## ONLINE SUPPLEMENTARY TABLES

**Supplementary Table 1. Inclusion and exclusion criteria for selection of studies, and data synthesis for network meta-analysis within a Bayesian framework.**

| Criteria | | Inclusion | Exclusion |
|---|---|---|---|
| **STUDY DESIGN** | **Abstract selection** | Randomised controlled trials | Crossover studies; if crossover occurred prior to 10 weeks in each arm.<br>Post hoc or retrospective analyses<br>Cost effectiveness analyses<br>Observational studies<br>Reviews or meta-analyses<br>Methodology studies or protocols<br>Trials in which N = 1 (sample size of 1 patient)<br>Studies lasting < 10 weeks<br>Conference abstracts prior to 2009<br>Studies not in the English or German language |
| | **Full-text selection** | Randomised controlled trials | Studies in which patients were required to spend time in a sleep laboratory. |
| **TREATMENT / INTERVENTION** | **Abstract selection** | <u>LAMA monotherapies</u><br>Umeclidinium 55 mcg OD<br>Aclidinium 400 mcg BID<br>Tiotropium 18 mcg OD<br>Glycopyrronium 50 mcg OD<br><br><u>LABA monotherapies</u><br>Salmeterol 50 mcg BID<br>Formoterol 12 mcg BID<br>Indacaterol 75, 150, 300 mcg OD<br>Olodaterol 5, 10 mcg OD<br><br><u>LABA + LAMA combinations</u><br>Umeclidinium/vilanterol<br>Tiotropium/indacaterol<br>Salmeterol/tiotropium<br>Formoterol/tiotropium<br>Indacaterol/glycopyrronium (QVA149)<br>Any other combination of a LABA and a LAMA | Beta-agonists (bambuterol, fenoterol, tulobuterol)<br>Short-acting anticholinergics (ipratropium, oxitropium)<br>Methylxanthines (theophylline)<br>Inhaled corticosteroids (ICS)<br>Inhaled glucocorticoids (beclomethasone; budesonide; fluticasone)<br>Leukotriene receptor antagonists (montelukast)<br>Combinations of long-acting anticholinergics or LABAs with an ICS formoterol + budesonide or fluticasone + salmeterol that are administered separately<br>COPD drugs in development or targeting other pathways (roflumilast, polyvalent mechanical bacterial lysate, lipopolysaccharides)<br>All other pharmaceutical interventions not treating COPD (enoxaparin sodium)<br>Nonpharmaceutical interventions such as pulmonary rehabilitation |

| Criteria | | Inclusion | Exclusion |
|---|---|---|---|
| | **Full text selection** | Umeclidinium/vilanterol 55/22 mcg OD;<br>Tiotropium/indacaterol 18/150 mcg OD;<br>Salmeterol/tiotropium 50/18 mcg<br>Formoterol/tiotropium 10/18 or 12/18 mcg<br>Indacaterol/glycopyrronium 110/50 mcg OD (QVA149)<br>Any other combination of a LABA and a LAMA<br>Tiotropium 18mcg OD<br><br>Administered using any inhalation device | Any treatments of interest with doses that differ from the doses of interest<br>Studies of arformoterol (the (R,R) isomer of formoterol) |
| **COMPARATOR** | **Abstract and full-text selection** | Studies that compare treatments of interest (above) with each other or with placebo | Studies that only compare treatments that are not of interest<br>Studies that only include the treatments of interest in combination with treatments not of interest (i.e., prednisolone + formoterol)<br>Studies that only include the partial combinations of treatments of interest (i.e., tiotropium + ICS) |
| **POPULATION** | **Abstract selection** | Patients with COPD as defined by GOLD guidelines (i.e., airflow limitation that is not fully reversible)<br>Studies that include asthma and COPD patients and report data for COPD patients separately<br>Adult patients<br>Studies that include adults and children and report data for adults separately | Studies with only healthy patients without COPD<br>Studies with patients who have reversible airway or obstructive lung disease<br>Studies with only patients with asthma<br>Studies that include asthma patients and COPD patients but do not report data for COPD patients separately<br>Studies with only patients who have alpha-1-antitrypsin-deficiency-related COPD<br>Studies that include only children<br>Studies that include adults and children but do not report data for adults separately<br>Trials in nonCaucasian populations e.g., Chinese, Japanese patients (including non-Caucasian registries) |

| Criteria | | Inclusion | Exclusion |
|---|---|---|---|
| | **Full-text selection** | Patients with COPD as defined by GOLD guidelines (i.e., airflow limitation that is not fully reversible)<br>Studies that include asthma patients and COPD patients and report data for COPD patients separately<br>Adult patients<br>Studies that include adults and children and report data for adults separately | Studies with only healthy patients without COPD<br>Studies with patients who have reversible airway or obstructive lung disease<br>Studies with only patients with asthma<br>Studies that include asthma and COPD patients but do not report data for COPD patients separately<br>Studies with only patients who have alpha-1-antitrypsin-deficiency-related COPD<br>Studies that include only children<br>Studies that include adults and children but do not report data for adults separately<br>Trials in nonCaucasian populations (e.g., Chinese, Japanese patients) |
| **OUTCOMES** | **Abstract selection** | No selection based on outcomes | No selection based on outcomes |
| | **Full-text selection** | Report results for at least one of the following outcomes (for all treatments):<br>o Trough $FEV_1$<br>o St. George's Respiratory Questionnaire total score (SGRQ)<br>o Transition dyspnoea index (TDI)<br>o Rescue medication use | None of the relevant outcomes (as listed in the inclusion criteria) are reported<br>Only the following outcomes (without any outcomes of interest) are reported:<br>mortality<br>bioactivity outcomes or biomarkers of inflammation<br>lung mucociliary clearance<br>arterial blood gases or degree of pulmonary hyper-inflation<br>plethysmography and oscillometry<br>nocturnal hypoxemia<br>quality of life in EuroQol |

| Criteria | Inclusion | Exclusion |
|---|---|---|
| **Data synthesis in NMA within Bayesian framework** | A linear model with normal likelihood distribution was used with flat (noninformative) prior distributions assumed for all outcomes. Prior distributions of the relative treatment effects were normal, with zero mean and a variance of 10,000. A uniform distribution ranging from zero to five was used as the prior of the interstudy SD.<br>For each outcome, fixed and random effects models were evaluated. The goodness of fit of each model to the data was assessed using the Deviance Information Criterion (DIC). The posterior densities for the outcomes of interest were estimated using the Markov chain Monte Carlo (MCMC) simulations for each model. The results were based on 80,000 iterations on three chains, with a burn-in of 20,000 iterations. Convergence assessment was based on visual inspection of trace plots. Accuracy of the posterior estimates was assessed using the Monte Carlo error for each parameter (Monte Carlo error < 1% of the posterior SD). The models used in this study were based on those defined by Dias et al [27] and were implemented using WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).<br>The posterior distributions were summarised with corresponding median values to reflect the most likely value of the estimate, and the $2.5^{th}$ and $97.5^{th}$ percentile to capture the 95% credible interval (95% CrI), which represents the range of true underlying effects with 95% probability. Moreover, the probability that each treatment is better than a certain comparator was estimated for each endpoint. If studies reported mean values without any measure of uncertainty (SE, SD, 95% CI), scenario analyses were performed excluding this study because of the lack of data; however, such studies were included with the reported mean value and an imputation for the SE. | |

## Supplementary Table 2: Detailed search strategies

1) Search strategy for the systematic review: MEDLINE and MEDLINE in-process

| | |
|---|---|
| **Database** | MEDLINE(R) In-Process and Other Non-Indexed Citations and MEDLINE(R) |
| **Platform** | Ovid |
| **Date of search** | 16.04.2014 |
| **Time limits** | 1946 to 2014 Week 15 |
| **Filters** | Line 6 - 13 are from the search filter: BMJ Clinical Evidence Strategy (MEDLINE randomised controlled trials strategy using Ovid). Available from: http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html (accessed on 14.04.2014) |

| # | Searches | Results |
|---|---|---|
| 1 | (formoterol or eformoterol or foradil or oxis or atimos modulite or atock or perforomist or salmeterol or serevent or tiotropium or spiriva or Ba 679 BR or indacaterol or onbrez or arcapta or NVA-237 or NVA237 or (NVA adj "237") or glycopyrronium bromide or glycopyrrolate or seebri or enurev breezhaler or aclidinium bromide or tudorza pressair or eklira genuair or symbicort or advair or seretide or olodaterol or striverdi or umeclidinium or GSK573719 or vilanterol or GW642444 or QVA149 or relvar/breo or zephyr or anoro ellipta).ti,ab,nm. | 5491 |
| 2 | exp Pulmonary Disease, Chronic Obstructive/ or exp Chronic obstructive lung disease/ | 35415 |
| 3 | (COPD or chronic obstructive pulmonary disease or COAD or chronic obstructive airway disease or chronic obstructive lung disease or chronic bronchitis or emphysema).ti,ab. | 60286 |
| 4 | 2 or 3 | 69295 |
| 5 | 1 and 4 | 1647 |
| 6 | "randomised controlled trial".pt. | 370219 |
| 7 | (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab. | 782910 |
| 8 | (retraction of publication or retracted publication).pt. | 6430 |
| 9 | 6 or 7 or 8 | 867607 |
| 10 | (animals not humans).sh. | 3829658 |
| 11 | ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomised controlled trial").pt. | 3187191 |
| 12 | (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomised controlled trial".pt. | 47025 |
| 13 | 9 not (10 or 11 or 12) | 649371 |
| 14 | 5 and 13 | 637 |
| 15 | limit 14 to (English or German) | 610 |

ab, nm, pt, sh, ti: searches performed in abstract, name of substance, publication type, subject heading and title fields, respectively

**2)** Search strategy for the systematic review: EMBASE

| | |
|---|---|
| **Database** | EMBASE |
| **Platform** | Ovid |
| **Date of search** | 16.04.2014 |
| **Time limits** | 1988 to 2014 Week 15 |
| **Filters** | Line 6 - 12 are from the search filter: BMJ Clinical Evidence Strategy (EMBASE randomised controlled trials strategy using Ovid). Available from: http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html (accessed on 14.04.2014) |

| # | Searches | Results |
|---|---|---|
| 1 | (formoterol or eformoterol or foradil or oxis or atimos modulite or atock or perforomist or salmeterol or serevent or tiotropium or spiriva or Ba 679 BR or indacaterol or onbrez or arcapta or NVA-237 or NVA237 or (NVA adj "237") or glycopyrronium bromide or glycopyrrolate or seebri or enurev breezhaler or aclidinium bromide or tudorza pressair or eklira genuair or symbicort or advair or seretide or olodaterol or striverdi or umeclidinium or GSK573719 or vilanterol or GW642444 or QVA149 or relovair or zephyr or anoro ellipta).ti,ab. | 6554 |
| 2 | exp Pulmonary Disease, Chronic Obstructive/ or exp Chronic obstructive lung disease/ | 62723 |
| 3 | (COPD or chronic obstructive pulmonary disease or COAD or chronic obstructive airway disease or chronic obstructive lung disease or chronic bronchitis or emphysema).ti,ab. | 65503 |
| 4 | 2 or 3 | 87605 |
| 5 | 1 and 4 | 2349 |
| 6 | (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab. | 893801 |
| 7 | RETRACTED ARTICLE/ | 6430 |
| 8 | 6 or 7 | 900087 |
| 9 | (animal$ not human$).sh,hw. | 2500858 |
| 10 | (book or conference paper or editorial or letter or review).pt. not exp randomised controlled trial/ | 3608293 |
| 11 | (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomised controlled trial/ | 51550 |
| 12 | 8 not (9 or 10 or 11) | 681639 |
| 13 | 5 and 12 | 914 |
| 14 | limit 13 to (English or German) | 881 |

3) Search strategy for the systematic review: Cochrane Library - CDSR, CENTRAL

| | |
|---|---|
| **Database** | CENTRAL and CDSR |
| **Platform** | Cochrane |
| **Date of search** | 16.04.2014 |
| **Time limits** | 1988 to 2014 |
| **Filters** | n.a. |

| # | Searches | Results |
|---|---|---|
| 1 | (formoterol or eformoterol or foradil or oxis or atimos modulite or atock or perforomist or salmeterol or serevent or tiotropium or spiriva or Ba 679 BR or indacaterol or onbrez or arcapta or NVA-237 or NVA237 or (NVA near/3 237) or glycopyrronium bromide or glycopyrrolate or seebri or enurev breezhaler or aclidinium bromide or tudorza pressair or eklira genuair or symbicort or advair or seretide or olodaterol or striverdi or umeclidinium or GSK573719 or vilanterol or GW642444 or QVA149 or relovair or zephyr or anoro ellipta):ti,ab,kw | 4609 |
| 2 | MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees | 2533 |
| 3 | (COPD or chronic obstructive pulmonary disease or COAD or chronic obstructive airway disease or chronic obstructive lung disease or chronic bronchitis or emphysema):ti,ab,kw | 10689 |
| 4 | #1 and (#2 or #3) in Trials | 1415 |
| 5 | #1 and (#2 or #3) (in Cochrane Reviews [Reviews and Protocols]) | 21 |

ab, kw, ti: searches performed in abstract, keyword and title fields, respectively; n.a: not applicable
Line 4 is corresponds to the CENTRAL database, line 5 to the CDSR database. Both results were exported.

4) Search strategy for the systematic review: DARE Database

| | |
|---|---|
| **Database** | DARE |
| **Platform** | CRD (http://www.crd.york.ac.uk/crdweb/) |
| **Date of search** | 16.04.2014 |
| **Time limits** | No time limits |
| **Filters** | n.a. |

| # | Searches | Results |
|---|---|---|
| 1 | (formoterol or eformoterol or foradil or oxis or atimos modulite or atock or perforomist or salmeterol or serevent or tiotropium or spiriva or Ba 679 BR or indacaterol or onbrez or arcapta or NVA-237 or NVA237 or (NVA and "237") or glycopyrronium bromide or glycopyrrolate or seebri or enurev breezhaler or aclidinium bromide or tudorza pressair or eklira genuair or symbicort or advair or seretide or olodaterol or striverdi or umeclidinium or GSK573719 or vilanterol or GW642444 or QVA149 or relovair or zephyr or anoro ellipta) [ANY FIELD] | 226 |
| 2 | (COPD or chronic obstructive pulmonary disease or COAD or chronic obstructive airway disease or chronic obstructive lung disease or chronic bronchitis or emphysema) [ANY FIELD] | 828 |
| 3 | 1 and 2 in DARE | 62 |

n.a.: not applicable

5) Search strategy for the systematic review: Health Technology Assessment Database

| | |
|---|---|
| **Database** | HTA |
| **Platform** | CRD (http://www.crd.york.ac.uk/crdweb/) |
| **Date of search** | 16.04.2014 |
| **Time limits** | No time limits |
| **Filters** | n.a. |

| # | Searches | Results |
|---|---|---|

| | | |
|---|---|---|
| 1 | (formoterol or eformoterol or foradil or oxis or atimos modulite or atock or perforomist or salmeterol or serevent or tiotropium or spiriva or Ba 679 BR or indacaterol or onbrez or arcapta or NVA-237 or NVA237 or (NVA and "237") or glycopyrronium bromide or glycopyrrolate or seebri or enurev breezhaler or aclidinium bromide or tudorza pressair or eklira genuair or symbicort or advair or seretide or olodaterol or striverdi or umeclidinium or GSK573719 or vilanterol or GW642444 or QVA149 or relovair or zephyr or anoro ellipta) [ANY FIELD] | 226 |
| 2 | (COPD or chronic obstructive pulmonary disease or COAD or chronic obstructive airway disease or chronic obstructive lung disease or chronic bronchitis or emphysema) [ANY FIELD] | 828 |
| 3 | 1 and 2 in HTA | 116 |
| 4 | HTA: HTA in progress and HTA published | 17 |

6) Trial registry: Search strategy for Clinicaltrials.gov

| | |
|---|---|
| **Trial registry** | clinicaltrials.gov |
| **URL** | http://www.clinicaltrials.gov/ |
| **Date of search** | 14.04.2014 |
| **Search strategy** | COPD OR COAD OR “Chronic obstructive pulmonary disease” OR “Chronic obstructive lung disease” OR “chronic obstructive airway disease” OR “chronic bronchitis” OR “emphysema” \| Phase 2, 3, 4 |
| **Results** | 949 |

**7)** Trial registry: Search strategy for World Health Organization International Clinical Trials Registry Platform

| | |
|---|---|
| **Trial registry** | WHO International Clinical Trials Registry Platform (ICTRP) |
| **URL** | http://apps.who.int/trialsearch/AdvSearch.aspx |
| **Date of search** | 14.04.2014 |
| **Search strategy** | COPD OR chronic obstructive pulmonary disease OR COAD OR chronic obstructive airway disease OR chronic obstructive lung disease OR chronic bronchitis OR emphysema |
| **Results** | 3852 records for 2922 trials found* |

* The WHO ICTRP imports records from several registries. Trials are sometimes recorded in more than one registry. These records can refer to each other using a secondary identification number. The search portal uses this secondary identification number to group records about the same trial together in the search results.

All results were reported in an excel database. However WHO ICTRP also collects data from Asian registries. As non-caucasian population is an exclusion criterion, trials listed on national non-caucasian registries were excluded for population not of interest. (i.e., Chinese Clinical Trial Registry; Clinical Trials Registry – India; Iranian Registry of Clinical Trials; Japan Primary Registries Network)

8) Trial registry: Search strategy for Current Controlled Trials

| | |
|---|---|
| **Trial registry** | Current controlled trials |
| **URL** | http://www.controlled-trials.com/ |
| **Date of search** | 15.04.2014 |
| **Search strategy** | (COPD or chronic obstructive pulmonary disease or COAD or chronic obstructive airway disease or chronic obstructive lung disease or chronic bronchitis or emphysema) in Databases: ISRCTN Register (International) - copy of ISRCTN Register; Action Medical Research (UK) - subset from ISRCTN Register; The |

| | |
|---|---|
| | Wellcome Trust (UK) - subset from ISRCTN Register; UK trials (UK) - subset from ISRCTN Register, UK trials only |
| **Results** | 87 |

ClinicalTrials.gov was removed from the list of resources searched in this aggregated database, as clinicaltrials.gov was searched directly in a separate search.

9) Trial registry: Search strategy for EU Clinical trials register

| | |
|---|---|
| **Trial registry** | EU Clinical Trials Register (EU-CTR) |
| **URL** | www.clinicaltrialsregister.eu |
| **Date of search** | 15.04.2014 |
| **Search strategy** | (COPD OR chronic obstructive pulmonary disease OR COAD OR chronic obstructive airway disease OR chronic obstructive lung disease OR chronic bronchitis OR emphysema) AND (Phase II OR Phase III or Phase IV [Select trial phase]) |
| **Results** | 307 |

10) Trial registry: Search strategy for Klinische Prüfungen PharmNet.Bund

| | |
|---|---|
| **Trial registry** | Klinische Prüfungen PharmNet.Bund |
| **URL** | http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm |
| **Date of search** | 15.04.2014 |
| **Search strategy** | COPD in Textfelder AND Limit to phase II or phase III or phase IV [Trial phase] AND Limit to therapy or safety or efficacy [Trial scope] AND Limit to patients [Trial population] |
| **Results** | 320 |

11) Trial registry: Search strategy for International Prospective Register of Systematic Reviews*

| | |
|---|---|
| **Trial registry** | International Prospective Register of Systematic Reviews (PROSPERO) |
| **URL** | http://www.crd.york.ac.uk/NIHR_PROSPERO/ |
| **Date of search** | 18.04.2014 |
| **Search strategy** | Separate searches for: COPD [ALL FIELDS] or chronic obstructive pulmonary disease [ALL FIELDS] or COAD [ALL FIELDS] or chronic obstructive airway disease [ALL FIELDS] or chronic obstructive lung disease [ALL FIELDS] or chronic bronchitis [ALL FIELDS] or Emphysema [ALL FIELDS]<br>Review status: Any review status |
| **Results** | 122 |

*Please note that search terms have to be searched for manually each and every one of them and them de-duplicated at the end.

12) Trial registry: Search strategy for NIHR Health Technology Assessment

| | |
|---|---|
| **Trial registry** | National Institute for Health Research - Health Technology Assessment (NIHR HTA) |
| **URL** | http://www.nets.nihr.ac.uk/projects |
| **Date of search** | 18.04.2014 |
| **Search strategy** | COPD [Keywords] and HTA [programme] in the advanced search |
| **Results** | 13 |

## Supplementary Table 3: Quality assessment for included studies

| Study | Adequate process of randomization | Allocation concealment | Blinding | | Independent reporting of all relevant outcomes | No other outcomes which were not reported | Risk of bias |
|---|---|---|---|---|---|---|---|
| | | | Patients | Caregivers | | | |
| | | | Yes | Yes | | | |
| Decramer 2014[9] | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Decramer 2014[9] | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Maleki-Yazdi 2014[28] | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| SPARK[16] | Yes | No | No | No | No | Yes | High |
| ENLIGHTEN[13] | Unclear | Unclear | Yes | Yes | Yes | No | Low |
| SHINE[11] | Yes | No | No | No | Yes | Yes | High |
| INTRUST-1[17] | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| INTRUST-2[17] | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Aaron 2007[20] | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Vogelmeier 2008[19] | Unclear | No | No | No | Yes | Yes | High |
| Tashkin 2009[18] | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Chan 2007 [29] (BI trial: 205.259) | Unclear | Yes | Yes | Yes | Yes | Yes | Low |
| TIPHON (Tonnel 2008) [30] | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Tashkin 2008 [31]and Celli 2009 [32]) | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Niewoehner 2005[33] | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Brusasco 2003[34] | Unclear | Yes | Yes | Yes | Yes | Yes | Low |
| Donohue 2002[35] | Unclear | Yes | Yes | Yes | Yes | Yes | Low |
| Casaburi 2002[36] | Unclear | Yes | Yes | Yes | Yes | Yes | Low |
| Donohue 2010[37] | Unclear | No | No | No | Yes | Yes | High |
| GLOW 2 (Kerwin 2012) [38] | Unclear | Unclear | Yes | Yes | Yes | Yes | Low |
| Verkindre 2006[39] | Unclear | Yes | Yes | Yes | Yes | Yes | Low |
| Casaburi 2000[40] | Unclear | Yes | Yes | Yes | Yes | Yes | Low |
| Covelli 2005[41] | Unclear | Yes | Yes | Yes | Yes | Yes | Low |
| Garcia 2007[42] | Unclear | Yes | Yes | Yes | Yes | Unclear | Low |
| Moita 2008[43] | Unclear | Yes | Yes | Yes | Yes | Yes | Low |

*Unclear randomization means it was mentioned that the study was randomised and in most cases even with which ratio (e.g., 1:1); however, not how the randomization was generated (e.g., with a computer); SPARK, SHINE, Vogelmeier 2008 and Donohue 2010 included tiotropium 18 mcg as open label arm and were categorised as high risk of bias.