Supplementary Material

Appendix 1 – supplementary materials for methods and analysis

Appendix 2 – supplementary material for results

Appendix 1 – supplementary materials for methods and analysis

Setting/data sources

TORCH

TORCH was a placebo controlled randomised trial of the combined inhaler fluticasone propionate (FP) + salmeterol (SAL) (FP-SAL) for the treatment of COPD, published in 2007 [ref to TORCH]. Key findings were a lower rate of exacerbations associated with use of FP-SAL, and a higher rate of pneumonia (when compared to placebo and when compared to the active comparator SAL). As one of the largest trials of COPD drug treatments, and with a three year follow up, TORCH is a landmark study, providing a validation point for our study. Individual patient data from the TORCH study were obtained from the study sponsor (GSK) via www.clinicalstudydatarequest.com.

CPRD

The CPRD is a very large database of nationally representative prospectively collected, anonymised UK population-based electronic health records containing comprehensive information on clinical diagnoses, prescribing, referrals, tests and demographic/lifestyle factors.[1] In order to contribute to the database, general practices and other health centres must meet prespecified standards for research-quality data (i.e. be "up to standard).[1, 2] A patient starts contributing follow-up time to the database at the date they join an "up to standard" practice (or the date that their practice starts contributing up to standard data), and stop contributing follow-up time on either their death date, their transfer out date (the date that they leave the database due to reasons other than death) or on the last collection date for their practice. Linkage between the primary care records in CPRD and hospital episode statistics (HES) is well established for around 60% of practices in the CPRD, providing a data set augmented with detailed secondary care diagnostic and procedural records. Algorithms have been established to detect COPD, COPD exacerbations and pneumonia (both hospital and primary care managed) in CPRD/HES linked data (including validated algorithms for COPD and exacerbations).[3, 4] See supplementary materials of Wing et al for a high-level overview of these algorithms.[5]

Selection of participants – TORCH inclusion and exclusion criteria

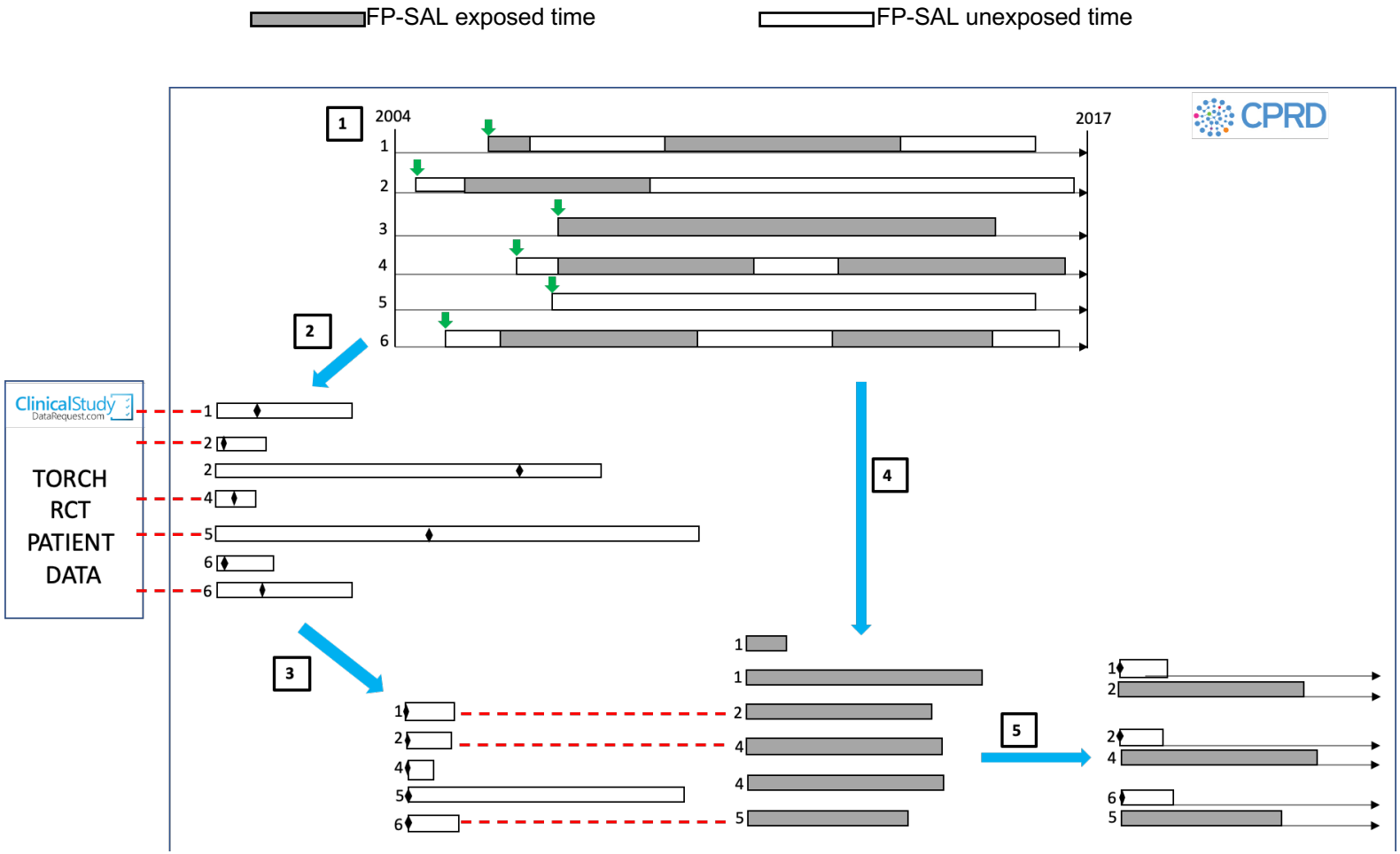
Table A1-1 – TORCH inclusion and exclusion criteria applied

TORCH inclusion criteria applied to cohort
1. a diagnosis of COPD
2. 40-80 years of age
3. smoking status of "current" or "ex-"
4. lung function criteria of FEV_1 <60% predicted and FEV_1/FVC ratio<70% (where FEV_1 is the forced expiratory volume in 1 second and FVC is the forced vital capacity).
TORCH exclusion criteria applied to cohort
Previous drug exposure criteria
1. any exposure to any of the TORCH study drugs (FP-SAL, SAL or FP) within the previous 4 weeks
2. current use of a long-acting bronchodilator[1]
3. current use of oral corticosteroid therapy[2]
Remaining exclusion criteria (after applying drug exposure criteria) – all at any time prior to the index date unless specified
1. a diagnosis of asthma (within the previous 5 years)
2. a diagnosis for any (non-COPD) respiratory disorder
3. a record of lung surgery
4. a diagnosis of alpha-1 antitrypsin deficiency
5. a record of having received long-term oxygen therapy
6. diagnoses for conditions likely to interfere with the TORCH trial or to cause death within the 3 years following the index date
7. record of an exacerbation requiring oral corticosteroid therapy or hospitalisation during the period equivalent to the trial "run-in" period (the 2-week period following the index date)

[1]: current use of a long-acting bronchodilator defined in the CPRD population as any prescription for a long-acting bronchodilator occurring within the period that one of the study drugs was prescribed (or that ended within 7 days prior to the start of a prescription for one of the study drugs).

[2]: current use of oral corticosteroid therapy in TORCH was defined as continuous use for >6 weeks, with courses of oral corticosteroids separated by a period of <7 days considered as continuous use. We applied the same approach to the CPRD population to define exclusion due to exposure to OCS.

Figure A1-1: Management of FP-SAL exposed and FP-SAL unexposed time periods in selection of people from CPRD



Step 1 – selection of all potentially eligible patients. 6 example patients in CPRD. Green arrow=date at which individual meets TORCH inclusion criteria. Grey time periods=FP-SAL exposed, white time periods=FP-SAL unexposed. **Step 2 - selection of pool of unexposed patients.** Green arrows: date at which patient meets all TORCH inclusion criteria. Unexposed time periods selected and exclusion criteria related to drug exposures applied. Unexposed record index date is then assigned as a random date within each unexposed period (indicated by diamond symbols), and further TORCH exclusion criteria applied based upon this date. In this example one unexposed record from each of person 1, 4 and 6 are excluded prior to step 3. **Step 3 – selection of unexposed to FP-SAL time periods by 1:1 matching to TORCH participants.** Dotted red lines indicate matching, matching characteristics assessed on index date of specific unexposed time period, only one time period per person could be matched to TORCH. **Step 4 - selection of exposed to FP-SAL time periods and application of TORCH exclusion criteria.** In this example, one exposed time period from person 3 and 6 is excluded based on TORCH exclusion criteria. **Step 5 – selection of comparable FP-SAL exposed participants.** Pre-matching, there is one record per person for the FP-SAL unexposed cohort and one or more per person for the FP-SAL exposed cohort, after matching there are an equal number of each. The same individual could appear in both unexposed and exposed cohorts, with

differing date of start of follow-up. Exposed and unexposed records are then followed up and analysed from index date onwards following an “intention to treat” approach.

Selection of participants – note related to Step 3
Based on the fact that TORCH randomisation resulted in highly comparable groups (Table 1 of [6]), we assumed that it would not matter whether we matched our FP-SAL unexposed time periods to the TORCH placebo group only or to all of the TORCH participants. The approach we selected was to match our FP-SAL unexposed records to all of the TORCH participants. As a post-hoc analysis to test our assumption, we examined the matched TORCH participants by intervention group – if our assumption was valid then we would expect to see that the proportion of matched TORCH participants from each intervention group was the same. The results are tabulated below, showing that there was an equal distribution by intervention group across the 4359 matched TORCH participants.

TORCH treatment group	n	%
FP-SAL	1090	25.00
Placebo	1111	25.48
Salmeterol	1071	24.58
Fluticasone	1087	24.95
	(4359)	(100.00)

Selection of participants – FP-SAL exposed vs SAL exposed (differences in participant selection procedure compared to FP-SAL exposed vs unexposed)
The participant selection approach was analogous to the FP-SAL exposed v versus FP-SAL unexposed participant selection, except the comparator group selected was those exposed to SAL (rather than those unexposed to FP-SAL). The resulting differences in participant selection are as follows. For Step 1, the study period was from 1st January 2000 to 1st January 2017 (increased to ensure sufficient numbers of eligible SAL-exposed individuals). For Step 2, instead of selecting unexposed to FP-SAL time periods occurring on or after the eligible-for-TORCH inclusion date, we selected periods of SAL exposure. Individuals in CPRD who had more than one SAL-exposed eligibility period within their record were able to contribute more than once to the pool of SAL-exposed participants (with the covariates and person-time contributed unique to the specific SAL-exposed eligibility period). The index date for each SAL-exposed record was the first date of the eligible SAL exposure period (i.e. first day of the SAL prescription). All other aspects of Step 2 and Steps 3 – 6 were then as described for the FP-SAL exposed vs FP-SAL unexposed participant selection (with SAL exposed records in place of FP-SAL unexposed records wherever mentioned).

Exposures, outcomes and co-variates
Exposures – further details on management of drug exposure data
In addition to FP-SAL and SAL, periods of exposure to oral corticosteroids (OCS), inhaled corticosteroids (ICS), fluticasone propionate (FP), any long action muscarinic antagonist (LAMA) or any long-acting beta agonist (LABA) were identified, in order to facilitate application of the inclusion and exclusion criteria described in the "Selection of participants" section.

For all drug exposures, duration of an exposure period was derived by multiplying the CPRD *quantity* variable by any relevant dose information stored in the *packtype* variable and then dividing by the value in the *numeric daily dose* CPRD variable. For example, for a prescription record with *quantity*=1, *packtype*="60 dose inhaler", and *numeric daily dose*=2, the duration of the exposure period was (1*60)/2=30 days. For prescription records where it was not possible to calculate this exposure period (due to e.g. a missing *quantity* variable), the median value for that specific drug substance and packtype combination was imputed as the exposure duration. In order to attempt to account for any uncertainty in the end date of an exposure period (due to, for example, people not taking the medicine as directed or relying on additional medication previously described and kept at home), a grace period of half the median duration for the specific drug substance/pack type combination was added to the calculated exposure duration in order to estimate the end date of the exposure period.

Outcomes – further details on outcome definitions
Outcomes were defined as follows:
1. COPD exacerbation: defined using a CPRD-HES algorithm developed previously by authors of this study. [3]
2. All-cause mortality: as recorded in Office of National Statistics (ONS) mortality statistics (data that is linked to CPRD data).
3. Pneumonia: as defined using a CPRD-HES algorithm published previously by authors of this study.[7]
4. Time to COPD treatment discontinuation, with treatment discontinuation classified as a period of 90 days or more with no further prescription for the specific drug.

Covariates
Covariates available for inclusion in the propensity score models included lung function, age, sex, alcohol consumption, vascular disease, prescriptions for aspirin or statins, prior treatment with other COPD medication, type II diabetes, history of cancer, renal disease and healthcare utilisation (rate of: consultations, hospitalisations, hospital procedures, drug prescriptions).

Statistical analysis
Methods of analysis – intention to treat
The "intention to treat" design meant that if a participant entered the study as either an FP-SAL exposed or an FP-SAL unexposed participant (or a SAL exposed participant), they remained assigned to that exposure category for the entire duration of their follow-up (irrespective as to whether their true exposure status changes). This mirrored the TORCH design.

Validation of results against TORCH - comparability criteria
Our FP-SAL vs no FP-SAL treatment analysis results were validated against TORCH by determining compatibility with the TORCH exacerbations rate ratio for FP-SAL versus placebo (0.75; 95% CI 0.69 to 0.81). We set two criteria that needed to be met for us to conclude that results were consistent [protocol ref]. First, the effect size needed to be clinically comparable with TORCH findings; the rate ratio for exacerbations in CPRD must be between 0.65 and 0.9. As this rule could have been met with a poorly powered, inconclusive result, our second criterion was that the 95% CI for the rate ratio must exclude 1. For the FP-SAL vs SAL, the criterion we set were that the 95% CI needed to exclude 1, and the rate ratio needed to be between 0.81 and 0.95 (compared with the TORCH FP-SAL vs SAL result of 0.88, 95% CI 0.81 to 0.95).

Analysis of impact of (1) TORCH matching (2) TORCH criteria (post-hoc analysis)

A post-hoc analysis was performed assessing the impact of (1) omitting TORCH matching and (2) omitting both TORCH matching and the application of TORCH trial inclusion/exclusion criteria. This was performed for the FP-SAL vs SAL exacerbations analysis, and effect estimates tabulated and compared with TORCH and each other. As for the main analysis, all exposure comparison groups were propensity score matched to each other, and the final number in each propensity score matched group was tabulated along with the effect estimates and 95% confidence intervals, in order to help assess the impact on both effect size/precision and sample size of applying the different selection methods.

Appendix 2 – supplementary materials for results

Table A2-1: Characteristics of the CPRD non-interventional COPD cohort for the FP-SAL vs no FP-SAL comparison showing (1) the cohort of all HES-linked patients in CPRD with a COPD diagnosis (2) the cohort after applying TORCH inclusion/exclusion criteria (unexposed to FP-SAL group only) and (2) the cohort after applying TORCH and inclusion/critera and matching to TORCH participants (unexposed to FP-SAL group only), in comparison to the baseline characteristics of the TORCH trial placebo group.

	CPRD non-interventional population			TORCH trial
	All	**Unexposed to FP-SAL**		**Placebo group**
	No TORCH criteria or TORCH matching applied[1]	After applying TORCH inclusion/exclusion criteria[2]	After matching[3] to individual TORCH patients	
Variable – n(%) *unless specified*	*(N=45939 patients)*	*(N=17176 unexposed time periods from 10193 people)*	*(N=4359 unexposed people)*	*(N=1524 trial participants)*
Age – year (median(IQR))	65 (58-74)	68.0 (61.0-73.0)	67.0 (61.0-73.0)	65 (59-71)
Male sex	24182 (53)	10671 (62)	3307 (76)	1163 (76)
Body-mass index (median(IQR))	26.7 (23.4-30.7)	26.3 (22.6-30.4)	25.5 (22.1-29.0)	25.0 (22.0-28.4)
Exacerbations requiring hospitalisation (mean±SD)[4]	0.1 (0.9)	0.0 (0.3)	0.1 (0.3)	0.2 (0.7)
History of cardiovascular disease	11564 (25)	4888 (28)	1987 (46)	784 (51)
Lung function: FEV_1 - % of predicted[5] (median(IQR))	66.3 (51.6-81.33)	51.7 (41.8-59.0)	47.2 (37.3-56.1)	44.2 (35.0-54.0)

Note 1: Includes all people in CPRD between 2004 – 2016 with a diagnosis for COPD who have spirometry data recorded. All variables in this column measured at the date of COPD diagnosis recorded in CPRD. **Note 2:** Inclusion criteria: diagnosis of COPD, age 40-80 years, all current or ex-smokers, lung function FEV_1<60% predicted, FEV_1/FVC ratio<70%. Exclusion criteria: diagnosis of asthma within the previous 5 years, diagnosis for any non-COPD respiratory disorder, a record of lung surgery, a diagnosis of alpha-1 antitrypsin deficiency, evidence of drug or alcohol abuse, a record of having received long-term oxygen therapy, diagnoses likely to interfere with the TORCH trial or cause death within 3 years, current use of oral corticosteroid therapy, any exposure to FP/SAL within the previous 4 weeks. All variables in this column measured at the earliest date that all inclusion criteria were met and all exclusion criteria were not met. **Note 3:** Matched on all variables in this table. **Note 4:** Within prior year. **Note 5:** FEV_1=Forced expiratory volume in 1 second.

Table A2-2: Characteristics of the CPRD non-interventional COPD cohort for the FP-SAL vs SAL analysis showing (1) the cohort of patients in CPRD with a COPD diagnosis (2) the cohort after applying TORCH inclusion/exclusion criteria (exposed to SAL group) and (2) the cohort after applying TORCH and inclusion/critera and matching to TORCH participants (exposed to SAL group), in comparison to the baseline characteristics of the TORCH trial salmeterol group.

	CPRD non-interventional population			TORCH trial
	All	**Exposed to salmeterol**		**Salmeterol group**
Variable – n(%) *unless specified*	No TORCH criteria or TORCH matching applied[1] *(N=53099 people)*	After applying TORCH inclusion/exclusion criteria[2] *(N=5671 salmeterol-exposed time periods from 1392 people)*	After matching[3] to individual TORCH patients *(N=1208 salmeterol-exposed people)*	*(N=1524 trial participants)*
Age – year (median(IQR))	66.0 (58.0-74.0)	68.0 (63.0-74.0)	68.0 (62.0-73.0)	65.1 (60.0-71.0)
Male sex	35045 (53)	3415 (60)	767 (63)	1160 (76)
Body-mass index (median(IQR))	25.8 (23.0-29.1)	26.9 (23.3-30.8)	26.2 (23.0-29.9)	24.8 (21.9-28.3)
Exacerbations requiring hospitalisation (mean±SD)[4]	0.0 (0.3)	0.0 (0.1)	0.0 (0.2)	0.2 (0.6)
History of cardiovascular disease	13274 (25)	1689 (30)	374 (31)	807 (53)
Lung function: FEV_1 - % of predicted[5] (median(IQR))	63.2 (49.1-76.8)	52.6 (43.4-61.1)	49.4 (40.5-57.1)	43.4 (33.8-53.4)

Note 1: Includes all people in CPRD between 2000 – 2016 with a diagnosis for COPD who have spirometry data recorded. All variables in this column measured at the date of first salmeterol exposure. **Note 2:** Inclusion criteria: diagnosis of COPD, age 40-80 years, all current or ex-smokers, lung function FEV_1<60% predicted, FEV_1/FVC ratio<70%. Exclusion criteria: diagnosis of asthma within the previous 5 years, diagnosis for any non-COPD respiratory disorder, a record of lung surgery, a diagnosis of alpha-1 antitrypsin deficiency, evidence of drug or alcohol abuse, a record of having received long-term oxygen therapy, diagnoses likely to interfere with the TORCH trial or cause death within 3 years, current use of oral corticosteroid therapy, any exposure to any of the study drugs within the previous 4 weeks. All variables in this column measured at the earliest date that all inclusion criteria were met and all exclusion criteria were not met. **Note 3:** Matched on all variables in this table. **Note 4:** Within prior year. **Note 5:** FEV_1=Forced expiratory volume in 1 second.

Propensity score matching of CPRD cohorts
Table A2-3 - Variables included in the final propensity score models

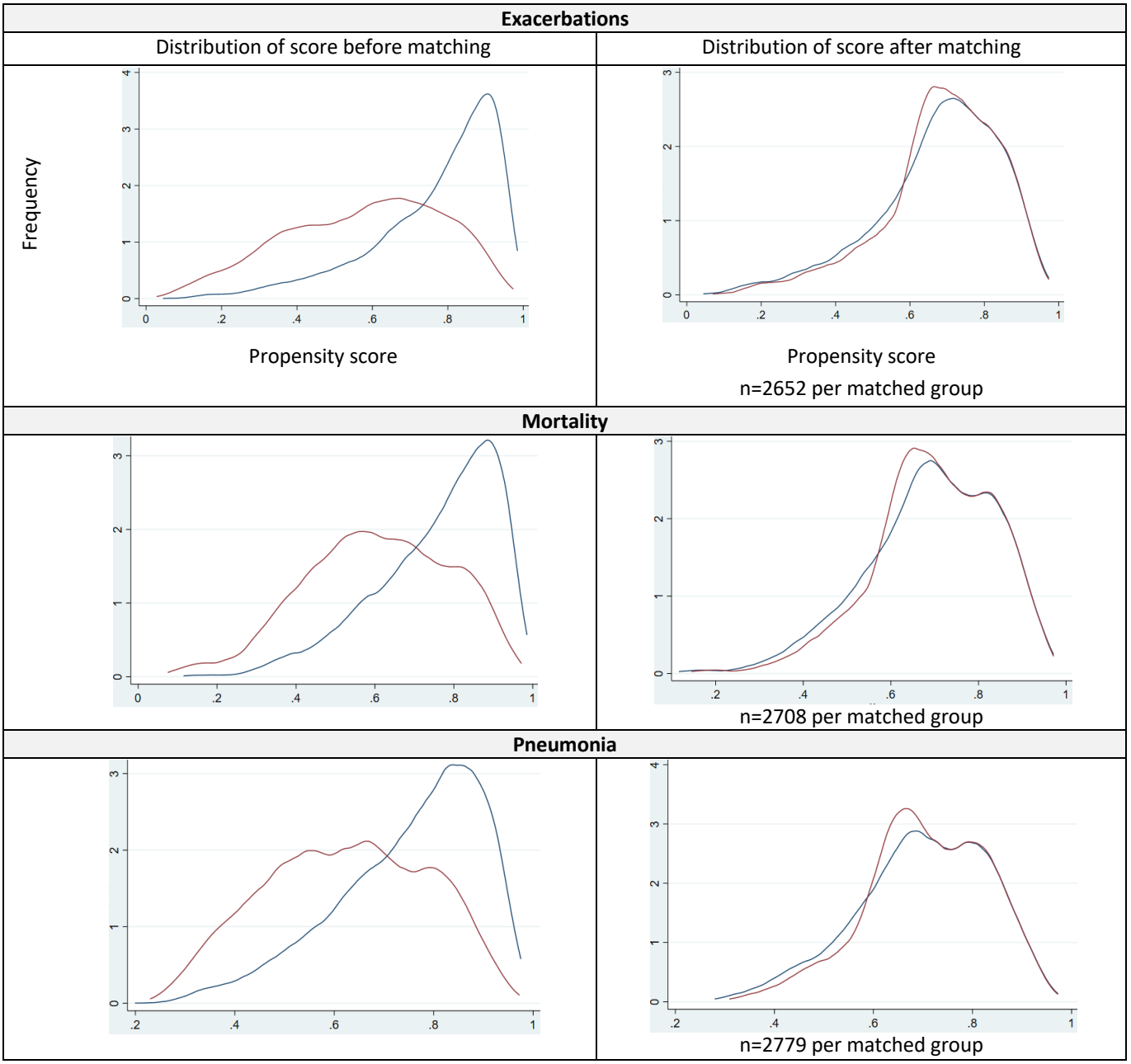
Analysis	Variables included in propensity score model	Matching
FP-SAL versus unexposed to FP-SAL analysis		
Exacerbations	Sex, age, FEV_1, FEV_1/FVC_2, BMI, year of index date, previous diagnosis of cerebrovascular disease, having at least one prescription of (1) statin (2) ICS (3) LABA_ICS (4) LAMA in the previous year and the frequency of consultations, prescriptions, hospitalisations, hospital procedures and exacerbations in the previous year.	1:1 nearest neighbour, caliper of 0.03
Mortality	Sex, age, FEV_1, FEV_1/FVC_2, BMI, SES, previous diagnosis of (1) coronary heart disease (2) peripheral vascular disease (3) cerebrovascular disease, having at least one prescription of (1) LAMA (2) LABA_ICS in the previous year and the frequency of consultations, prescriptions, hospitalisations and exacerbations in the previous year.	1:1 nearest neighbour, caliper of 0.03
Pneumonia	Sex, age, FEV_1, FEV_1/FVC_2, BMI, alcohol, previous diagnosis of (1) coronary heart disease (2) peripheral vascular disease (3) cerebrovascular disease, having at least one prescription of (1) LAMA (2) aspirin in the previous year and the frequency of prescriptions, hospitalisations and exacerbations in the previous year.	1:1 nearest neighbour, caliper of 0.03
FP-SAL versus SAL analysis		
Exacerbations	Sex, FEV_1, previous diagnoses for (1) Type 2 diabetes (2) chronic kidney disease, year of index date, having at least one prescription of an ICS in the previous year and the frequency of, consultations, hospitalisations and hospital procedures in the previous year.	1:1 nearest neighbour, caliper of 0.03
Mortality	Sex, age, year of index date, BMI, SES, FEV_1, FEV_1/FVC_2, diagnoses for: (1) peripheral vascular disease (2) coronary heart disease (3) cerebrovascular disease (4) Type 2 diabetes (5) cancer (6) chronic kidney disease; having at least one prescription of (1) statin (2) aspirin (3) LAMA (4) LABA (5) LABA_ICS in the previous year and the frequency of consultations, exacerbations, prescriptions, hospitalisations and hospital procedures in the previous year.	1:1 nearest neighbour, caliper of 0.03
Pneumonia	FEV_1, year of index date, SES, diagnoses for chronic kidney disease, and the frequency of: consultations, prescriptions, hospitalisations and hospital procedures in the previous year.	1:1 nearest neighbour, caliper of 0.03
Time to treatment discontinuation	FEV_1, FEV_1/FVC_2, alcohol intake, SES, year of index date, diagnoses for: (1) peripheral vascular disease (2) coronary heart disease (3) cancer (4) chronic kidney disease; having	1:1 nearest neighbour, caliper of 0.03

Analysis	Variables included in propensity score model	Matching
	at least one prescription of (1) statin (2) aspirin (3) ICS (4) LABA_ICS in the previous year and the frequency of consultations, exacerbations, prescriptions, hospitalisations and hospital procedures in the previous year.	

Figure A2-1 – propensity score distributions before and after matching*

FP-SAL exposed (n=10926 before matching) versus FP-SAL unexposed (n=4391 before matching)

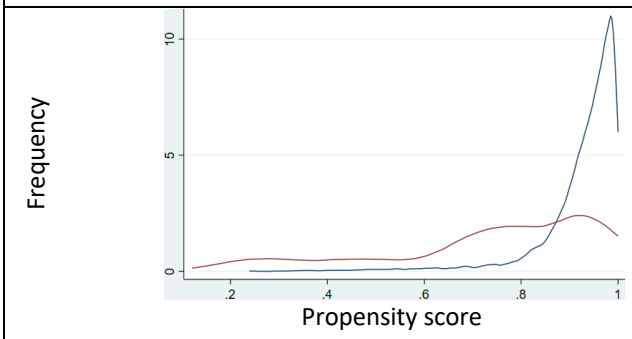
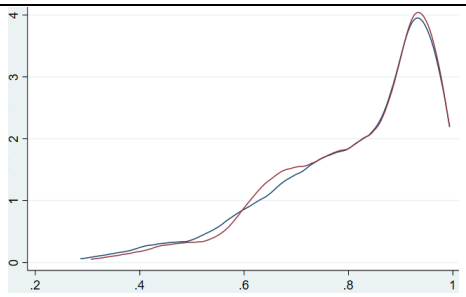
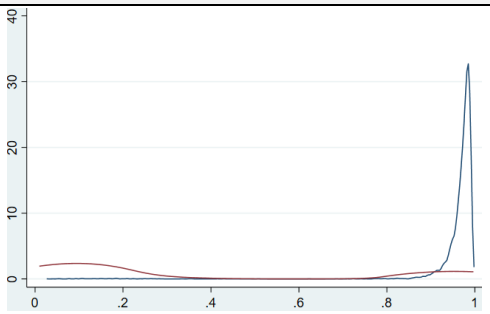
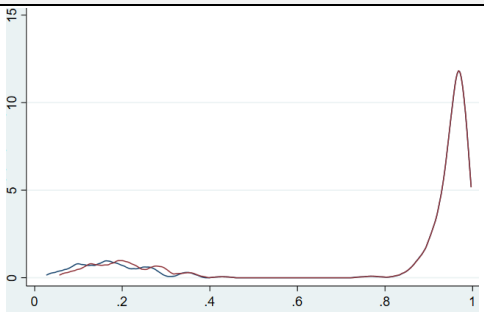
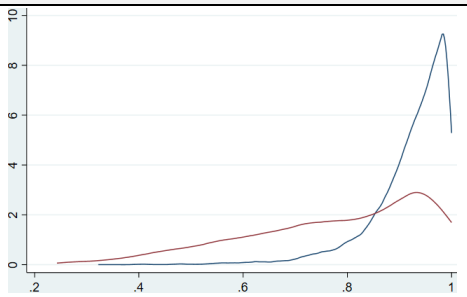
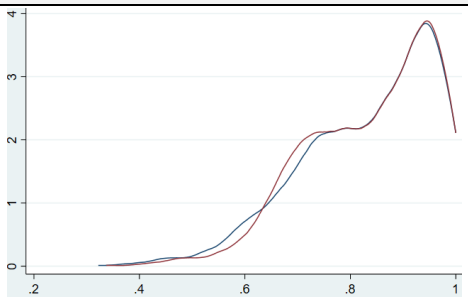
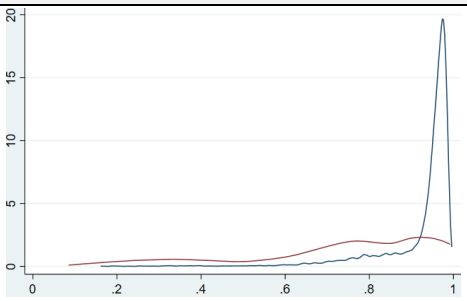
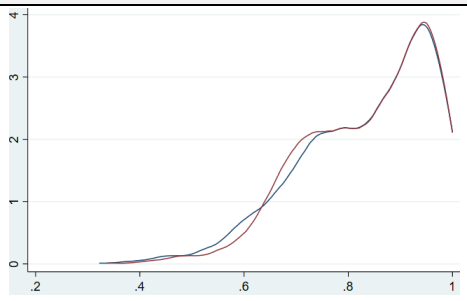
exposed to FP-SAL
unexposed to FP-SAL



*Treatment discontinuation not included for this analysis as only one of the exposure groups was receiving treatment

FP-SAL exposed (n=11235 before matching) versus SAL exposed (n=1146 before matching)

exposed to FP-SAL
exposed to SAL

Exacerbations	
Distribution of score before matching	Distribution of score after matching
	 n=991 per matched group
Mortality	
	 n=432 per matched group
Pneumonia	
	 n=935 per matched group
Time to treatment discontinuation	
	 n=996 per matched group

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