Health e-Research Centre

Harnessing health data for patient and public benefit

Pragmatic trials

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Disclosures

- My department has received funding from GSK (sponsor of Salford Lung Study) for the conduct of an observational study comparing the generalisability of SLS patients to those in CPRD; I am co-investigator of this observational study

- I have participated in advisory meetings with GSK, Novonordisk, Sanofi and Novartis (on pragmatic trials)

- Some of the slides were provided by GSK but contents of this presentation has not been discussed with GSK

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Explanatory and pragmatic trials

- Explanatory efficacy trials
  - Can it work?
  - To verify the biological effects of molecule
    - Randomisation
    - Close monitoring / selection
    - Blinding / comparator often placebo

- Point-of-care (pragmatic) effectiveness trials
  - Does it work?
  - To compare different clinical strategies in actual practice
    - Randomisation
    - Replicate actual clinical practice for selection, monitoring and follow up
    - No blinding / comparator standard care

Schwartz and Lellouch J Chronic Dis. 1967 Aug;20(8):637-48.

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Salford Lung Study

- Randomised open label trial
- Conduct in Salford, Greater Manchester
  - Deprived area
  - Integrated electronic health records between hospital and primary care
- Study intervention (Relvar, Fluticasone furoate/vilanterol) unlicensed at start trial

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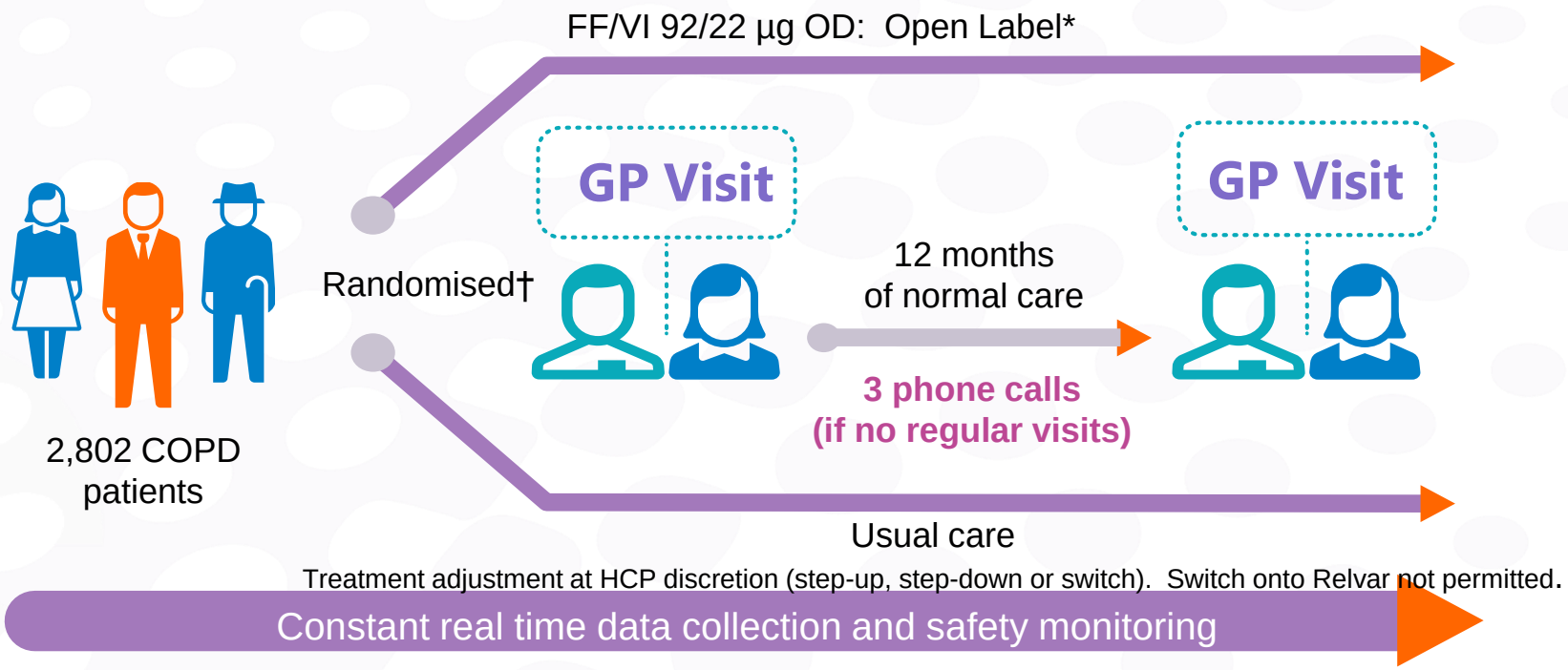
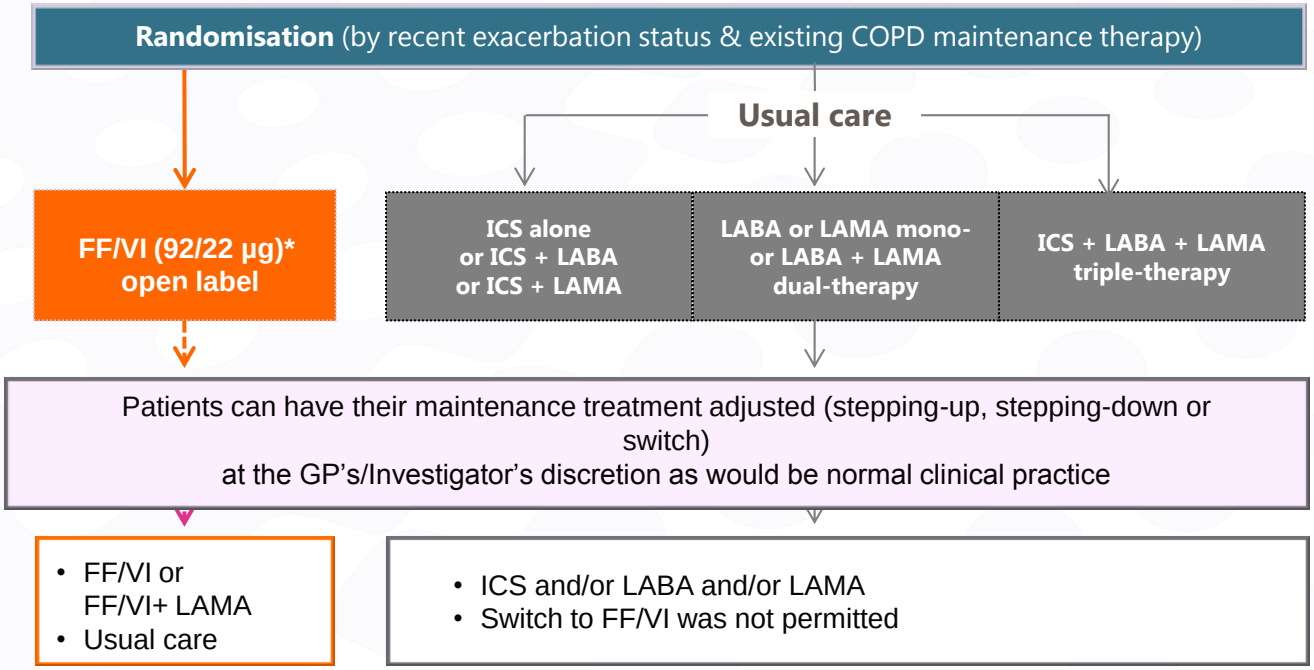
Salford Lung Study COPD
Study design[1,2]



*Patient allowed to remain on LAMA in addition to their randomised treatment if already receiving LAMA therapy at randomisation †Randomisation stratified by recent exacerbation status and existing COPD maintenance therapy at baseline. The usual care are could not change onto Relvar.

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

Salford Lung COPD Study
Randomisation and treatment stratification

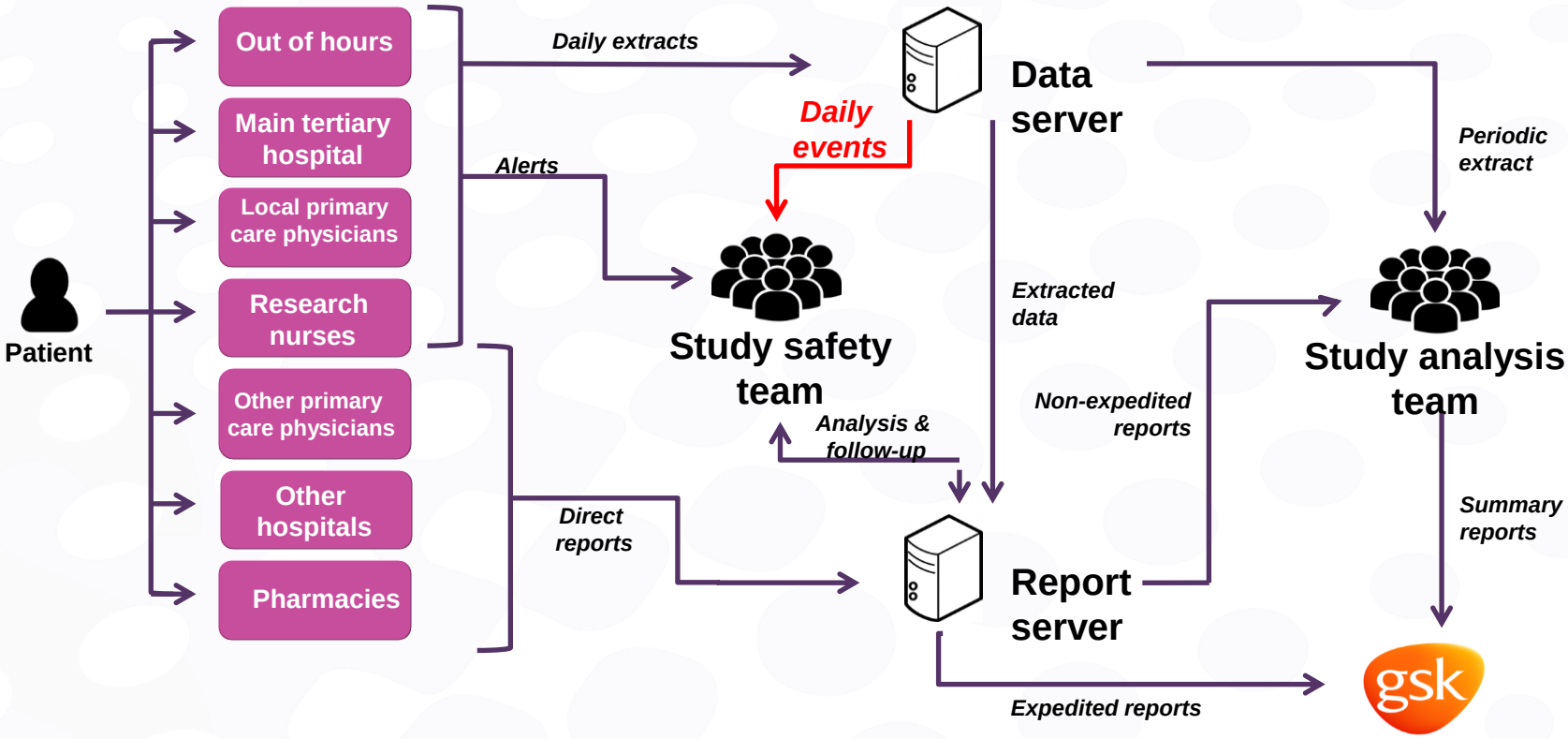


*Patient allowed to remain on LAMA in addition to FF/VI if already receiving LAMA therapy at randomisation

ICS monotherapy is not licensed for COPD

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

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)

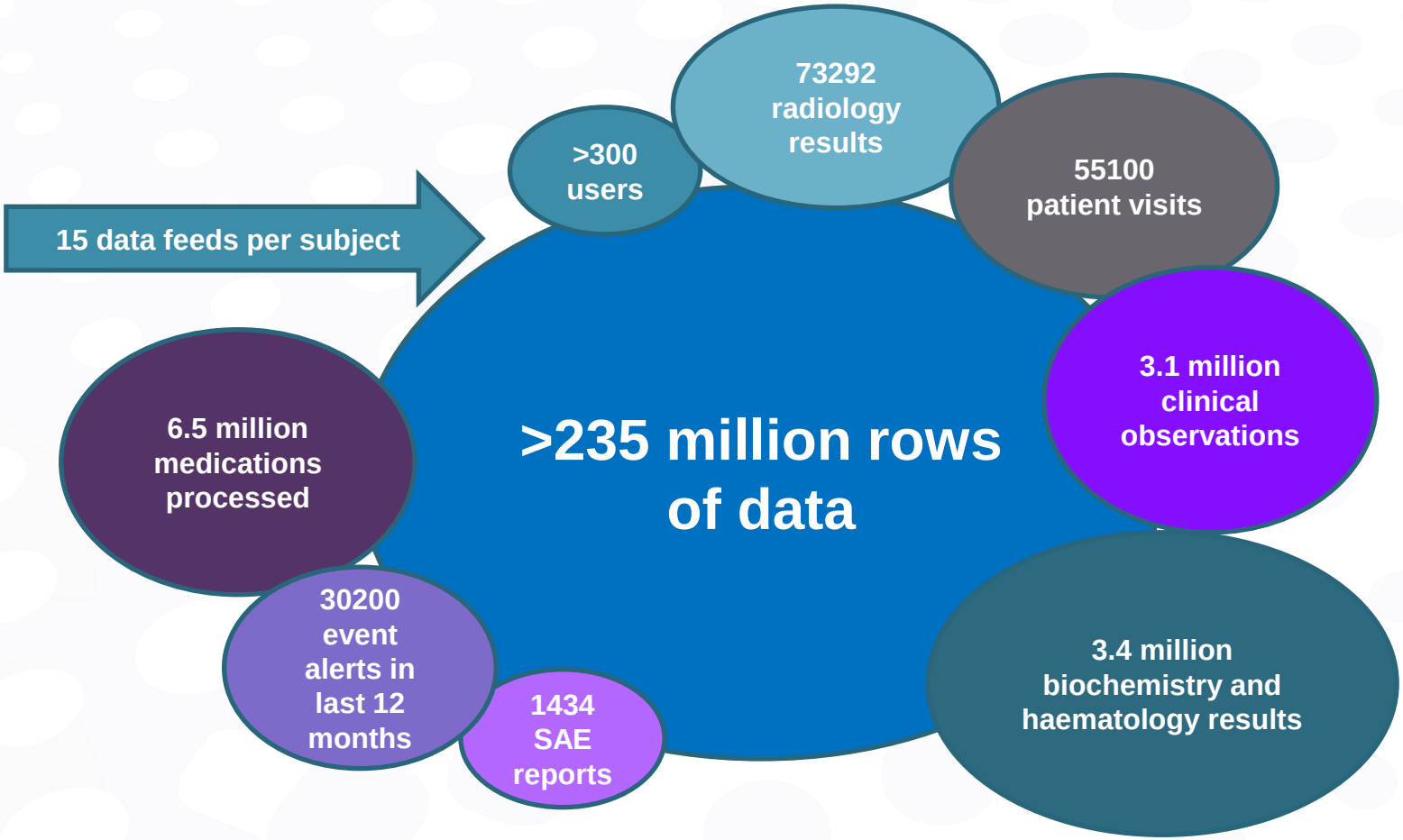
Challenges and Solutions

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

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 (EHR) 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 EHR wherever possible • Excellent and auditable IT systems and support staff

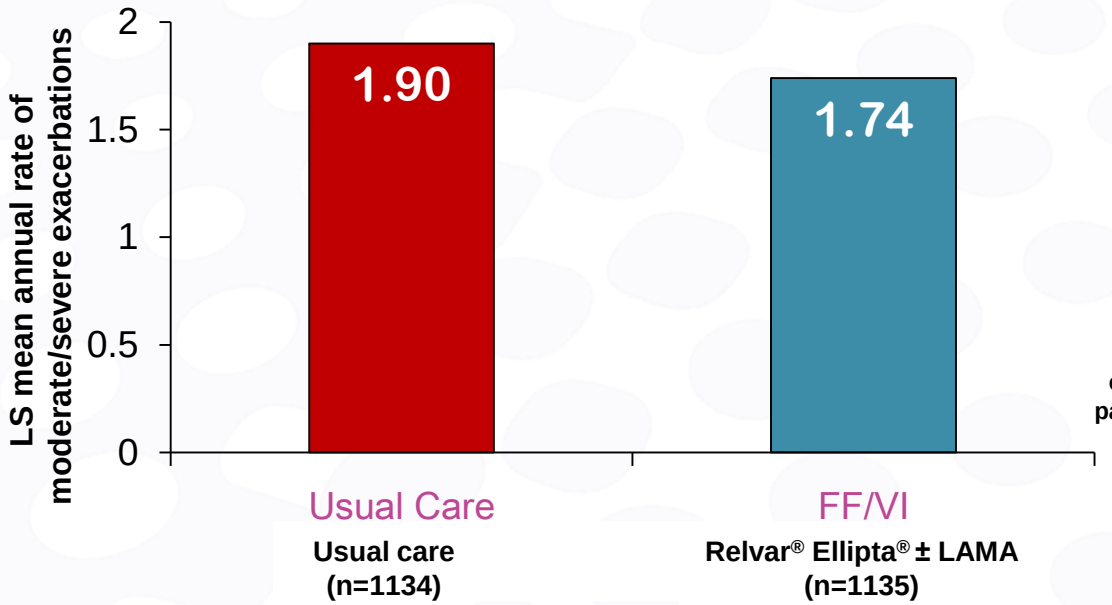
Electronic Clinical Monitoring



Salford Lung Study

Once-daily Relvar® 92/22mcg significantly reduced moderate/severe COPD exacerbations compared with usual care

Relvar® Ellipta® versus usual care, defined as physician's free choice of LAMA and or LABA only (12%), or an ICS-containing regimen (88%), which included triple therapy (54%)



8.4% reduction
95% CI (1.1, 15.2)
P=0.02

NNT=7*

One additional moderate/severe exacerbation is prevented for every 7 patients treated with Relvar® compared with usual care over 12 months

ITT patients with ≥1 exacerbation in the year prior to randomisation.

*Analysis based on NNT = 6.25 (CI: 3.47, 46.99)

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

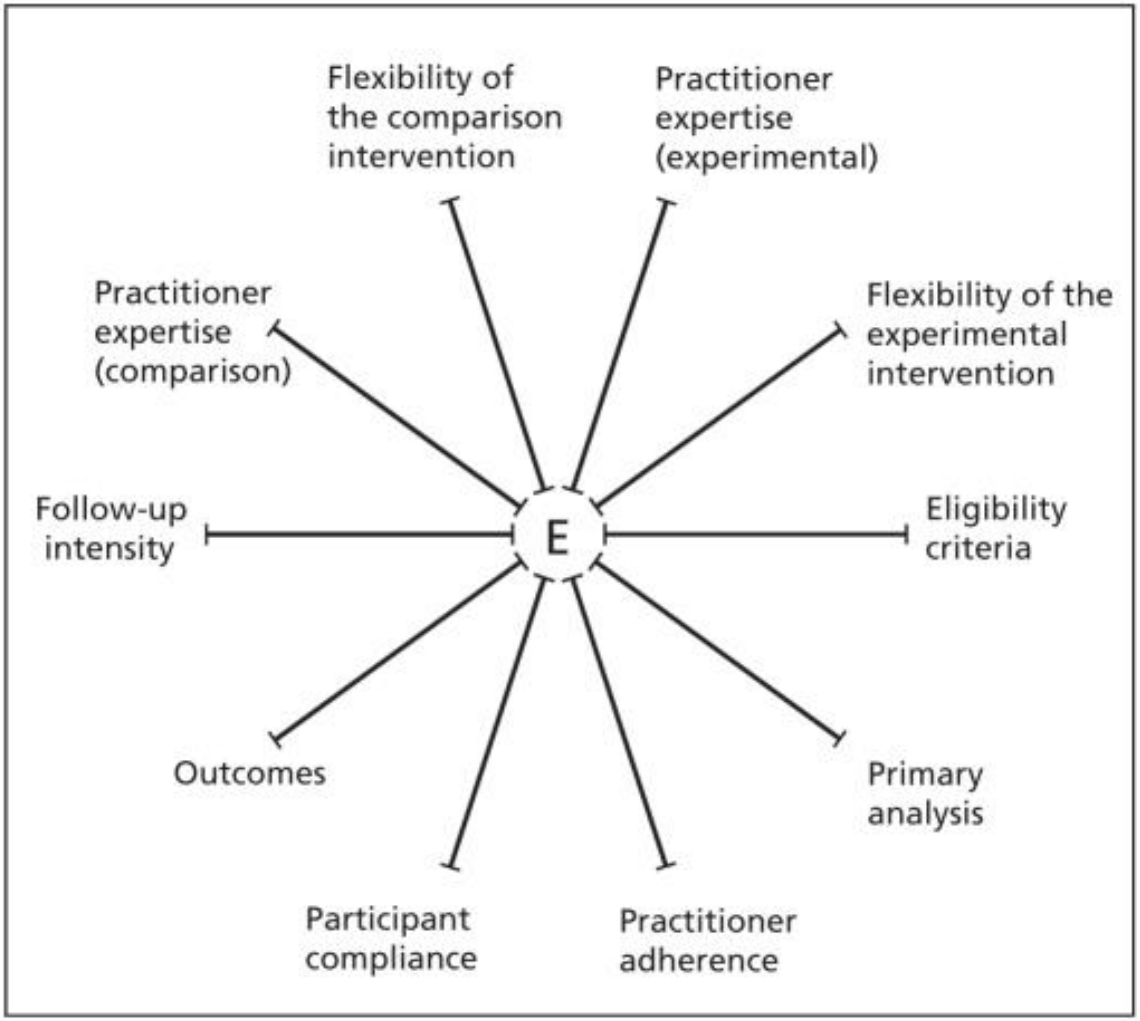
Salford Lung Study COPD: Primary Manuscript

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*

Published on September 4, 2016, at NEJM.org

Dimension of pragmatic trials

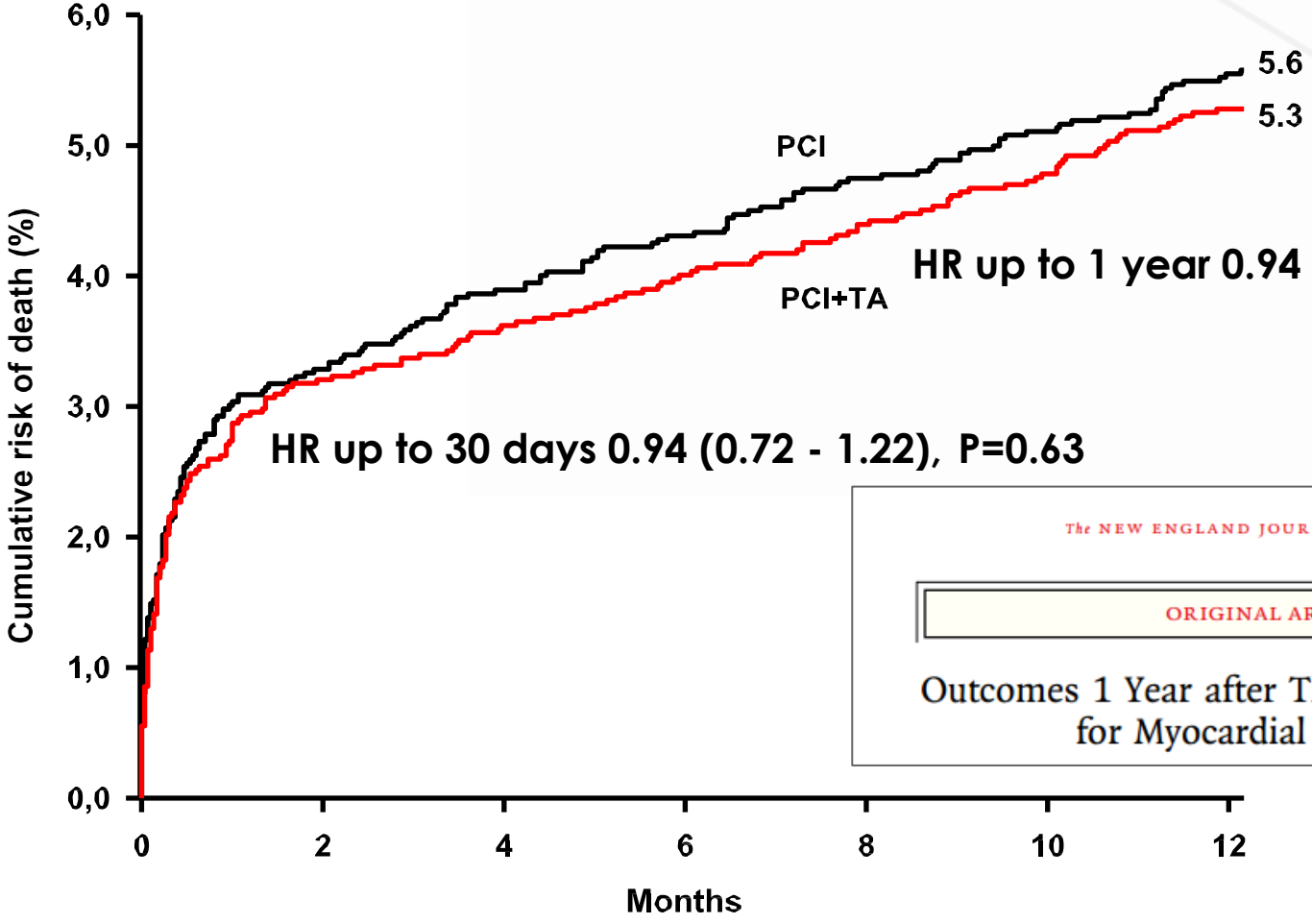


Thorpe et al. CMAJ 2009

TASTE

SWEDE HEART

All-cause mortality up to 1 year



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Outcomes 1 Year after Thrombus Aspiration for Myocardial Infarction

Farr The Farr Institute of Health Informatics Research

Lagerqvist B et al. N Engl J Med 2014; 371;12

Discussion - personal reflection

- Salford Lung Study important step forward as it utilised digital data sources
- But it was not 'simple' with large research staff overhead, intensive training of clinical staff and close patient monitoring
- Costly digital infrastructure but this can be reutilised
- Comparison of incident versus prevalent users

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