CHESS: CPRD-COPD Hawthorne Effect Study in Salford: A UK cohort study to characterise patients enrolled in the Salford Lung Study and to evaluate a potential Hawthorne effect

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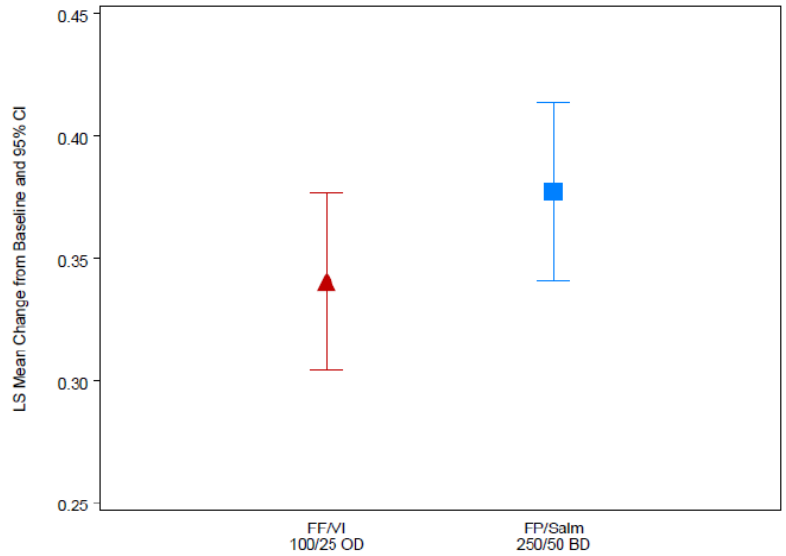
Outline of Presentation

- Background
- Study Design
- PO2 “Hawthorne effect?” challenges
- PO2 addressing challenges
- PO2 key results
- SO1/S03 key results
- Backup slides: PO1 “Characterisation” key results

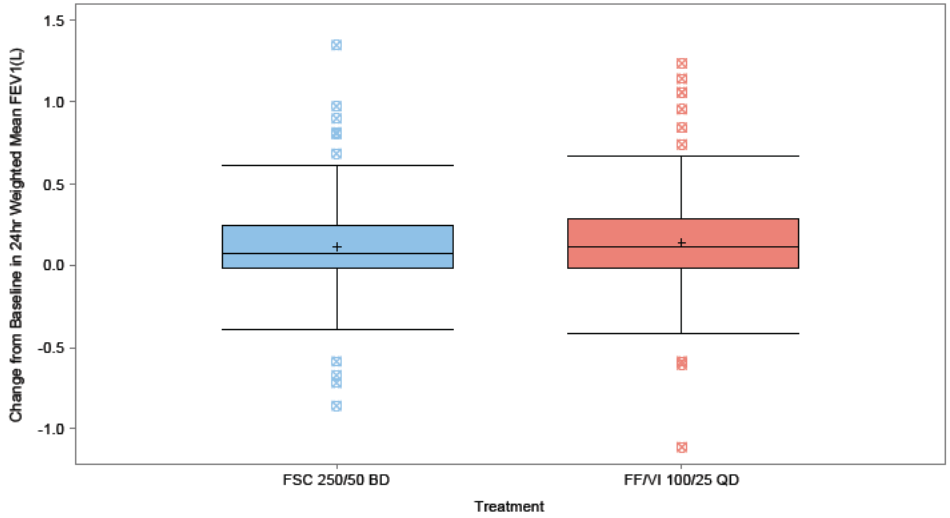
Background: Head to head Relvar Efficacy studies on lung function

Figure 2 **Adjusted Means for Weighted Mean 0-24 h FEV_1 (L) at Day 168/Week 24 (ITT Population)**



Source: Protocol HZA113091

Figure 7.01
Box Plot of Change from Baseline in 24hr Weighted Mean FEV1(L) on Day 84

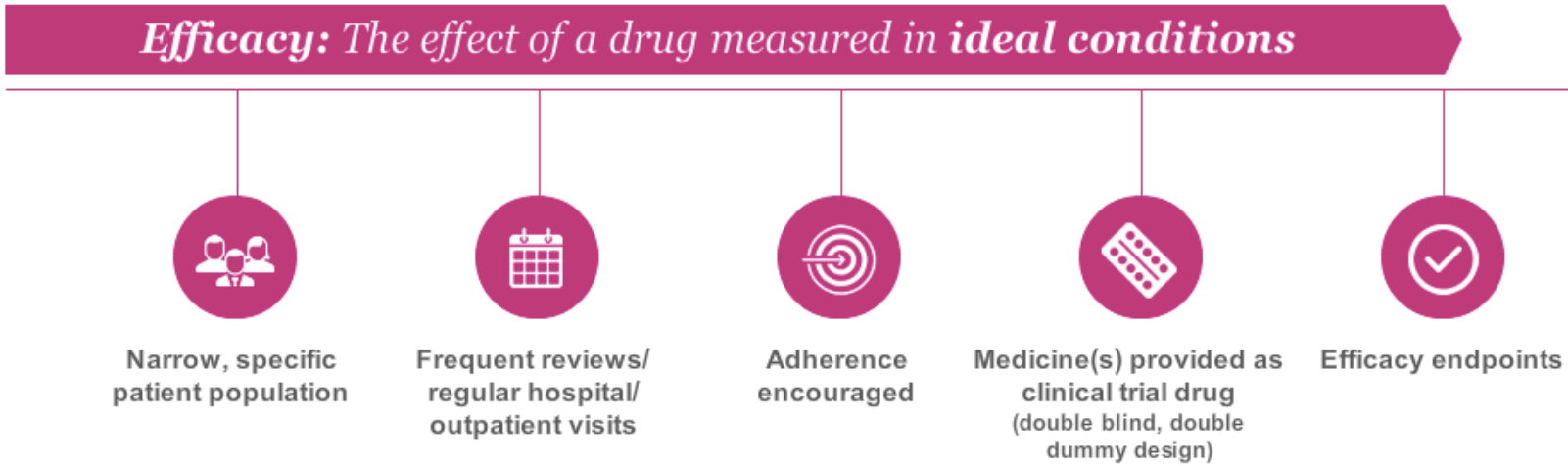


Source: Protocol HZC112352

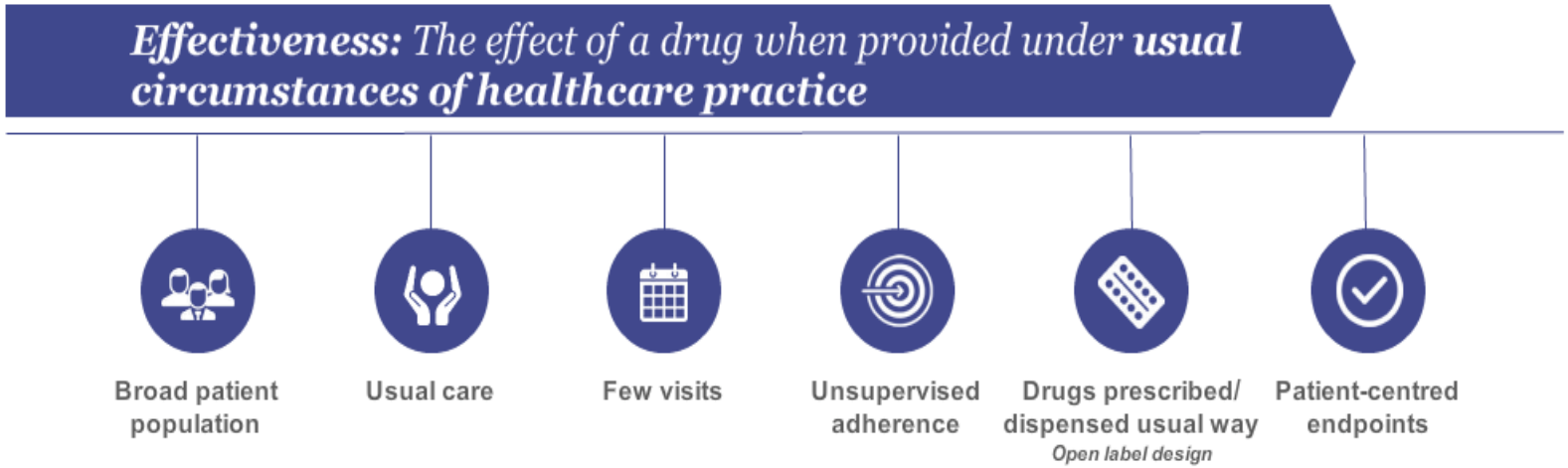
- Four out of five phase III efficacy head to head studies have not shown a difference between Relvar **once** daily and Seretide **twice** daily on **lung function endpoints**

Efficacy and Effectiveness

- Typical Phase III studies focussed on **efficacy** estimands



- Pragmatic trials focused on **effectiveness** estimand.



Salford Lung Study

What was the intent behind the study design?

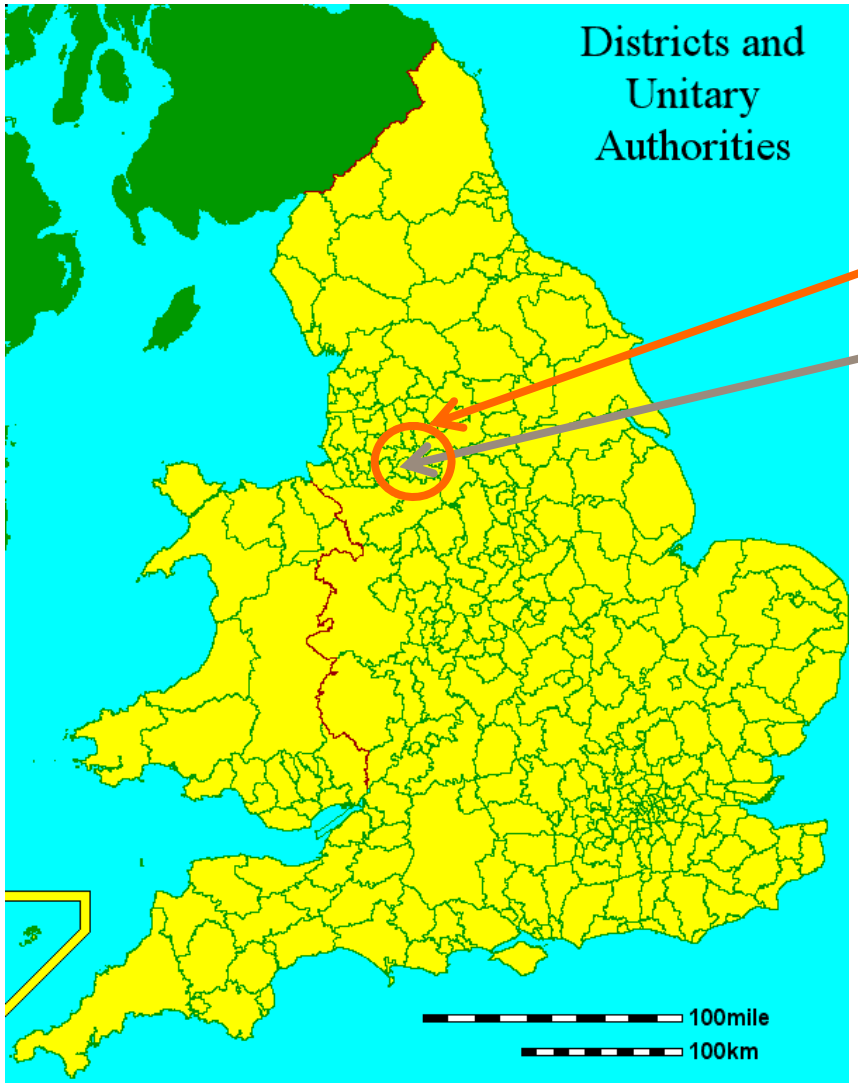
- **To maintain the scientific rigour one associates with a traditional randomised controlled trial (RCT)**
  - Interventional, randomised, control arm
- **But…to keep it as near to everyday clinical practice as possible**
  - Embracing heterogeneity of the patient population
  - Maintaining patient experience as close to normal as possible
  - Collecting endpoints relevant to patients and healthcare decision makers
  - Comparing Relvar (FF/VI) with ‘usual care’
    - In the usual care arm, the physician is free to choose the appropriate COPD treatment for each patient, based on his/her clinical judgement

CHESS: CPRD-COPD Hawthorne Effect Study in Salford

- Aims to address potential concerns with SLS
  - Salford may not be representative of the wider population in which the medicine may be used
  - **There may be an Hawthorne effect**
    - **the process where human subjects (patients or providers) of an experiment change their behaviour, simply because they are within a study**
    - **this effect may artificially inflate the benefits of both RELVAR and usual care arm (UC)**
- Primary Objectives (PO)
  - PO1: To characterize the patients enrolled in the UC arm of SLS compared with the England population of COPD patients using CPRD*
  - **PO2:To compare the rate of COPD exacerbation over the 12 months in UC arm of the SLS to the rate within matched patients from the CPRD**

* Clinical Practice Research Datalink Electronic Healthcare Record (EHR)

Local Authorities in England (and Wales)



Greater Manchester

Salford

Aim to compare Salford to other local authorities (LA) within England

Data Sources

- Comparing Salford (Greater Manchester: GM) to rest of England (xGM)
  - Using SLS trial data and CPRD for GM (two sources)
  - CPRD for England, excluding GM
- Clinical Practice Research datalink (CPRD)
  - Electronic Healthcare Record database
  - Contains GP records for ~6% of UK population
  - Linked to hospital episodes (HES) &

    Office of National Statistics (ONS) death certificate records

Data Source - challenges

- Linkage to HES for ~ 70% of English GPs within CPRD
- Time lag while wait for HES data
- Data from sources largely complimentary but sometimes inconsistent
- Variables of interest not always directly collected
  - Clinical insight required to create and validate algorithms
- Missing 1+ data point used in modelling
  - xGM (4,682/16,745) ~ 28 %
  - SLS UC arm (540/1403) ~ 39 %

Selection of patients within CPRD

- Identify all patients eligible for SLS during the SLS recruitment phase
  - Alive at date first patient recruited to SLS usual care (UC) arm
  - Diagnosed with COPD
  - Aged 40 years+

- Match each patient with one from SLS
  - Randomly sample (with replacement) a patient from the SLS UC arm
  - Assign date of randomisation as index date for next CPRD patient
  - Check CPRD patient meets entry criteria for SLS at this date
  - Flag if patient registered at GPs within/outside of Greater Manchester

Primary Objective 2

To compare the rate of COPD exacerbation over the 12 months in UC arm of the SLS to the rate within matched patients from the CPRD

Is a simple comparison of Salford and CPRD informative?

- A simple Salford v CPRD comparison is not interesting
  - Comparing averages
  - May disguise regional variation
- Instead place data from SLS UC in the context of regional variation
  - Local Authority (LA) level, in CPRD
- Are measures in SLS-UC unusually high or low?
  - e.g. Is the mean exacerbation rate during follow-up found in SLS-UC outside of the 2.5-97.5 percentile ranking of mean exacerbation rate by Local Authority (excluding Greater Manchester xGM)?

Comparing Salford with rest of England. Exacerbation rates (using EHR) as an example

Mean Rate (per 1,000 patient yr)	Rank Order	Centile	LA Number
0	1	0	42
111.7	2	0.68	98
276.2	3	1.37	164
…			
1904.2	128	86.39	122
1907.2		**86.94**	**Salford**
1907.9	129	87.07	75
…			
4395.6	148	100	137

Crude rates of COPD exacerbation (PO2): EHR data

The rate* of COPD exacerbations episodes in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups - Exacerbations recorded in primary care only.

For each subgroup the number of COPD exacerbations is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The number of exacerbations in SLS_UC for a given subgroup is deemed unusual if it lies outside of this range.

**Rate is calculated per 1000 person years*

Obs	Subgroup	CPRD_xGM_IC_lower	CPRD_xGM_IC_median	CPRD_xGM_IC_upper	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
1	All	0.33	1.43	2.16	1.91	86.94	0
2	Male	0.00	1.40	2.72	1.75	77.99	0
3	Female	0.33	1.49	2.55	2.08	85.54	0
4	Never Smoked	0.00	1.14	3.16	1.30	60.82	0
5	Ex Smoker	0.39	1.36	2.37	2.00	92.13	0
6	Current Smoker	0.10	1.68	2.94	1.87	66.09	0
7	Over 75	0.00	1.25	2.34	1.86	88.63	0
8	Below 75	0.29	1.56	2.57	1.92	79.05	0
9	SES IMD 2010 = 5 (least deprived)	0.00	1.21	2.92	1.29	55.99	0
10	SES IMD 2010 = 4	0.00	1.38	2.77	1.92	87.41	0
11	SES IMD 2010 = 3	0.00	1.44	3.74	1.85	74.42	0
12	SES IMD 2010 = 2	0.00	1.46	3.76	2.08	83.91	0
13	SES IMD 2010 = 1 (most deprived)	0.00	1.57	3.64	1.92	74.22	0

Salford rates are towards the high end of normal (but not outside defined normal range).

* per patient year

Mixed modelling

```
proc glimmix data= bothf pconv=1e-4 method=laplace;
class LAR sex (ref='0') SES (ref='1') MedHist (ref='1‘) ...;
model COPDcount = sex  age* agesq*  SES MedHist DepressionHist
AnxietyHist AsthmaHist  PneumoniaHist GastroPepticHist exbhist*
exbhistsq* MRCDyspnoea FluVax fev1*  fev1sq*  fev1_fvc*  fev1_fvcsq*
SmokeStatus
 / link=log offset = ln_validtime s cl;
            random intercept / subject = LAR solution cl;
                        xi = (1 - 1/exp(_phi_));
      _variance_ = _mu_ / (1-xi)/(1-xi);
      if (_mu_=.) or (_linp_ = .) then _logl_ = .;
      else do;
         mustar = _mu_ - xi*(_mu_ - COPDcount);
         if (mustar < 1E-12) or (_mu_*(1-xi) < 1e-12) then
            _logl_ = -1E20;
         else do;
            _logl_ = log(_mu_*(1-xi)) + (COPDcount-1)*log(mustar) -
                     mustar - lgamma(COPDcount+1);
         end;
      end;
nloptions Maxiter=500 Tech=nrridg; run;
```

*** Continuous variables were normalised**

Adjusted 'rates' of COPD exacerbation (PO2)

EHR for SLS-UC

Variable	CPRD_xGM_IC_lower	CPRD_xGM_IC_median	CPRD_xGM_IC_upper	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.90	0.99	1.13	1.14	**98.37**	1

Entries are relative rates compared with population average. **Salford relative rate above usual range.**

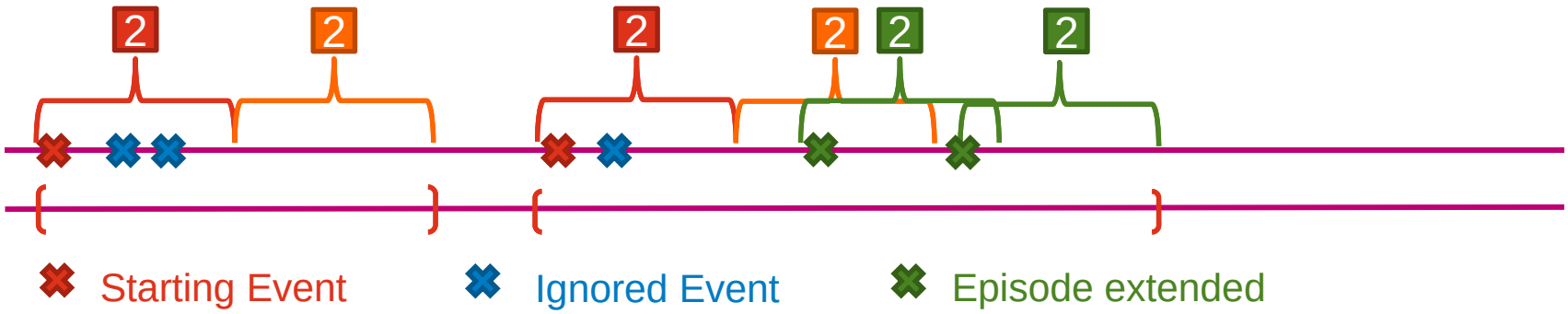
EHR for SLS-UC complete cases

Variable	CPRD_xGM_IC_lower	CPRD_xGM_IC_median	CPRD_xGM_IC_upper	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.91	1.00	1.13	1.11	**94.06**	0

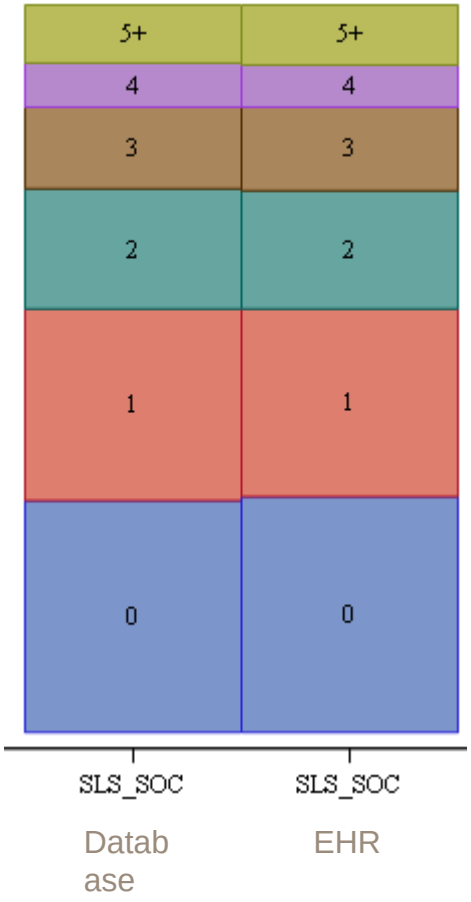
Entries are relative rates compared with population average. Salford relative rate within usual range (but similar to results from imputed datasets).

Detecting Exacerbation in primary care EHRs: Quint algorithm

- Criteria used to define an exacerbation event in any given day:
  1. AECOPD Code
  2. Lower Respiratory Tract Infection Code
  3. Two different symptoms (cough, sputum or breathlessness) coupled with an ATB or OCS prescription
  4. ATB prescription and OCS prescription
- Once all events identified episodes are identified from these:
  1. For each event, project two weeks ahead as the end of episode
  2. Any events in this two week period are ignored
  3. If there is an event within 2 weeks of this end date, re-set end date to be two weeks after that event
  4. Repeat until no event is two weeks after end date



Trial database versus EHR exacerbation definitions



- Agreement at individual patient level…
- Bigger difference in *episode* definition
- Quint algorithm does not allow two episodes to begin within 28 days of each other (to ensure that associated events do not relate to same episode).
- Episodes can occur close together in SLS collected data eCRF (e.g. within 5 days).
- No linkage to HES in SLS EMR

		EMR						
		0	1	2	3	4	5+	T
	0	359	69	8	5	3	2	446
	1	73	222	52	14	2	8	371
	2	16	47	106	43	10	8	230
	3	3	16	42	59	25	13	158
	4	3	4	13	22	24	19	85
	5+	1	4	5	21	16	66	113
eCRF	T	455	362	226	164	80	116	1403

Adjusted ‘rates’ of COPD exacerbation (PO2)

EHR for SLS-UC

Variable	CPRD_xGM_IC_lower	CPRD_xGM_IC_median	CPRD_xGM_IC_upper	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.90	0.99	1.13	1.14	**98.37**	1

Entries are relative rates compared with population average. **Salford relative rate above usual range.**

Trial Database for SLS-UC

Variable	CPRD_xGM_IC_lower	CPRD_xGM_IC_median	CPRD_xGM_IC_upper	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.92	1.00	1.11	0.98	**35.84**	0

Entries are relative rates compared with population average. Salford relative rate within usual range.

Interpretation

- Hard to assess Hawthorne effect from examining reported exacerbation rates in SLS vs xGM alone
- What about other proxies for changing behaviours?
- What about changes before/during SLS?
- **SO1**: To make comparisons between the SLS UC and the CPRD cohort on the following health care utilisation (HCU) endpoints: GP visits, hospital admissions, mortality and adherence
- **SO3**: Self-controlled comparison of COPD and HCU endpoints in Salford before and after SLS commenced, using data from the SLS, accounting for secular trends using the CPRD

Before/After Analyses

- Examine change in key outcomes: comparing the year before the trial with the year during.
- CPRD used as a control for secular trends (difference in differences design).
- Each patient is their own control:
  - cut-off time = index date
  - patient is a level in multilevel models
    - with each contributing twice (before, during).

Key results from model for change in exacerbation rates

- Fixed effect for during:before (secular trend) relative rate = 0.97
- Random coefficient represents change in exacerbation rate after accounting for secular trend
- Salford adjusted change in rates (1.04) is not unusually high relative to average for LAs (64th centile)
- Model estimates actual change in SLS, relative to average LA as 1.02 = 0.97*1.04

Variable	CPRD_xGM_IC_lower	CPRD_xGM_IC_median	CPRD_xGM_IC_upper	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Coefficient#	0.90	1.02	1.18	1.04	64.17	0
DURING:BEFORE rate ratio	0.88	1.00	1.15	1.02	64.17	0

Overall summary of results
Hawthorne effect? At practice and/or patient level?

Endpoints	SLS versus xGM		Before versus during	
Rate of:	Unadjusted	Adjusted	Unadjusted	Adjusted
Exacerbations	High but not unusual	Unusually high	Does not change unusually	Does not change unusually (slight increase)
Primary care contact	Unusually high	Unusually high	Does not change unusually	Does not change unusually
COPD prescriptions	Not unusual	Not unusual	Unusually high decrease	Unusually high decrease
COPD Tx switching	Unusually high	High but not unusual	Unusually high decrease	Unusually high decrease
Mortality	Not unusual	Unusually low	NA	NA

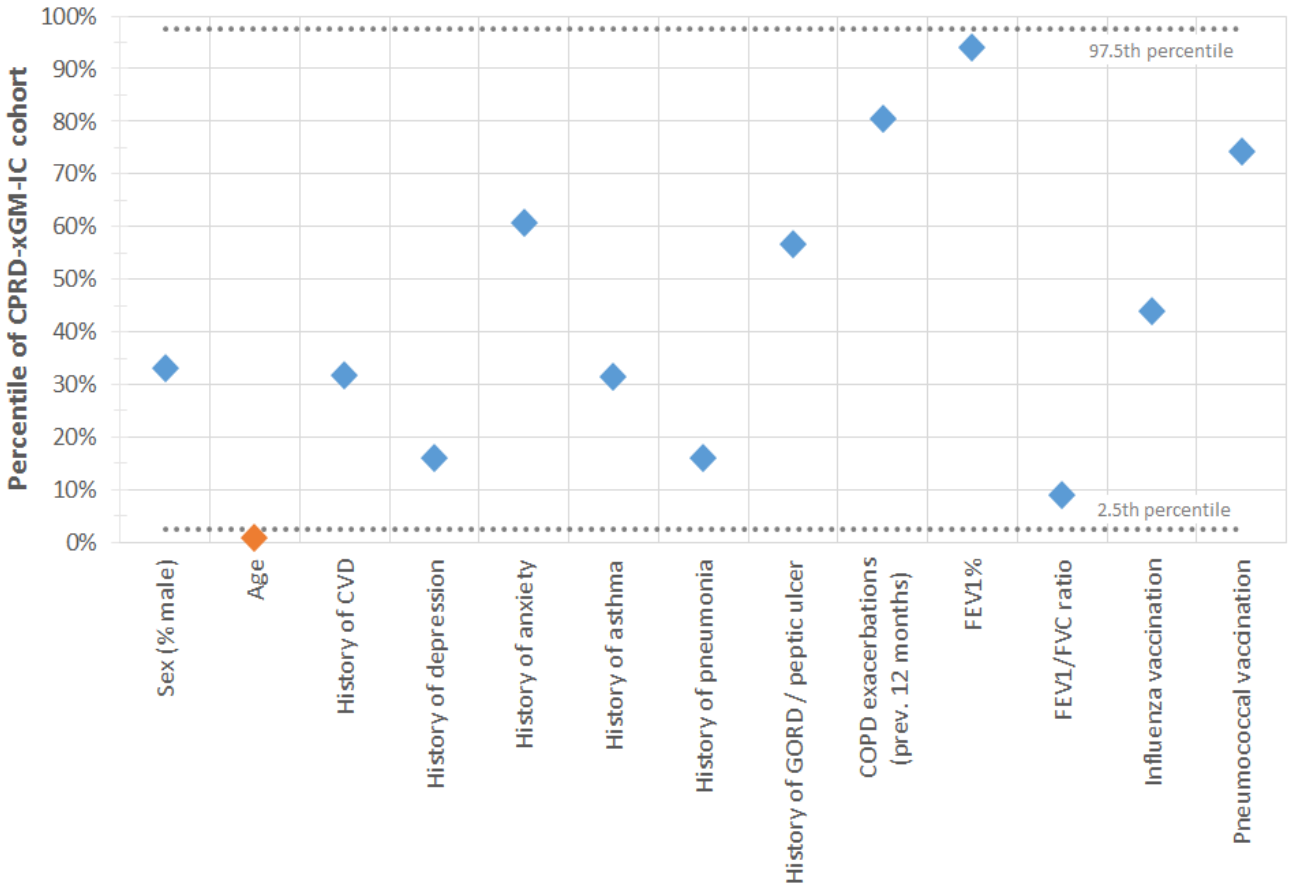
Collaboration has been key

- Real World Evidence (RWE) group
  - oversight of study, data expertise and analysis
- Vendors
  - provided data and advised on appropriate use of data
- Clinical team
  - experts on trial management, disease understanding and eCRFs
  - QC'd components of study using eCRF data
- Academic partners
  - FARR http://www.farrinstitute.org/
  - Insight into appropriate study design and methods
    - Propensity scores, mixed modelling, imputation, self controlled analyses

Back up slides

PO1:SLS percentile in context regional variation within the CPRD at local authority level

A: Continuous variables



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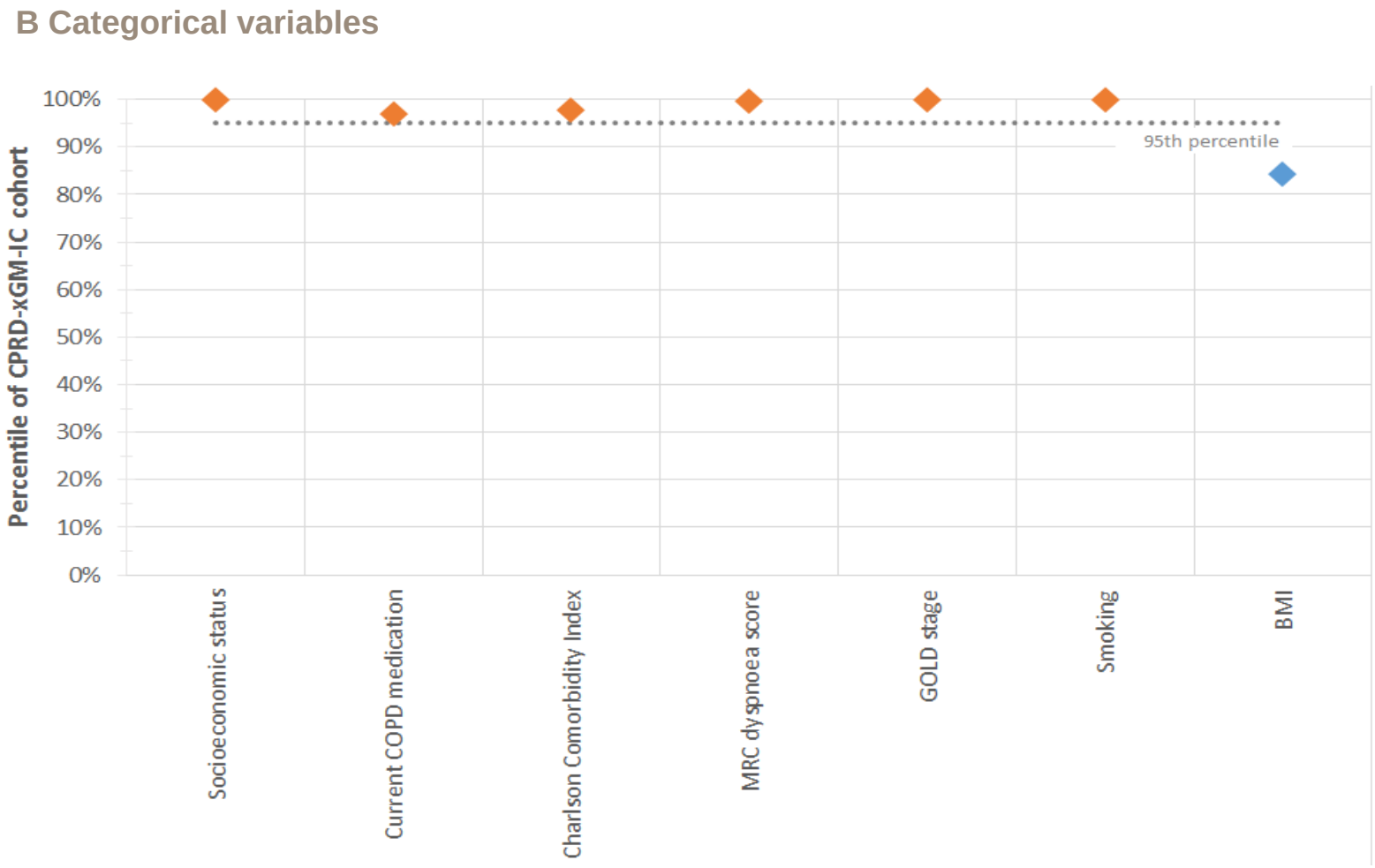
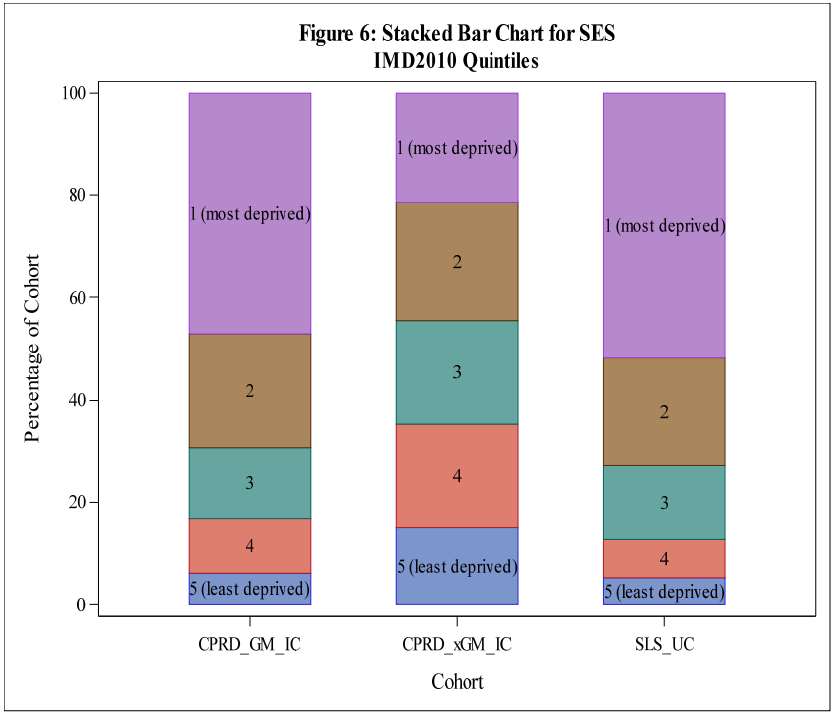
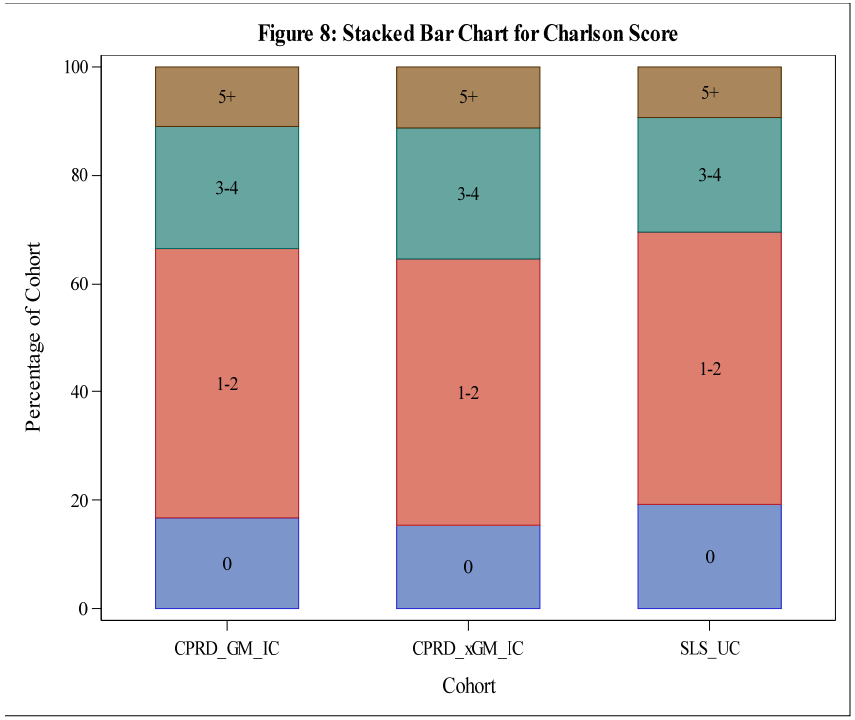


PO1: Stacked bar charts comparing CPRD (x-GM-IC) to SLS-UC





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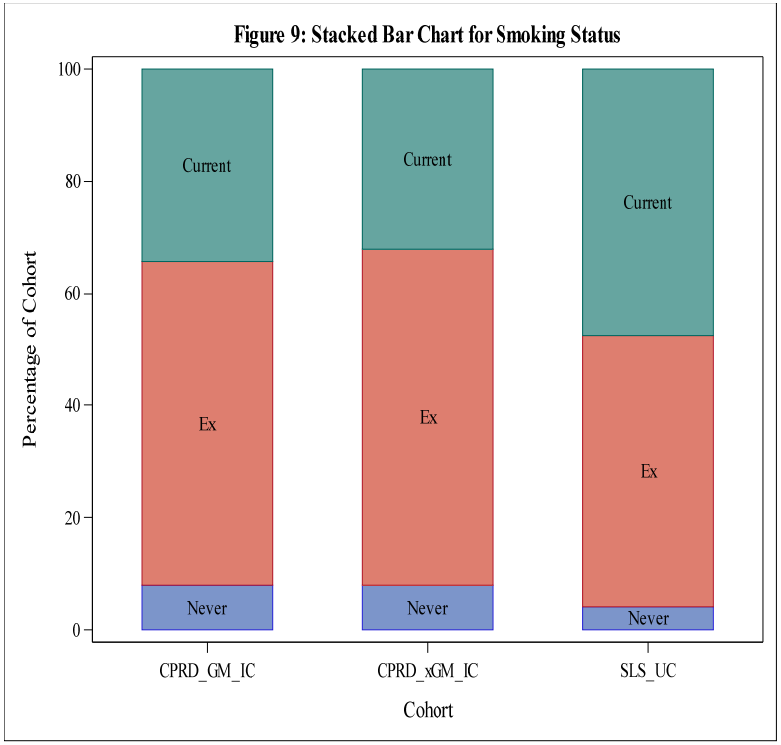

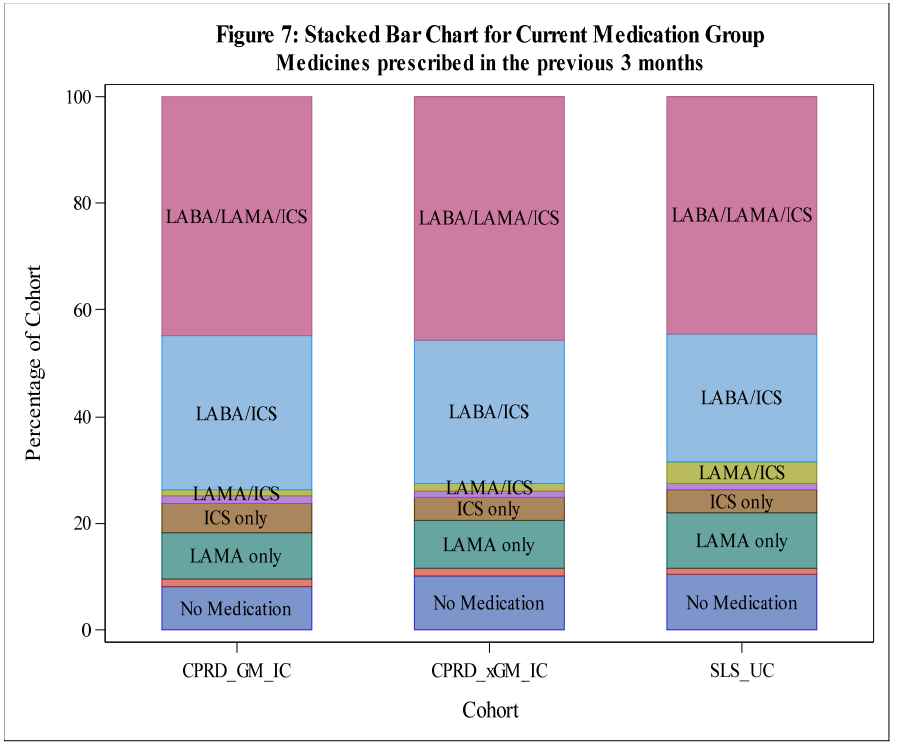

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