing generically for budesonide/formoterol to ensure that patients get the device they are familiar with from their pharmacist. More LABA/ICS inhalers are currently in clinical trials, such that the Breezhaler and Genuair devices chosen in table 3 for LAMA and LABA/LAMA will also have LABA/ICS options in the near future, which we will review for future versions of the guideline.

6.1 Safety

The side effect profiles of LABA/ICS combinations are effectively the sum of their component parts, as described above. Similar to the use of ICS the most significant adverse event is the risk of pneumonia with combination inhalers. The risk is significantly higher than placebo or LABA but not so when compared with ICS. A recent systematic review and indirect comparison of trials looking at Symbicort and Seretide suggest that the risk of pneumonia is greater with Seretide, perhaps due to overall elevation in steroid load. The caveat to this is that data from the TORCH trial had a large bearing on the overall findings.

7. Theophylline

Theophylline is a non-selective phosphodiesterase inhibitor. By the enzymatic inhibition of phosphodiesterase levels of cAMP and cGMP are increased giving it its weak bronchodilator effect. To achieve this however, fairly high concentration of theophylline are needed. Recent evidence has shown that theophylline has some anti-inflammatory action and maybe able to modulate inflammatory gene expression by its interaction with the histone deacetylase. Despite widespread use there have been few parallel group studies of oral theophyllines; the Cochrane review in 2002 included 20 relatively small crossover studies and concluded that there were moderate beneficial effects on lung function, with the caveat that results may not be generalisable.

8. Mucolytics

Mucus hypersecretion and resultant chronic cough can often be a feature of COPD. Mucolytics have been used to reduce sputum viscosity and to aid expectoration; those most widely used are carbocisteine and N-acetylcysteine (NAC). Others include erdosteine and ambroxol. NAC and to a lesser extent carbocisteine have anti-oxidant properties. The awareness that oxidative stress and the formation of reactive oxygen species play a role in COPD especially during exacerbations has suggested that treatment with mucolytics may be able to influence exacerbation rates. The Cochrane review of clinical effectiveness of mucolytics included 30 studies and demonstrated a small but significant reduction in exacerbations in treated patients with COPD. There was no improvement in lung function and little effect on QoL.
9. Oxygen

Overt or relative hypoxia is one of the hallmarks of COPD, especially in the latter stages of the disease. Oxygen therapy to ameliorate this has been proven to be effective for patients who have severe resting hypoxia. The basis for LTOT (>15 hours daily) is derived from two landmark RCTs: the NOTT trial which compared 12 hours (nocturnal) and 24 hours oxygen therapy and the MRC trial which compared more than 15 hours oxygen therapy to placebo. The main outcome in both trials was improved survival in patients receiving oxygen for at least 15 hours daily, though this improved survival was not seen in the MRC trial until one year after the initiation of oxygen therapy. The NOTT trial also demonstrated a fall in mean pulmonary artery pressure (PAP). Whilst a fall in mean PAP was not shown in the MRC trial increases in PAP seen in the control arm did not occur in the patients undergoing oxygen therapy. LTOT is indicated for patients in a clinically stable state who have PaO2 < 7.3 kPa or 7.3-8 kPa in the presence of pulmonary hypertension, nocturnal hypoxia or secondary polycythaemia when assessed on two separate occasions. Aside from LTOT two other modes of oxygen therapy exist: ambulatory and short burst (SBOT); both have been reviewed relatively recently. Ambulatory oxygen is indicated in mobile patients who meet the LTOT criteria and is commonly considered in other COPD patients who exhibit exertional desaturation to less than 90%, although only if there is objective evidence of improvement with oxygen (e.g. 6 minute walk test distance is better on oxygen than on air) after the patient has completed pulmonary rehabilitation. SBOT criteria are poorly defined, and in general no benefits are seen; it should therefore be used only in a palliative setting.

10. Advanced treatments which may be considered for secondary care initiation

Patients symptomatic on the treatments described in this guideline may be eligible for more advanced therapies initiated in secondary care, examples of these are macrolide antibiotics as prophylaxis for frequent exacerbations, lung volume reduction surgery for upper zone dominant emphysema, endobronchial valve placement for emphysema, non-invasive ventilation for type 2 respiratory failure or lung transplant. In some patients long term low dose steroids may also be tried. In the interests of avoiding undue length to this document the evidence base for these will not be discussed here.

11. Palliative care

There will be many patients in whom despite optimised therapy, decline occurs and palliative or end-of-life care is needed. Treatments to consider at this stage are oral morphine for relief of breathlessness and benzodiazepines for relief of anxiety and breathlessness. Cognitive behavioural therapy, or classes in which this features heavily, are also available locally and may be suitable for patients in whom symptom palliation is needed but they have not yet reached the end of life. These classes include the Fatigue Anxiety Breathlessness (FAB) course, and are run at local hospices, such as Marie Curie in Solihull, John Taylor in Erdington and St Marys in Selly Oak.

12. Overlap between COPD and asthma

When a patient presents symptoms of increased variability of airflow alongside airflow obstruction which is only partially reversible it is known as the asthma-COPD overlap syndrome (ACOS). A consensus conference has proposed that an ACOS patient must fulfil 2
major criteria or one major and two minor from: A) Major criteria: very positive bronchodilator response (>400ml and >15% FEV1), sputum eosinophilia or previous diagnosis of asthma. B) Minor criteria: increased total serum IgE, history of atopy or positive bronchodilator test (>200ml, >12%) on at least 2 occasions. ACOS typically includes patients with early onset asthma and long disease duration who then fulfil criteria for COPD with age, COPD patients with increased reversibility and smoking asthmatics who have fixed airflow obstruction. Overall 13-19% of patients with obstructive lung diseases have some overlap and this increases with age. In UPLIFT two thirds of moderate to severe COPD patients exhibited bronchodilator responsiveness, yet most clinical trials for either asthma or COPD exclude patients with features of the other disease, implying that their results will be poorly generalisable in real-life. ACOS has been extensively reviewed in published literature, our reasoning for including it here is to acknowledge its existence and the effect it may have on prescribing relative to our main guideline recommendations. Furthermore, patients exhibiting features consistent with the ACOS definition are more likely to be frequent exacerbators, have more respiratory symptoms, higher mortality, higher co-morbidity rates, greater healthcare utilization and worse HRQoL.

Overlap patients are generally thought to exhibit phenotypes part way between COPD and asthma; for example Gibson et al reported prevalence of atopy that was highest in asthma (100%) intermediate in ACOS (64%) and lowest in COPD (25%). There are some differences which may depend on the predominant pathology - positive bronchodilator response observed in COPD is associated with increased eosinophilic inflammation whilst irreversible COPD more frequently exhibits neutrophilia. Smoking asthmatics typically have inflammatory features that resemble COPD with increased neutrophilia and sometimes airway remodelling. Classical asthma drivers, such as occupation, associate with fixed airflow obstruction after chronic exposure and ABPA has also been reported in patients in COPD. During exacerbations of ACOS airway mucosal eosinophils rise more than neutrophils explaining the improvement with systemic CS or ICS. In general there should therefore be a lower threshold for use of ICS if there is definite overlap of COPD with asthma, however if the diagnosis is not clear we would advocate use of the guideline for the condition most prominent in the patient (i.e. patients with COPD who exhibit reversibility to bronchodilators should be treated using the COPD guideline and those with lifelong asthma, with fixed airflow obstruction, should be treated using the asthma guideline).
References

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