
Welcome -
you are now
IN Salford
Salford is twinned with: Lunen, Germany;
Saint-Ouen, Clermont-Ferrand and Narbonne, France

The Salford Lung Study

Professor Ashley Woodcock,
University of Manchester
Chief Investigator Salford Lung Study
Dr David Leather
Medical Vice President GSK Global Respiratory Franchise
Salford Lung Study Lead

EMA December 8th 2016

Conflict of Interests Declaration

- Prof Ashley Woodcock (Last 3 years):
  - Co-Chair of the Technology and Economic Assessment Panel to the Montreal Protocol, which has managed safe phase-out of CFC MDIs
  - Chair of Reacta Biotech, a spinout for manufacture of Food Allergy Diagnostics
  - Consulted for Chiesi
  - (No consulting fees for SLS/GSK.)

- Dr David Leather is a full time employee of GSK and holds stocks and shares in GSK

The Salford Lung Study: What is it?

- A randomised prospective effectiveness study,
- Performed in everyday clinical practice
- Commenced with a pre-license medicine (Relvar) in COPD

- Patients recruited between March 13, 2012, and October 23, 2014,
- The study was published in the NEJM September 2016

Vestbo, J et al 2016 *NEJM* (DOI: 10.1056/NEJMoa1608033)

What was the intent behind the study design?[1,2]

To maintain the scientific rigour of an RCT

- Interventional, randomised, control arm

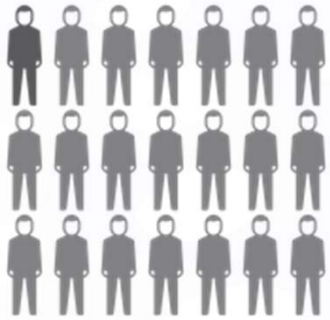
But…to keep it as near to everyday clinical practice as possible

- Minimal exclusion criteria
- Patient experience as normal as possible
- Collecting endpoints relevant to patients and healthcare decision makers
- Comparing Relvar® Ellipta® with ‘usual care’
- In the usual care arm, the physician was free to choose the appropriate COPD treatment for each patient, based on his/her clinical judgement

Salford Lung Study

[1]New JP, et al. *Thorax* 2014;69:1152–4; [2]Bakerly N et al. *Respir Res* 2015;16:101

Efficacy vs Effectiveness?



Assess Safety and Efficacy

RCTs

Double blind

Double dummy

Strict inclusion criteria

Exclusions

Adherence encouraged

Frequent reviews

Drugs provided

Effectiveness in Ordinary Patients in Everyday Care

Effectiveness

Open label

Broad population

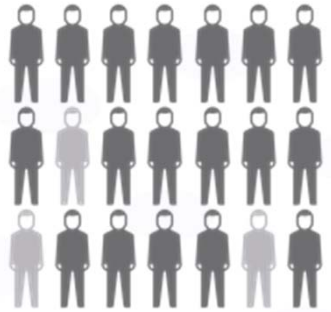
All comers

Co-morbid included

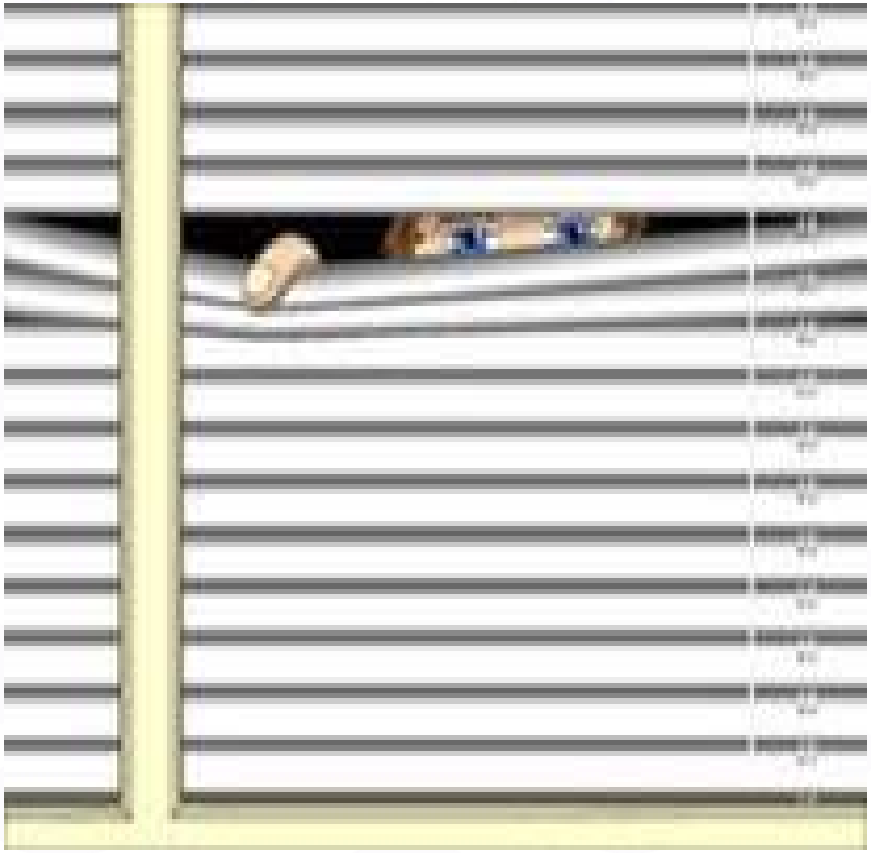
Set in normal care

No extra review

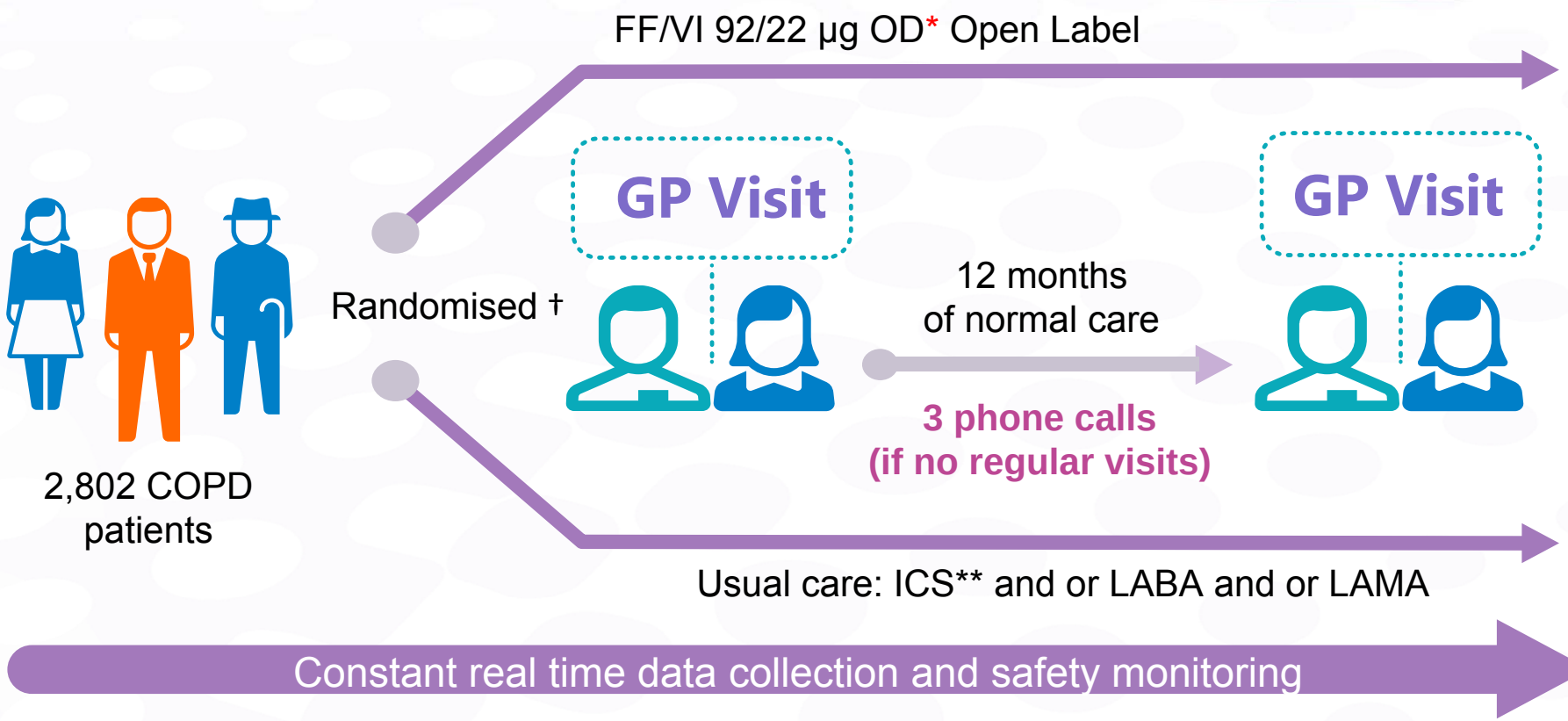
Drugs prescribed and collected in usual way



Study monitoring: Efficacy vs Effectiveness



Salford Lung Study
Study design[1,2]



* Patient allowed to remain on LAMA in addition to their randomised treatment if already receiving LAMA therapy at randomisation
** ICS monotherapy is not licensed for use in COPD
†Randomisation stratified by recent exacerbation status and existing COPD maintenance therapy at baseline

1. Bakerly N, et al. *Respir Res* 2015;16:101 2. Vestbo, J et al 2016 *NEJM* (DOI: 10.1056/NEJMoa1608033)

Salford Lung Study

Salford Lung COPD Study
Study design

2,802 patients

- Patients in primary care
- Aged 40+ years
- GP diagnosis of COPD
- Taking ICS* and/or LABA and/or LAMA
- Exacerbation in the last 3 yrs
- Consented

* ICS monotherapy is not licensed for use in COPD

Vestbo, J et al 2016 *NEJM* (DOI: 10.1056/NEJMoa1608033)

Salford Lung Study

Consent in the Salford Lung Study

- The process of consent and randomisation was supported by study staff
- Consent forms were available in different languages and in audio format
- Consent was obtained by the Patient's GP in their usual practice
- Some sites used study nurses to take patients through the consent process
- Processes all discussed and agreed with local Ethics Committee

Challenges and Solutions

Challenges	Solutions
How to find 2802 COPD subjects willing to take part in a clinical trial?	• **Identify suitable GP sites**
How to identify and encourage GPs to take part?	• **Grassroots approach** • **Ensure excellent set-up, training and ongoing support of sites** • **Large and expert CRA and nurse team**
How to recruit patients to the studies?	• **Write to every eligible patient directly from their own GP** • **Local advertising** • **Detailed F2F explanation of study by staff to allow informed consent**

Salford Lung Study

Challenges….. and Solutions

Challenges	Solutions
How to ensure that we do not interfere with “normal” care?	• Intensive training of all study and site staff • Study drug accessed through “high street” community pharmacy network
How to ensure robust safety monitoring, without routine study visits?	• Integrated electronic patient record (EMR) with real-time access ensures that the safety team are aware wherever and whenever patient accesses healthcare • Dedicated safety team
How to ensure robust collection of study end points?	• Direct extraction of study endpoints from EMR wherever possible • Excellent and auditable IT systems and support staff

Salford Lung Study

The SLS Study collaboration

A pioneering collaboration between GSK, academia, healthcare commissioning groups, hospitals and an entire regional healthcare community [1-3]

April 2011
Joint Advice

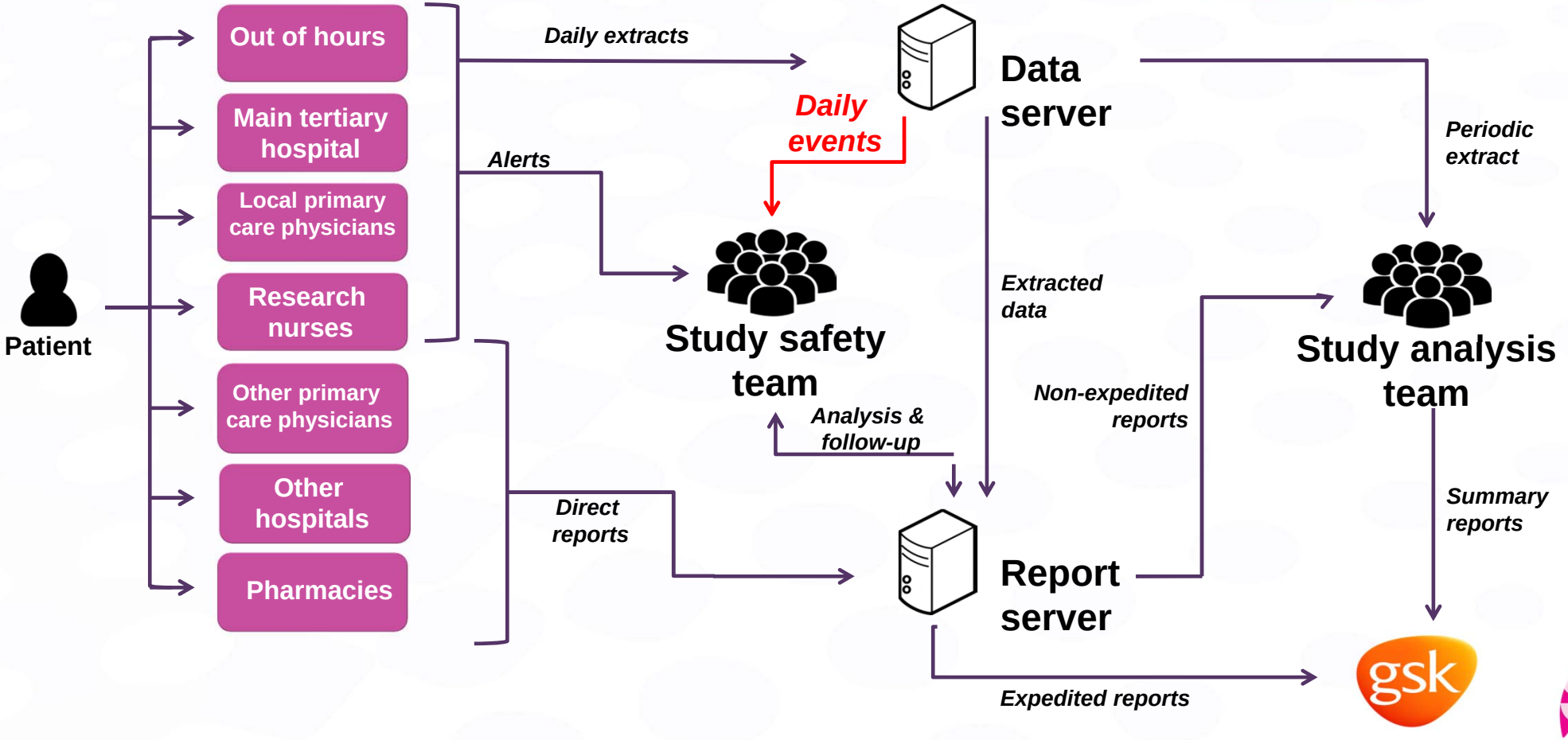
National Regulatory Agency
MHRA
+
Health Technology Assessment / Payer Authority
NICE

MHRA, Medicines and Healthcare Products Regulatory Agency; NICE, National Institute for Health and Care Excellence.

1. New JP, et al. *Thorax* 2014;69:1152–4; 2. Bakerly et al. Respiratory Research 2015; 16: 101; 3. Limb M. *BMJ* 2015;351:h6343

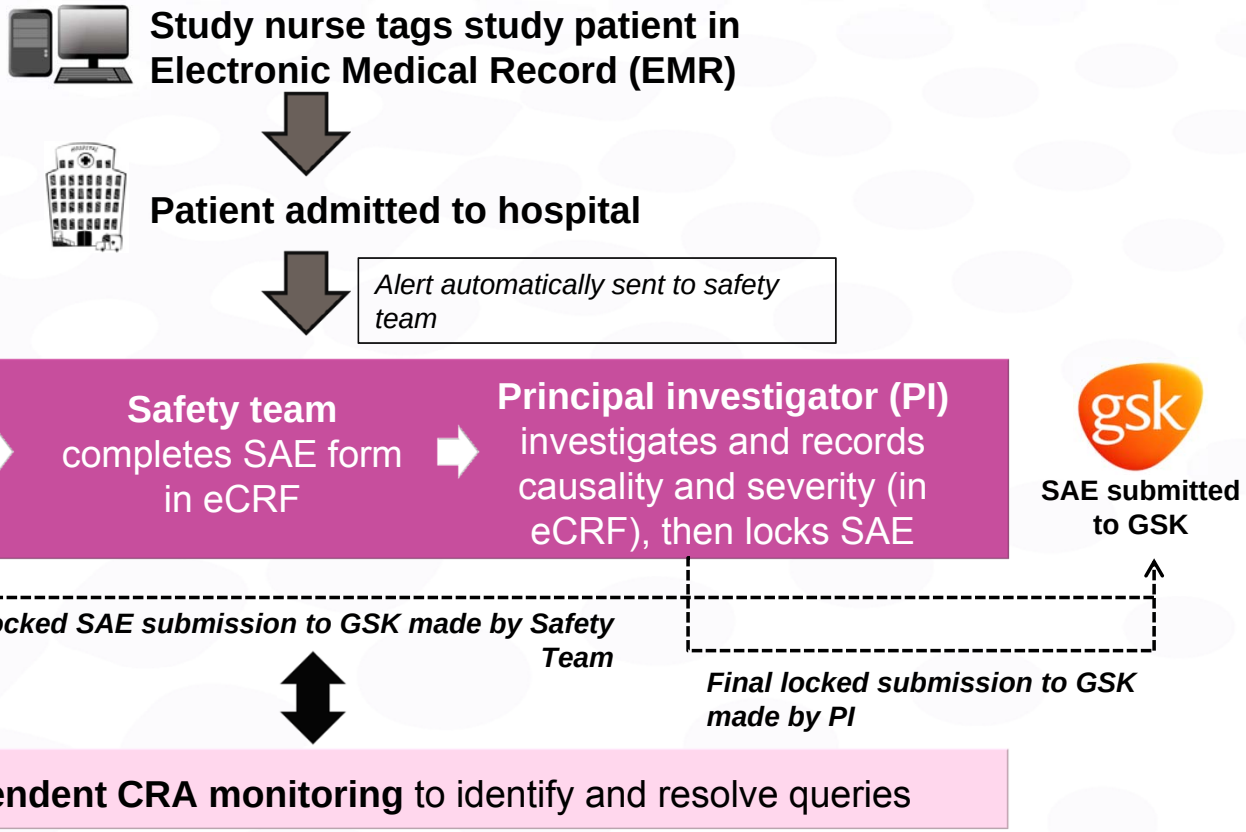
Salford Lung Study

Electronic surveillance in the Salford Lung Study[1-3]
Using a linked database to gather real-time data



[1]New JP, et al. *Thorax* 2014;69:1152–4; [2]Bakerly N et al. *Respir Res* 2015;16:101; [3]Vestbo, J et al 2016 *NEJM* (DOI: 10.1056/NEJMoa1608033)

A unique process for identifying and reporting of Serious Adverse Events (SAEs) within the study[1,2]

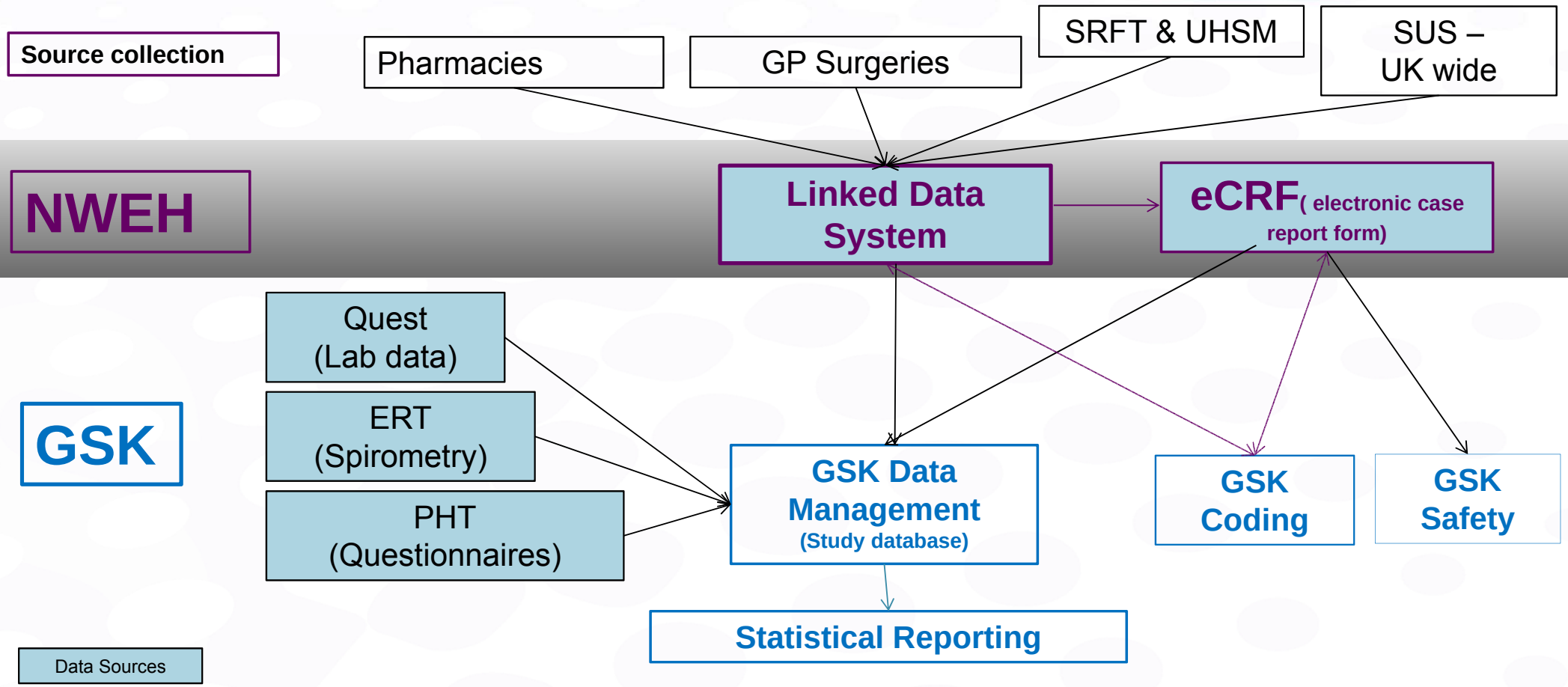


eCRF, electronic case report form; CRA, clinical research associate

1. Bakerly N et al. *Respir Res* 2015;16:101; 2. Vestbo, J et al 2016 *NEJM* (DOI: 10.1056/NEJMoa1608033)

Salford Lung Study

The Data Journey



Ensuring data quality in the Salford lung Study

The study used the NHS health record as the tool to detect endpoints
Unique NHS number "cradle to grave record"- low potential for data loss

Effectiveness endpoint data	**Potential endpoints flagged by EHR confirmed with Investigator and entered into eCRF**	**eCRF is the main tool for endpoints and safety data**	**All eCRF data Source data verified by CRAs**
Safety data	**Flagged by EHR Checked by safety team**	**Supplemented by eCRF**	**Reported as per regulations**
Electronic information	**Data extracted using validated linked data system**	**Data double checked by NWeH**	**Data checked again by GSK data quality team**

[1]New JP, et al. *Thorax* 2014;69:1152–4; [2]Bakerly N et al. *Respir Res* 2015;16:101; [3]Vestbo, J et al 2016 *NEJM* (DOI: 10.1056/NEJMoa1608033)

SLS Teams

Community Pharmacy Sites

GP Sites

Data Managers

NWEH

SLS Study Patients

Governance Board
IDMC
Scientific Committee
Publications

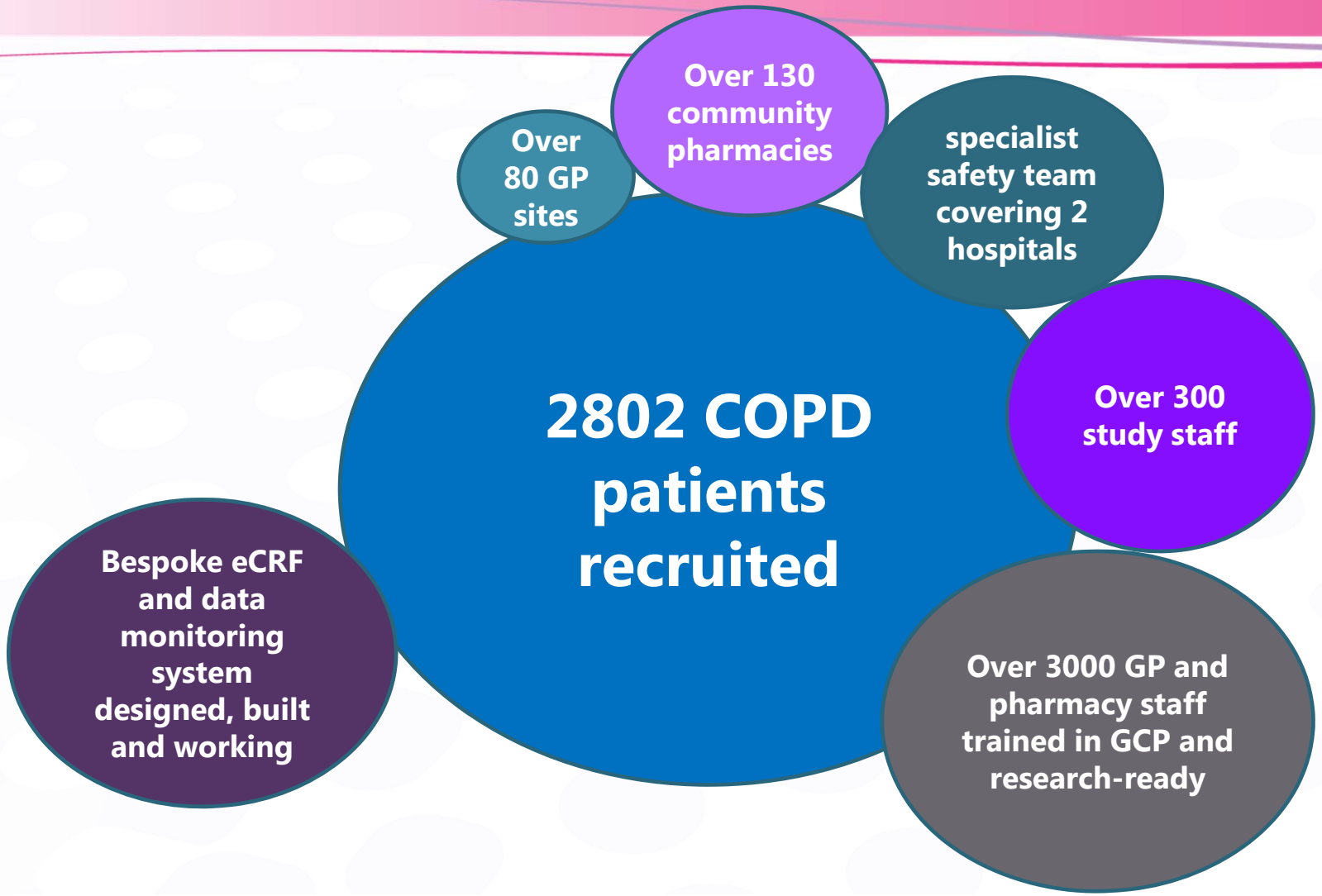
Community Research Team

CRA Team

GSK
Stats
Regulatory
Safety
Medical
R and D

Salford Lung Study

Scale of the project



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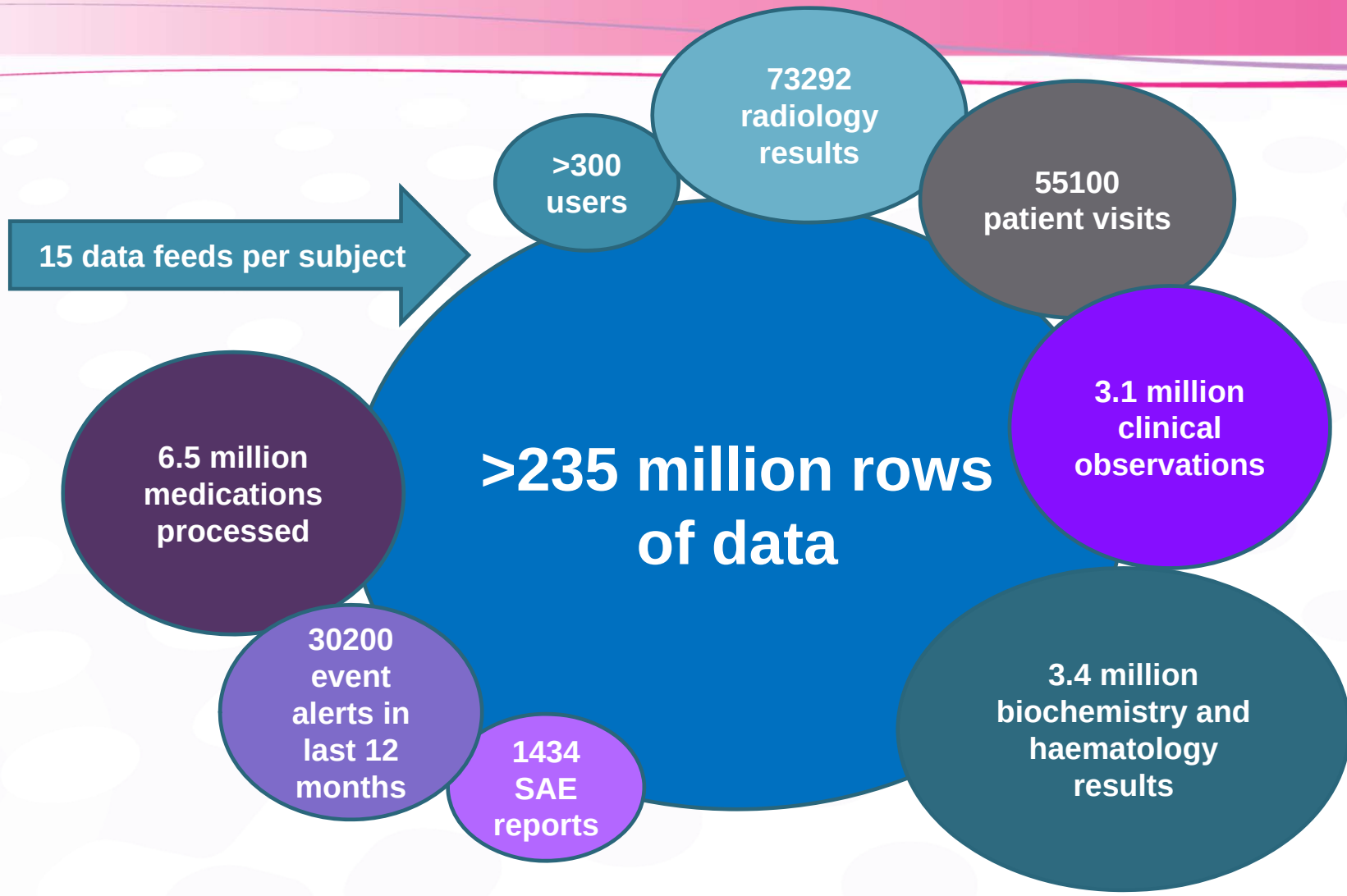
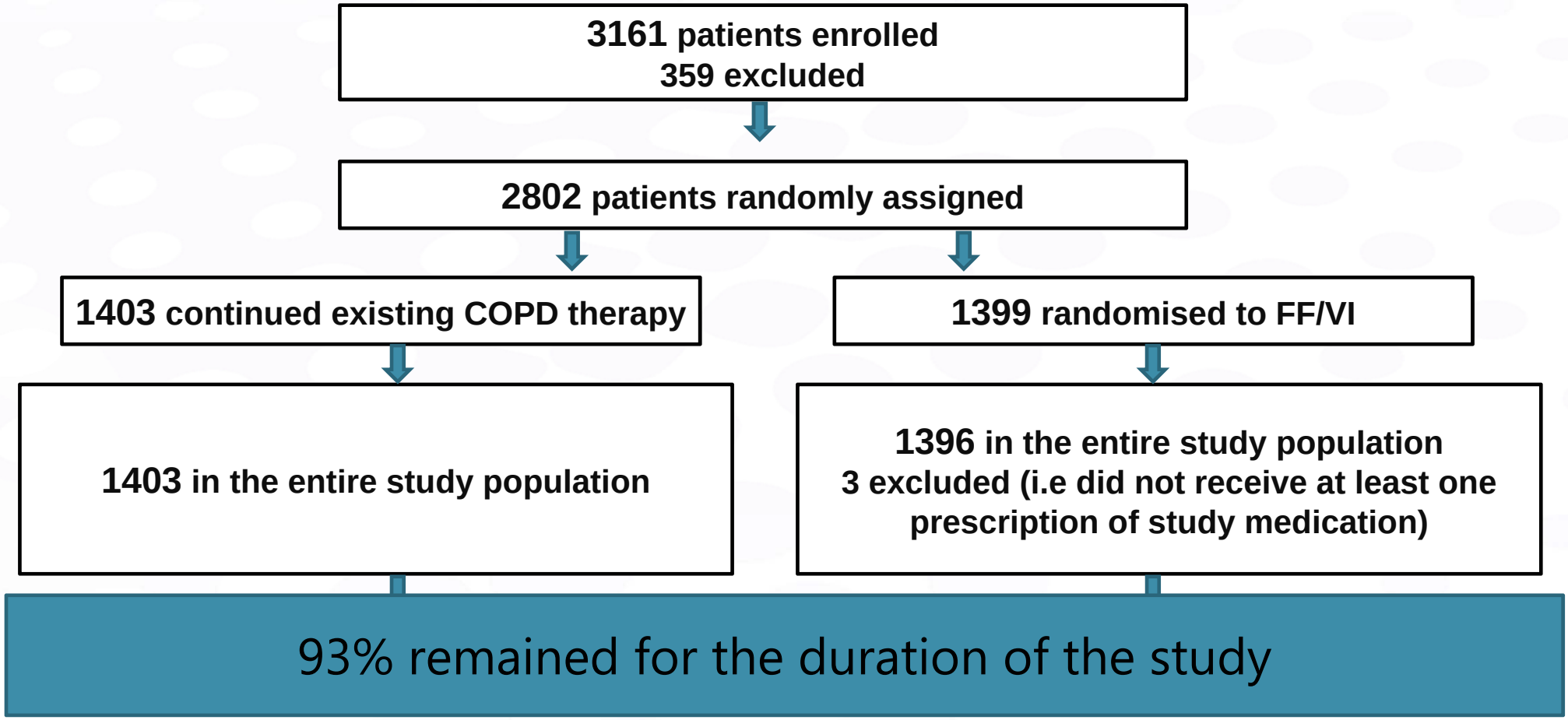
Electronic Clinical Monitoring

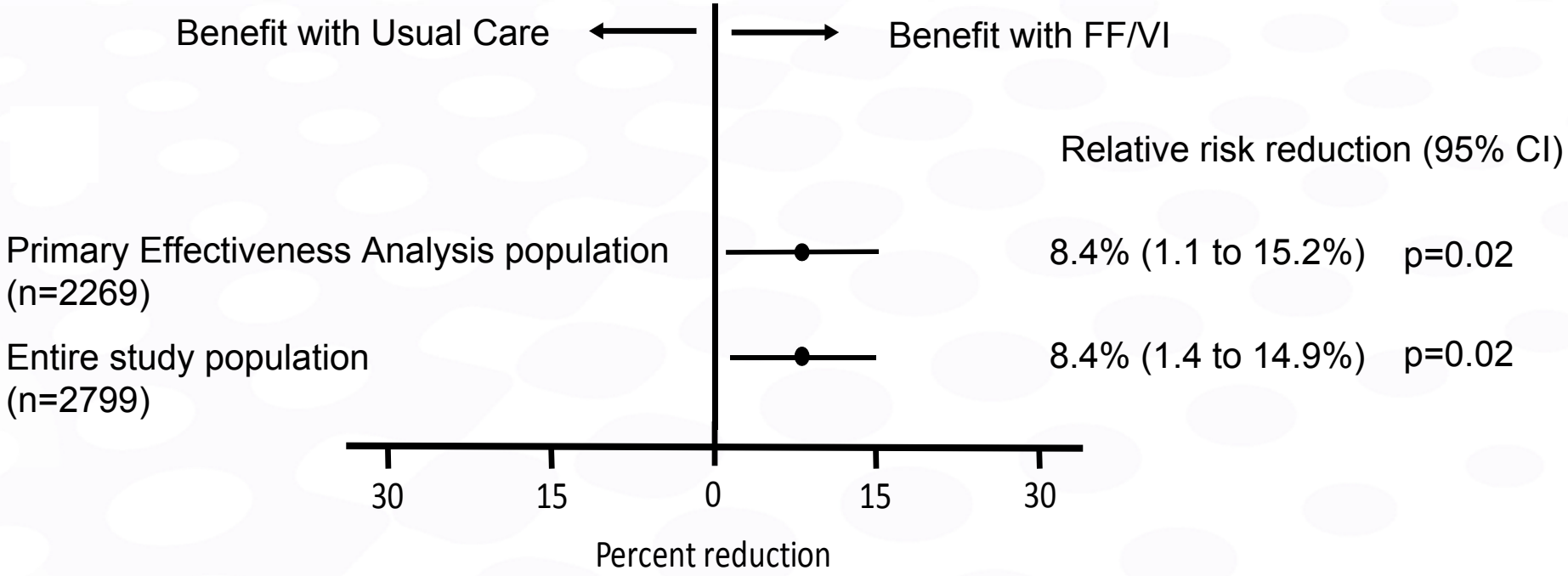


Study enrollment and completion



Vestbo, J et al 2016 *NEJM* (DOI: 10.1056/NEJMoa1608033)

Results: primary endpoint: Moderate /severe exacerbations



NUMBER NEEDED TO TREAT (NNT): One additional moderate/severe exacerbation is prevented for every 7 patients treated with Relvar® 92/22 µg compared with usual care over 12 months

Adapted from Vestbo, J et al 2016 *NEJM* (DOI: 10.1056/NEJMoa1608033)

Salford Lung Study

What was ‘usual care’?

A physician-determined COPD maintenance treatment in accordance with usual clinical practice

Overall intent-to-treat (ITT) population (n=2,799)

COPD THERAPY PRE-RANDOMISATION

LABA or LAMA or LABA+LAMA	ICS*, ICS/LABA or ICS+LAMA	ICS/LABA+LAMA
14% (n=391)	34% (n=958)	52% (n=1450)

86% on an ICS-containing regimen (n=958)

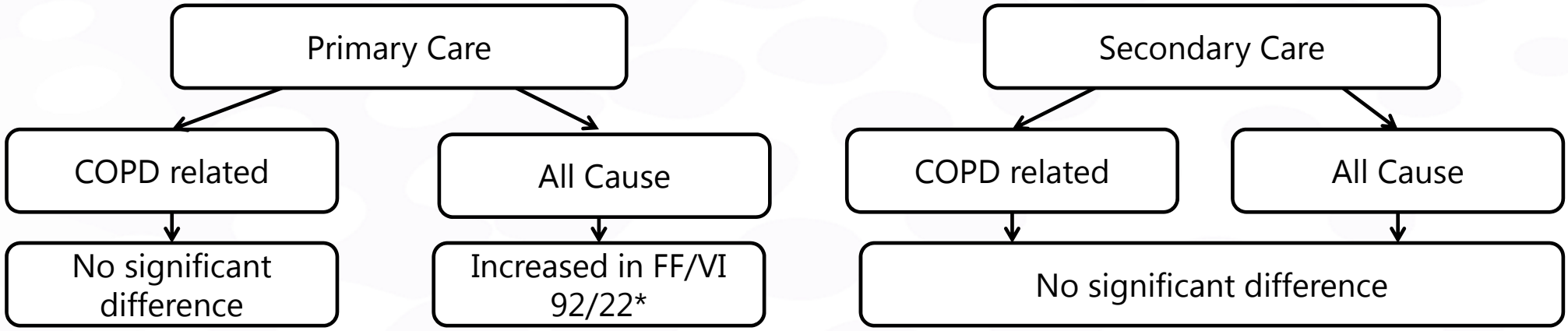
* ICS monotherapy is not licensed for use in COPD

Vestbo, J et al. NEJM 2016 (DOI: 10.1056/NEJMoa1608033)

Salford Lung Study

Other clinical effectiveness outcomes[1]

- Severe exacerbations- no significant difference (0.09 and 0.08 exacerbations per year on FF/VI 92/22 and usual care respectively, p = 0.52)
- Time to first moderate-severe exacerbation- no significant difference between FF/VI 92/22 and usual care; HR 0.93 (0.85-1.02).
- Healthcare utilisation:



*There was a 12.3% increase (95% CI: 5.4, 19.6) in the annual rate of all primary care contacts in the FF/VI 92/22 group vs usual care.

(1) Vestbo, J et al. *NEJM* 2016 (doi: 10.1056/NEJMoa1608033)

SLS: Main Safety Outcomes

- **On-treatment serious adverse events (SAEs):**

FF/VI 92/22	Usual Care
29%	27%

- **Any serious adverse events of specific interest (SAESI):** no notable difference
- **Mortality:**

FF/VI 92/22	Usual Care
45 (3%)	30 (2%)

- One patient in each group died from a SAE that was recorded as related to the trial medication.

(1) Vestbo J et al. *NEJM* 2016 (doi: 10.1056/NEJMoa1608033).
Tables adapted from Vestbo J et al. *NEJM* 2016 (doi: 10.1056/NEJMoa1608033).

Relvar® Ellipta® 92/22mcg is associated with a similar incidence of on-treatment serious pneumonia as usual care[1]

	Usual Care (N=1403)	FF/VI (N=1396)
No. (%) of subjects who had at least one: SAE of pneumonia	83 (6%)	94 (7%)
Comparison of FF/VI vs usual care Incidence ratio 95% CI		1.1 (0.9, 1.5)

(ITT Population: defined by the Pneumonia Special Interest Group)

The non-inferiority margin for the ratio of the proportions with serious pneumonia on FF/VI versus usual care is set at 2. Non-inferiority is demonstrated if the upper limit of the two-sided 95% confidence interval for the incidence ratio FF/VI / usual care is less than 2.

In common with other ICS-containing medicines, there is an increased risk of pneumonia in COPD patients treated with FF/VI.[2]

1. Vestbo, J et al. NEJM 2016 (DOI: 10.1056/NEJMoa1608033) 2.GlaxoSmithKline. Relvar Ellipta 92 mcg/22 mcg Summary of Product Characteristics 2016

Salford Lung Study

Groups well matched
Typical of everyday clinical practice (1)

	Entire study population (ITT)	
	Usual care (N=1,403)	Relvar Ellipta (N=1396)
Age (year)	67±10	67±10
Female Sex	671 (48%)	698 (50%)
BMI (kg/m^2)*	28±6	28±7
Current Smokers	666(47%)	623(45%)
Post-bronchodilator FEV$_1$(L)	1.62±0.65	1.62±0.64
CAT score**		
mean (±SD)	21.9 ± 8.75	21.6 ±8.89
<10,n(%)	135 (10%)	151 (11%)
≥10,n(%)	1267 (90%)	1243(89%)
Mean number of exacerbations during the 12 months prior to randomisation	2.04±2.08	1.98±1.90

Vestbo, J et al. NEJM 2016 (DOI: 10.1056/NEJMoa1608033)
GSK Data on file RF/FFT/0120/16

* Analysis based on number of patients who height and weight recorded (ie usual care n=1,122 and FF/VI n=1,103)
** Analysis based on patients who completed CAT questionnaire at baseline (ie usual care, n=1,402 and FF/VI, n=1,394)

Salford Lung Study

Groups well matched
Typical of everyday clinical practice(2)

	Entire study population (ITT)	
	Usual care (N=1,403)	Relvar Ellipta (N=1396)
Co-morbidities		
Any	1076 (77%)	1069 (77%)
Cardiac	367(26%)	353 (25%)
Vascular	675(48%)	688(49%)
Asthma	293(21%)	316(23%)
Diabetes	208(15%)	230(16%)

Vestbo, J et al. NEJM 2016 (DOI: 10.1056/NEJMoa1608033)

Salford Lung Study

Comparison of baseline data: SLS versus FLAME

	SLS[1,2]	FLAME[3,4]
Age (years)	67	65
Sex	51% male	76% male
Post-bronchodilator FEV_1	1.62	1.2
CAT Score	22*	17
Exacerbation history**	≥ 2 moderate exacerbations (47%) At least 1 severe exacerbation (7%) No exacerbations (19%)	≥ 2 exacerbations (19%)# 1 exacerbation (81%) #

* Analysis based on patients who completed CAT questionnaire at baseline
# exacerbation for which patient received treatment with systemic glucocorticoids, antibiotic agents or both

1. Vestbo, J et al. NEJM 2016 (DOI: 10.1056/NEJMoa1608033).2. GSK Data on file RF/FFT/0120/16.
3. Wedzicha et al; 2016; 374; 2222-34. 4. Wedzicha et al; 2016; 374; 2222-34 Suppl. Info

Slide 29

Office [9] [2]1 Microsoft Office User, 30/11/2016

Office [11] [2]1 eWhy not compare to Dransfield? One year, RCT Efficacy and Safety, Emphasis great for its purpose. Compare CAT, FEV1, Co-morbidity, Excerbation pre-entry and within study year. OK to go with FLAME. Maybe take out SUMMIT which is observational study for different purpose. Too much for length of talk.
Microsoft Office User, 30/11/2016

Office [12]1 Much easier comparison now without complication of SUMMITT
Microsoft Office User, 30/11/2016

Office [15]1 Do we have co-morbidity data for FLAME?
Microsoft Office User, 30/11/2016

Very few Drop Outs

Study (Total number of patients randomised)	Drop out (% of patients)
SLS[1] (2802)	7
TORCH[2] (6184)	34-44
SUMMIT[3] (16590)	23-29
FLAME[4] (3362)	16.6-19

1. Vestbo, J et al. NEJM 2016 (DOI: 10.1056/NEJMoa1608033) 2. Calverley et al; NEJM; 2007; 356; 775-789. 3. Vestbo et al; Lancet; 2016; 387; 1817-1826.
4. Wedzicha et al; NEJM; 2016; 374; 2222-34.

SLS What's next?

>235 million rows of data to explore!

- In-depth interviews conducted post study-exit in a subset of patients to identify and assess additional patient outcomes
- Optional blood sample post study exit for genetics studies
- A matched "virtual cohort" study using data from patients elsewhere in UK to understand representativeness of SLS population
- SLS Asthma study (n = 4036) Q3 2017

Limb M et al, BMJ 2015;351:h6343

Salford Lung Study

Salford Lung Study COPD: Primary Manuscript

Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice

Jørgen Vestbo, D.M.Sc., David Leather, M.B., Ch.B., Nawar Diar Bakerly, M.D., John New, M.B., B.S., J. Martin Gibson, Ph.D., Sheila McCorkindale, M.B., Ch.B., Susan Collier, M.B., Ch.B., Jodie Crawford, M.Sc., Lucy Frith, M.Sc., Catherine Harvey, D.Phil., Henrik Svedsater, Ph.D., and Ashley Woodcock, M.D., for the Salford Lung Study Investigators*

A very big "thank you" to our collaborators, the study staff the GPs, Pharmcists, hospsital and their staff- and especially to the Patients who volunteered

Published on September 4, 2016, at NEJM.org

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The Salford Lung Study

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