# Supplementary Appendix

**Table S1** Patient baseline characteristics assessed in the study: demographic variables and comorbidities

| **Variable** | **Parameterization** | **Timing** |
| --- | --- | --- |
| Age at index date | Continuous variable, or as categorical (35–49, 50–59, 60–69, 70–79, 80–89, 90+) | At index |
| Gender | Male, female  | N/A |
| Strategic Health Authority region | East of England; East Midlands; London; North East; North West; South Central; South East Coast; South West; West Midlands; Yorkshire and the Humber | At index |
| Socioeconomic status | English index of multiple deprivation 2015 – based on postcode at index, quintiles | At index |
| BMI in last 3 years of patient history (measurement closest to index date will be selected) | Weight in kilograms divided by height in meters squared, utilized as either a continuous variable or a categorical variable using the following categories widely referenced as WHO classification: Underweight (below 18.5), Normal (18.5–24.9), Overweight (25.0–29.9), and Obese (30.0 and greater) | Any time in patient history, most recent measurement |
| Smoking status, most recent in patient history, relative to the index date | Four categories will be created: ex-smoker, current smoker, non-smoker, and unknown smoking status containing patients with missing entries or other types of tobacco exposure (eg passive smoking) | Any time in patient history, most recent measurement |
| Comorbidities ever in patient history | Patients were classified (separately for each comorbidity) as having a history of the following comorbidities any time in CPRD history preceding the index date:* Depression
* Anxiety
* Gastroesophageal reflux disease
* Acute myocardial infarction
* Congestive heart failure
* Stroke
* Bronchiectasis
* Dementia/cognitive impairment
* Rheumatoid/osteoarthritis
 | Any time in patient history |
| Current asthma diagnosis | Asthma defined according to a validated algorithm1 consisting of a set of validated specific codesThe positive predictive value of this algorithm has been estimated at 0.86 (95% CI 0.77 to 0.95), with validation against a reference standard of physician review of patient notes Current asthma defined as current asthma medical diagnosis record (=1) vs no current asthma (=0) in the CPRD over at least 12 months prior to index date (maximum 24 months prior to index date) | In 24 months prior to index |
| Historical asthma diagnosis | Defined as historical asthma medical diagnosis record (=1) vs no historical asthma (=0) in the CPRD any time in the patient history prior to index. Historical asthma diagnosis defined using the same diagnostic codes as current asthma diagnosis | Any time in patient history prior to index |

**Abbreviations:** BMI, body mass index; CI, confidence interval; CPRD, Clinical Practice Research Datalink; GOLD, Global Initiative for Chronic Obstructive Lung Disease; WHO, World Health Organization.

**Table S2** Patient baseline characteristics assessed in the study: COPD disease burden, prior treatment, and prior healthcare resource use

| **Variable** | **Parameterization** | **Timing** |
| --- | --- | --- |
| MRC dyspnea scale measurement within the 24 months prior to index date | A single-question instrument measuring severity of dyspnea related to exercise, which is a part of the Quality Outcomes Framework recommended investigations. The following Read codes were recorded in the CPRD, corresponding with each of the following grades:* Grade 1: no dyspnea except on strenuous exercise
* Grade 2: short of breath when walking up a short hill
* Grade 3: dyspnea limits walking pace (slower than others) and stops to catch breath
* Grade 4: stops to catch breath after walking 100 meters (328 feet) on level ground
* Grade 5: dyspnea prevents leaving house and performing Activities of Daily Living
* Additionally, a category of unknown/unavailable if no record available within the 24 months prior to index date was defined
 | Most recent measurement in 24 months prior to index date |
| COPD GOLD grade of airflow limitation measurement closest to index date within the window of 24 months prior the index date  | Modified according to GOLD-defined lung obstruction-based classification: * GOLD 1: FEV1% predicted ≥80%
* GOLD 2: FEV1% predicted ≥50–<80%
* GOLD 3: FEV1% predicted ≥30–<50%
* GOLD 4: FEV1% predicted <30%
 | Most recent measurement in 24 months prior to index date |
| GOLD 2019 stage2The most recent MRC dyspnea score within the 24 months prior to index date was used. If MRC was missing, the variable was to be set as ‘missing’ |

|  |  |  |
| --- | --- | --- |
| **Category** | **Exacerbations per year** | **MRC dyspnea score** |
| A | ≤1 moderate | 1–2 |
| B | ≤1 moderate | ≥3 |
| C | ≥2 moderate/ severe OR ≥1 severe | 1–2 |
| D | ≥2 moderate/ severe OR ≥1 severe | ≥3 |

 | Most recent measurement in 24 months prior to index date |
| Number of primary-care consultations in 12 months prior to index date | Count variable reported as mean (SD) and proportion of patients with a prespecified number of visits; the following distribution was considered: 0, 1–2, 3–4, and 5+ visits after checking their distribution in the final cohort of eligible patients. One encounter per contact type was allowed per day to avoid multiple counting of the same events | 12 months prior to index date |
| Attendance at secondary care respiratory outpatient clinic in 12 months prior to index date | Number of attendances at respiratory outpatient clinic in previous 12 months prior to initiation of inhaled triple therapy. Reported as number in previous 3 months and number in previous 12 monthsRespiratory clinic attendance was identified using HES-OP data and defined as attendance at an outpatient appointment where the consultant’s treatment speciality is respiratory medicine or, if treatment speciality is missing, main speciality is respiratory medicine | 12 months prior to index date |
| Attendance at any secondary care outpatient clinic in 12 months prior to index date | Number of attendances at respiratory outpatient clinic in previous 12 months prior to initiation of inhaled triple therapy. Reported as number in previous 3 months and number in previous 12 months | 12 months prior to index date |
| Respiratory medication exposure in 12 months prior to index date  | Exposure to specific respiratory therapies over the 12 months prior to the index date; ≥1 Rx ‘any use’ will be flagged vs those with Rx ‘0’ ‘no use’. The following respiratory therapies will be included:* + Roflumilast
	+ Theophyllines
	+ LAMA only
	+ LABA only
	+ LAMA/LABA fixed and open combinations
	+ ICS only
	+ ICS/LABA fixed and open combinations
	+ SABA/SAMA
	+ SABA only
	+ SAMA only
	+ ICS/SABA
	+ None of the treatments of interest (for patients who don’t have a claim for the above treatments)
 | 12 months prior to index date |
| Immediately previous treatment strategy | Immediately previous treatment strategy. Defined as treatment strategy immediately prior to index date (initiation of inhaled triple therapy):* LABA/ICS
* LAMA/LABA
* LAMA only
* LABA only
* ICS only
* SABA/SAMA inhaled therapy
* No inhaled therapy
 | Immediately prior to index date (treatment on index day –1) |
| Moderate-severe AECOPD history in 12 months prior to, and including, index date | Reported as mean (SD) number and binary (yes/no) of 1) any AECOPDs (moderate or severe), 2) moderate AECOPDs, 3) severe AECOPDs. AECOPDs on index date are excludedFurther, a proportion of patients with at least two or more moderate events or one or more severe exacerbations was also reportedAECOPDs were identified from the CPRD Aurum and HES-APC based on a validated algorithm.3 Exacerbations in primary care were defined as the presence of a record for one of the four following events: (1) prescriptions for ATB AND OCS for a length of 5 to 14 days each (both prescriptions must have the same start date but each can last for a different number of days); (2) presence of respiratory symptoms (codes suggesting an increase in two or more of: breathlessness, cough, or sputum volume and/or purulence recorded on the same date) and a prescription for ATB or OCS (or both) on the same day; (3) LRTI medical code; (4) AECOPD-specific medical code3 As GP records lack sufficient sensitivity and positive predictive value to ascertain hospitalized exacerbation events, HES data were used to identify exacerbations that were associated with a hospitalization, through the use of ICD-10 codes. Exacerbations resulting in hospitalization were considered as **severe** (ie recorded in HES-APC and/or CPRD Aurum), while exacerbations managed only in primary care (ie only recorded in CPRD Aurum) were defined as **moderate**  | 12 months prior to index date |
| Eosinophil levels in previous 12 months, closest to index date | Eosinophil level in 12 months prior to index date, closest to index date. Eosinophil results will be provided as counts in cells/μL and as a binary variable (<150, ≥150 cells/μL). To maximize the available data, results may be provided from counts, calculated counts, and percentages. When eosinophil results are provided as percentages, the values were converted to counts by multiplying by the total white blood cell count, where available | 12 months prior to/on index date |

**Abbreviations:** AECOPD, acute exacerbation of COPD; ATB, antibiotic; COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GP, general practitioner; HES-APC, Hospital Episode Statistics, Admitted Patient Care; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; LRTI, lower respiratory tract infection; MRC, Medical Research Council; Rx, prescription; OCS, oral corticosteroids; SABA, short-acting β2-agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

**Table S3** Sociodemographics, clinical characteristics, and healthcare resource utilization for FF/UMEC/VI new users (with prior MITT)

|  |  |
| --- | --- |
|  | **FF/UMEC/VI users (with prior MITT)****(*N* = 2,926)** |
|  |  |
| Age, mean (SD)  | 71.1 (10.0) |
| Male, *n* (%) | 1,543 (53) |
| Smoking status, *n* (%) |  |
| Current smoker | 1,306 (45) |
| Ex-smoker | 1,572 (54) |
| Non-smoker | 48 (2) |
|  |  |
|  Comorbidities, *n* (%) |  |
| Current asthmaa | 731 (25) |
| Coronary artery bypass graft  | 74 (3) |
| Congestive heart failure | 263 (9) |
| Acute myocardial infarction  | 247 (8) |
| Stroke  | 371 (13) |
| Depression | 1,352 (46) |
| Anxiety | 841 (29) |
| GERD | 626 (21) |
| Dementia | 307 (10) |
| Rheumatoid/osteoarthritis | 1,069 (37) |
| Bronchiectasis  | 236 (8) |
|  |  |
| Eosinophil level (GI/L), median (IQR)  | 0.20 (0.1–0.3)  |
|  |  |
| Number of GP attendances in last year, mean (SD)  | 12.3 (8.8) |
| Any attendance at secondary care outpatients in the last 3 months, *n* (%)  | 1,413 (48) |
| Any attendance at secondary care respiratory outpatients in the last 3 months, *n* (%)  | 514 (18) |

**Notes:** aCurrent asthma defined as a diagnosis record in the CPRD within the 24 months prior to index.

**Abbreviations:** FF/UMEC/VI, fluticasone furoate, umeclidinium, and vilanterol; GERD, Gastroesophageal reflux disease; GP, general practitioner; IQR, interquartile range; SD, standard deviation.

**Table S4** Characteristics among patients with comorbid current asthma

|  |  |  |
| --- | --- | --- |
|  | **All FF/UMEC/VI users*****N* = 885** | **First-time triple-therapy users**  |
| **MITT*****N* =1,752** | **BEC/FOR/GLY*****N* =167** | **FF/UMEC/VI*****N* =154** |
| Age, mean (SD)  | 69.5 (11.1) | 66.1 (11.6) | 66.9 (11.8) | 68.1 (11.8) |
| Male, *n* (%) | 440 (50) | 855 (49) | 72 (43) | 89 (58) |
| Smoking status, *n* (%)a |  |  |  |  |
| Current smoker | 381 (43) | 848 (48) | 77 (46) | 75 (49) |
| Ex-smoker | 474 (54) | 794 (45) | 84 (50) | 76 (49) |
| Non-smoker | 30 (3) | 110 (6) | 6 (4) | 3 (2) |
| FEV1 % predicted, mean (SD)b | 57.4 (19.8) | 62.1 (18.8) | 60.2 (21.9) | 58.9 (17.6) |
| MRC ≥3, *n* (%)c | 479 (59) | 527 (41) | 56 (46) | 56 (46) |
| ≥1 moderate to severe exacerbations in last year, *n* (%) | 550 (62) | 866 (49) | 94 (56) | 76 (49) |
| ≥1 severe exacerbations in last year, *n* (%) | 164 (19) | 164 (9) | 16 (10) | 21 (14) |

**Notes:** aLatest available assessment to/on index date in the 12 months prior to index. bBased on patients with an FEV value. All FF/UMEC/VI users (n=763). First-time triple-therapy users: MITT (n=1,508); BEC/FOR/GLY (n=141); FF/UMEC/VI (n=132). cBased on patients with an MRC score. All FF/UMEC/VI users (n=810). First-time triple-therapy users: MITT (n=1,277); BEC/FOR/GLY (n=122); FF/UMEC/VI (n=122).

**Abbreviations:** BEC, beclomethasone; FEV1, forced expiratory volume in one second; FF, fluticasone furoate; FOR, formoterol; GLY, glycopyrronium bromide; MITT, multiple-inhaler triple therapy; MRC, Medical Research Council; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol.

**Table S5** Characteristics among patients with no comorbid current asthma

|  |  |  |
| --- | --- | --- |
|  | **All FF/UMEC/VI users*****N* = 2,651** | **First-time triple-therapy users**  |
| **MITT*****N* = 3,476** | **BEC/FOR/GLY*****N* = 535**  | **FF/UMEC/VI*****N* = 456**  |
| Age, mean (SD)  | 71.4 (9.8) | 69.3 (10.5) | 71.4 (10.7) | 70.2 (10.9) |
| Male, *n* (%) | 1,468 (55) | 1,890 (54) | 296 (55) | 276 (61) |
| Smoking status, *n* (%)a |  |  |  |  |
| Current smoker | 1,248 (47) | 1,779 (51) | 263 (49) | 248 (54) |
| Ex-smoker | 1,376 (52) | 1,617 (47) | 266 (50) | 202 (44) |
| Non-smoker | 27 (1) | 80 (2) | 6 (1) | 6 (1) |
| FEV1 % predicted, mean (SD)b | 53.2 (19.7) | 58.8 (19.5)  | 54.5 (19.2) | 56.9 (19.4) |
| MRC ≥3, *n* (%)c | 1670 (66) | 1,475 (49) | 281 (59) | 215 (52) |
| ≥1 moderate to severe exacerbations in last year, *n* (%) | 1,727 (65) | 1771 (51) | 312 (58) | 258 (57) |
| ≥1 severe exacerbations in last year, *n* (%) | 556 (21) | 430 (12) | 102 (19) | 49 (11) |

**Notes:** aLatest available assessment to/on index date in the 12 months prior to index. bBased on patients with an FEV value. All FF/UMEC/VI users (n=2,212). First-time triple-therapy users: MITT (n=3,040); BEC/FOR/GLY (n=457); FF/UMEC/VI (n=391). cBased on patients with an MRC score. All FF/UMEC/VI users (n=2,520). First-time triple-therapy users: MITT (n=3,034); BEC/FOR/GLY (n=480); FF/UMEC/VI (n=410).

**Abbreviations:** BEC, beclomethasone; FEV1, forced expiratory volume in one second; FF, fluticasone furoate; FOR, formoterol; GLY, glycopyrronium bromide; MITT, multiple-inhaler triple therapy; MRC, Medical Research Council; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol.

**Figure S1** Study design



**Abbreviations:** COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; MITT, multiple-inhaler triple therapy; UMEC, umeclidinium; VI, vilanterol.

**References**

1. Nissen F, Quint JK, Wilkinson S, Mullerova H, Smeeth L, Douglas IJ. Validation of asthma recording in electronic health records: a systematic review. *Clin Epidemiol.* 2017;9:643.

2. GOLD. Global Initiative for Chronic Obstructive Lung Disease - global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease - 2019 report 2019; https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf. Accessed April 1, 2021.

3. Rothnie KJ, Müllerová H, Hurst JR, et al. Validation of the recording of acute exacerbations of COPD in UK primary care electronic healthcare records. *PLoS One.* 2016;11(3):e0151357.