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The INVESTED Trial

Rationale and Implementation of a “pseudo” Pragmatic Randomized Clinical Effectiveness Trial

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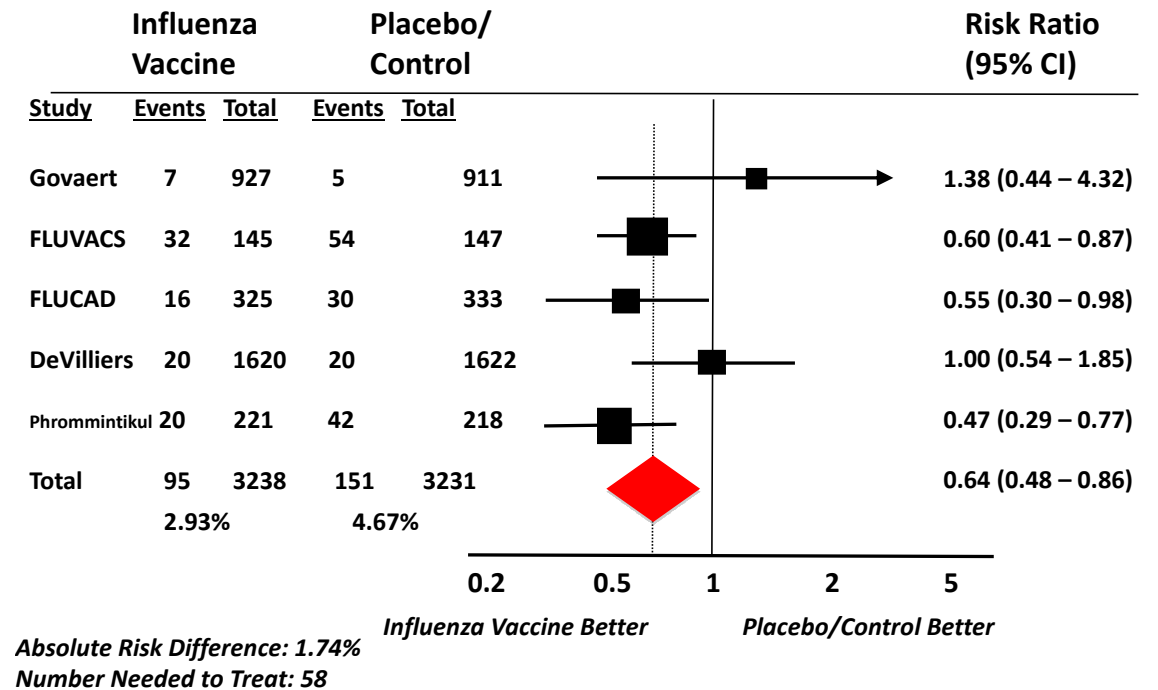
Boston, MA



Rationale for INVESTED

- ~ 36,000 influenza-associated deaths and 200,000 influenza-related excess hospitalizations during each influenza season
- Observational association between acute respiratory infections and cardiovascular events, including MIs and HF Hospitalizations
- Influenza vaccine reduces CV risk in a large meta-analysis of randomized trials
- Our own data suggested that high-risk CV patients are somewhat immunocompromised and that high dose influenza vaccine can overcome a deficient response to vaccine
- A 30,000 patient influenza vaccine trial comparing high to standard dose vaccine showed reduced influenza-like illness, yet high dose vaccine is currently approved for healthy older adults only; ACIP does not preferentially recommend one vaccine formulation over another
- The results of this trial have the potential to inform health care policy regarding optimal influenza vaccination for individuals with high risk cardiovascular disease

Influenza Vaccination Reduces CV Risk: A Meta-Analysis

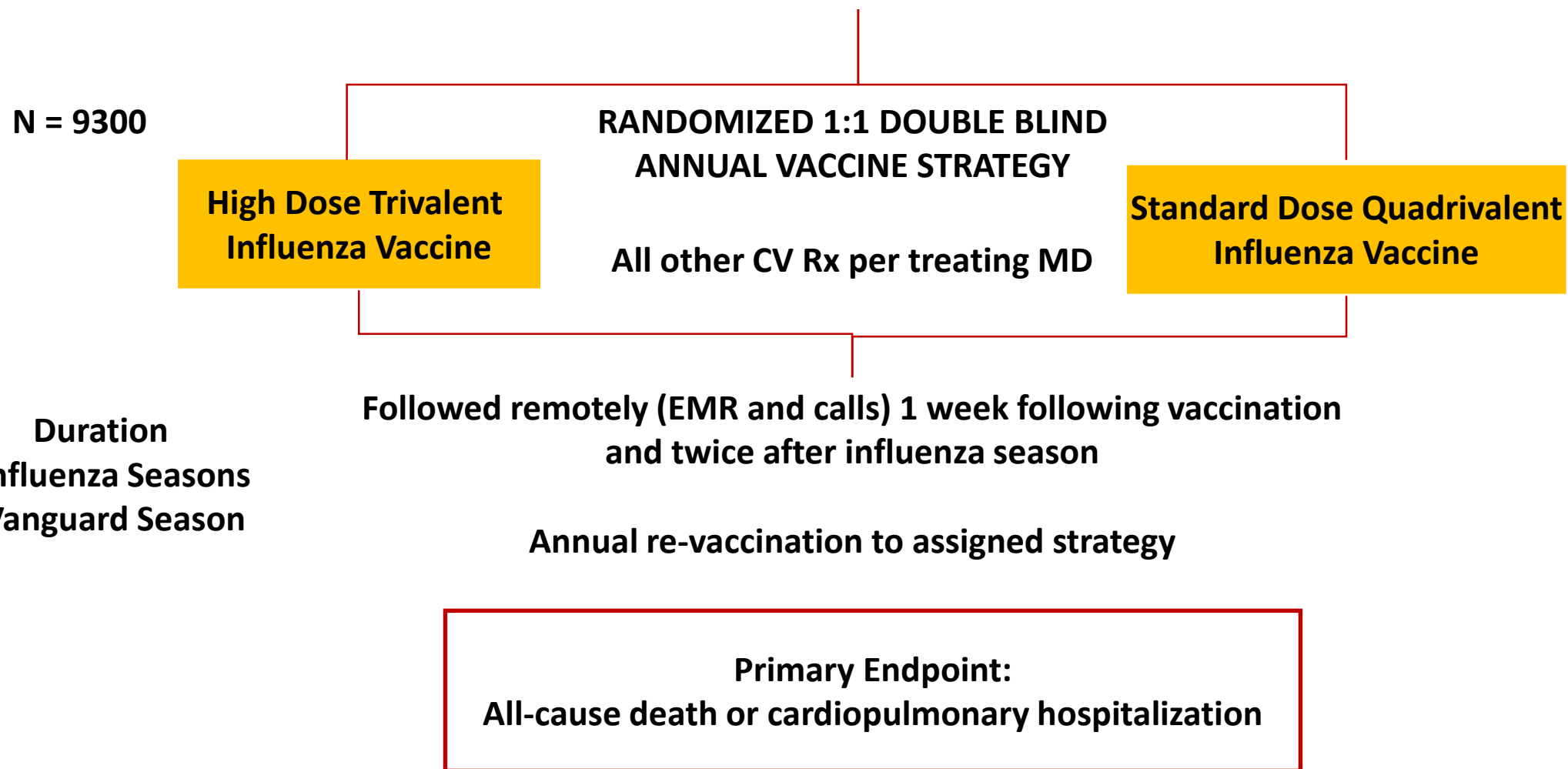


Udell JA, et al. JAMA 2013;310: 1711-1720.

INVESTED Trial Design

Broad Inclusion Criteria: Age > 18, Post-MI (1 yr) or HF Hospitalization (2 yrs), one additional risk factor (age > 65, diabetes, obesity, smoker, CKD, reduced LVEF)

Minimal Exclusions: Prior intolerance, pregnancy, vaccination this season



Pragmatic Elements in INVESTED

- Broad inclusion criteria with minimal exclusions
- Easy, annual administration: “A one shot deal”
- 100% adherence within season
- Well established low risk, low cost intervention
- IND exemption with substantially streamlined adverse event reporting needs
- Non-intrusive follow-up plan
- Central EHR based identification of eligible patients in VA Network
- Three year strategy to allow realistic seasonal variation in influenza virulence and protection
- Remote risk-based monitoring with “sampled” and “cause-based” eligibility verification
- Relatively simple web-based electronic data capture with “just enough” information required
- Simple broad primary endpoint
- Network strategy (Canada, VA, PCORnet)

Non-Pragmatic (traditional) elements in INVESTED

- Inclusion criteria require some degree of “human” assessment as reliance on DRGs for “heart failure” is limited
- Major reason for exclusion is “uncaptured” prior vaccination during season
- Identification of potential subjects can use EMR approaches in only selected locations (VA centrally) and some individual sites
- SC felt strong need for blinding given potential bias for safety endpoints and differential dropout over seasons
- EMR approaches to event ascertainment not feasible at all sites and felt to be susceptible to unacceptable “leakage”
- All events centrally “classified” to allow for further categorization of hospitalizations

Could INVESTED have been performed as a EHR-Based Trial?

Identification of Patients

- In some but not all networks maybe
- Most IRBs don't allow study personnel to directly approach patients and requirement to go through PCPs can be onerous
- Eligibility list to enrolled patient ratio ~ 10:1 to 50:1
- Despite simplicity of design and low-risk nature, patients in this demographic still require human discussion

Ascertainment of Events

- Many sites currently don't have the capability to perform EHR ascertainment
- Discussions with networks suggested that EHR approaches to event ascertainment would be incomplete and subject to substantial "leakage"
- Only the VA system had a comprehensive enough EHR to perform EHR-based ascertainment

INVESTED as an opportunity to test more pragmatic approaches

- In VA system, EHR is being used centrally for patient identification with sites being provided lists of potentially eligible patients with clinic visit schedules
- Several grants under review to compare EHR-only based ascertainment of events with traditional approach in same patients

SMART IRB: Trials and Tribulations

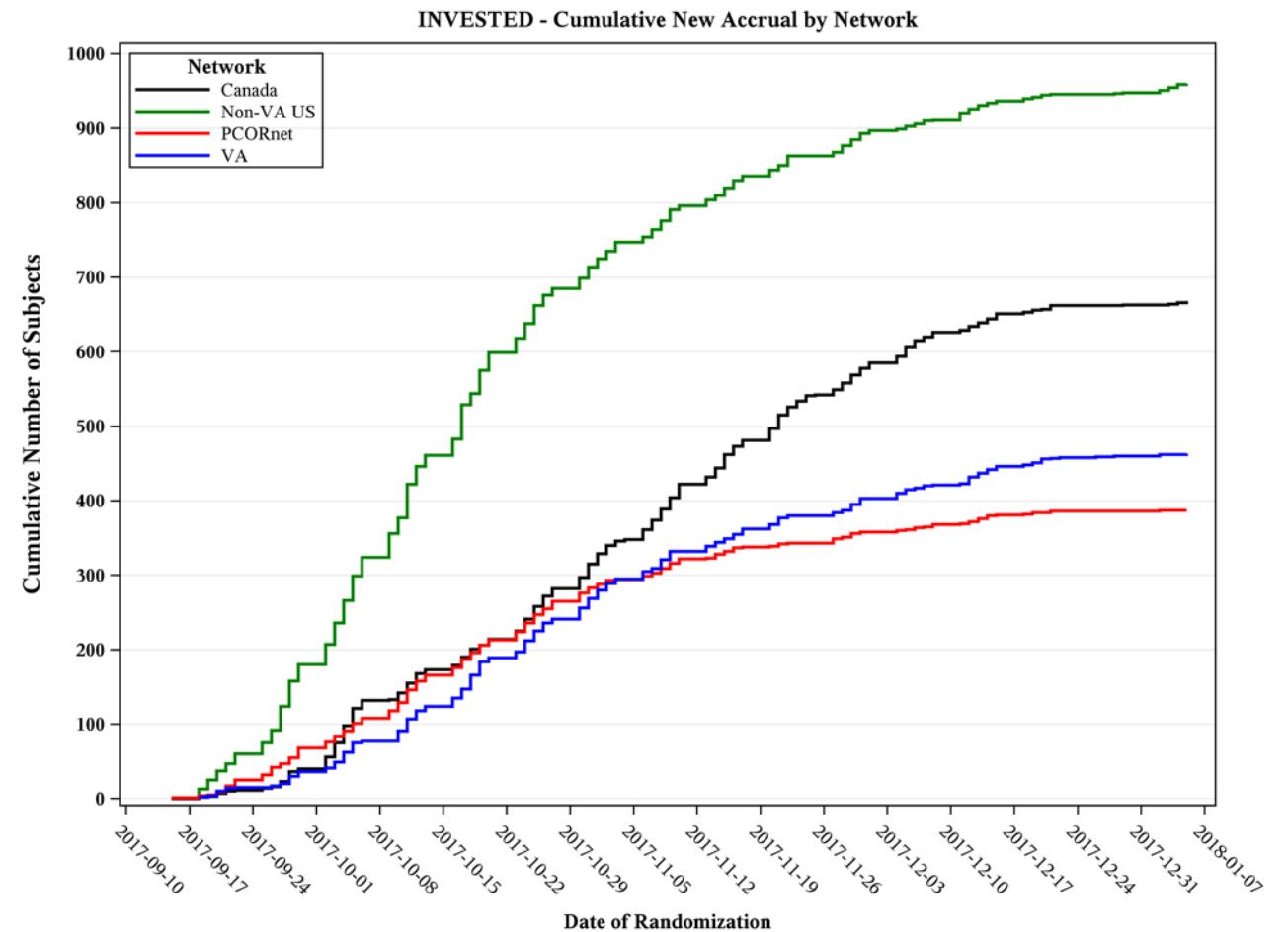
The Theory

- NIH policy: sites participating in multi-center NIH-funded studies involving human subjects research will use a single Institutional Review Board (sIRB) for grants received on or after Jan 25, 2018
- SMART IRB (formerly IRBrelly) developed from a CTSA IRB reliance project funded by National Center for Advancing Translational Sciences (NCATS)
- IRB Master Reliance agreement developed for INVESTED, with UW-Madison serving as the IRB of record
- Out of 17 sites (from Midwest consortium of CTSA and PCORnet) initially approached, 15 agreed to cede review

The Reality

- Ceding process has not been straightforward, with individual IRBs insisting on retaining much of their “independence”
- Shift the burden and cost of IRB submission and administration from sites to the trial requiring additional trial resources
- Even administrative changes (adding a study coordinator at a site, onboarding new sites) onerous and costly
- Most felt that inclusion of SMART IRB doubled the up-front work required
- Continuing review has been smooth

INVESTED has 180 sites and has enrolled 3000+ patients in vanguard and one full season



Final Musings of a Clinical Trialist about “Pragmatic” Trials

- Enormous need to make our trials simpler, cheaper, more efficient
- “Pragmatic” means something different to everyone you ask and there is no formal definition of a pragmatic trial. Often practical in implementation, few visits, less patient contact and burden, non-intrusive means of ascertaining events (EMR, death index, administrative records etc.)
- Fewer “checks and balances” at every point
- Lack of monitoring and eligibility verification increases risk for inclusion of inappropriate patients and even overt fraud (and not just overseas!)
- INVESTED has an IND exemption but regulatory requirement for adverse event reporting, and safety data collection can be onerous making pragmatic trials more appealing for Phase IV than pivotal registration trials
- The less information we collect the fewer questions we can ultimately answer
- The noisier the data, the larger the trials need to be – a large simple trial may not always be better (or easier) than a smaller more carefully done trial
- We need, as a community, to explore how we can incorporate more pragmatic elements into our trials while retaining the ability to answer the questions we need to answer



Rachael Florence, PhD

NESTcc Executive Director

May 16, 2018



Successes in Device Pragmatic Trials



Challenges in Device Pragmatic Trials

KEY DIFFERENCES BETWEEN DRUGS VS. DEVICES

Regulatory and clinical context for devices is different from drugs with implications for feasibility of pragmatic trials.



MEDICATIONS

- Approval: At least two, very large (pivotal) RCT
- Adverse Events required in approval RCT
- Massive Post-Approval safety studies required
- National Drug Code (NDC) is universal in EHR and claims since 1972, permits surveillance of AE



MEDICAL DEVICES

- Approval pathways: PMA and 510K
- Single (small) study required for PMA
- Variable requirements for Post Approval Studies (PMA only)
- Universal device identifier (UDI) implemented in 2015
- Impact of “Learning Curve” on device performance
- Current MDR system in need of overhaul (lack of denominator)

Source: Fred Resnic, Leahy Clinic; Faris&Shuren, NEJM 2017



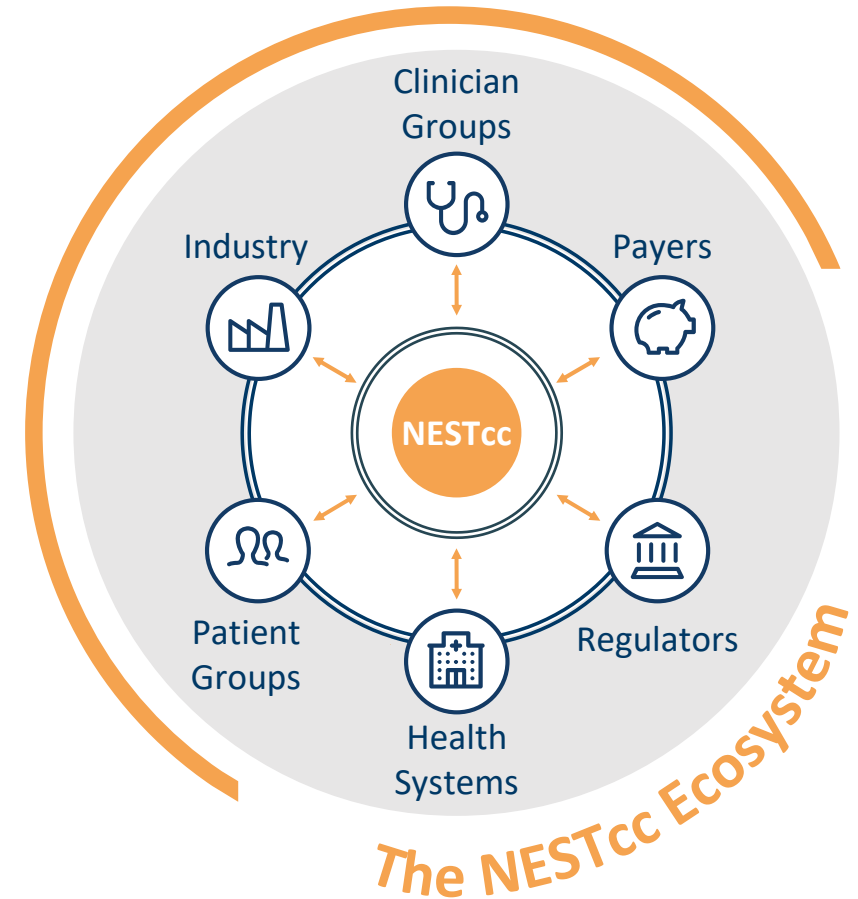
NESTcc'S ROLE IN THE ECOSYSTEM

NESTcc Mission Statement

To accelerate the development and translation of new and safe health technologies, leveraging Real-World Evidence (RWE), and innovative research.

History of NESTcc

- 2015 NEST envisioned as a **voluntary data network** of collaborators by Planning Board
- 2016 FDA awarded grant for NESTcc to **Medical Device Innovation Consortium (MDIC)**
- 2017 **Executive Director** of NESTcc named
- 2017 NESTcc **Governing Committee** selected
- 2017 NESTcc **Strategic and Operational Plan** developed



- Establish initial **NESTcc Data Network** with 11 collaborators
- Implement test-cases** with manufacturers and NESTcc network collaborators
- Work with stakeholders to **establish data and methods standards, and operating processes**
- Identify gaps in data infrastructure** to support robust medical device studies and find solutions
- Expand NESTcc Data Network**



DEVELOP NESTcc'S ROLE: BUILDING A DATA NETWORK

NESTcc has established relationships with network collaborators to advance evaluation and use of high-quality RWD from various sources.

TO DATE, MEMORANDA OF UNDERSTANDING (MOUs) HAVE BEEN SIGNED WITH 11 COLLABORATORS:



DEVELOP NESTcc'S ROLE: LAUNCHING TEST-CASES

To better understand the capabilities of its Data Network, NESTcc is facilitating collaboration between network collaborators and test-case manufacturers, whose de-identified concepts are summarized below:

TOTAL-PRODUCT LIFE CYCLE (TPLC) ALIGNMENT	PRODUCT(S)	AREA
Pre-Market Submission	Topical Skin Adhesive	Dermatology
Label Expansion	Devices used in Rx of Atrial Fibrillation	Cardiovascular
Label Expansion	Stent graft component product	Vascular
Move from General to Specific Indication	Device used in surgery	Surgery
Post-market Surveillance	Knee replacement	Orthopedics
Post-market Surveillance	Various Devices	Orthopedics
Patient Management Clinical Guidelines	Anti-coagulation dosage following mechanical heart valve (MHV) replacement	Cardiovascular

Note: No Pragmatic Trial Design



THE ROLE OF REGISTRIES IN THE DEVICE ECOSYSTEM

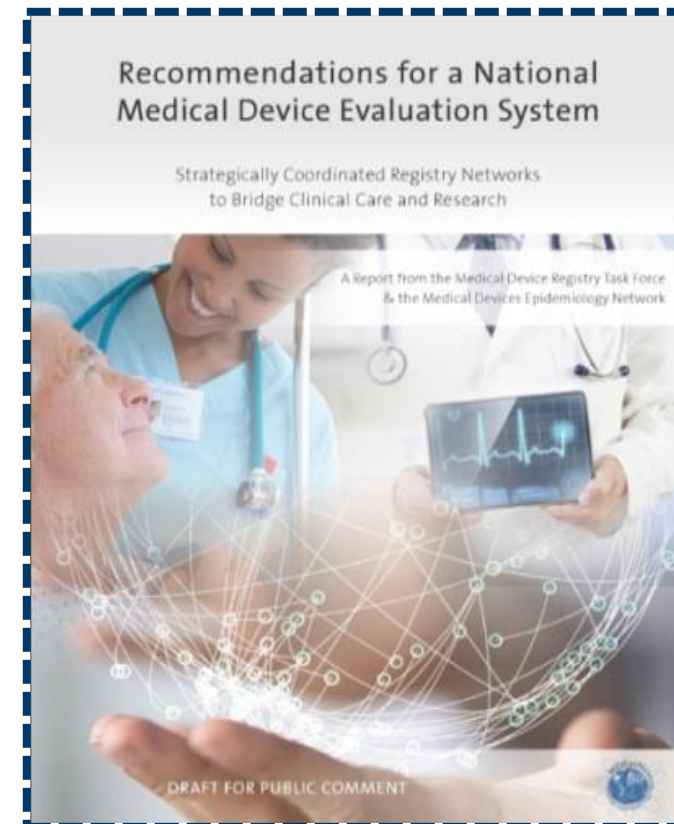
Registries have historically played an important role in the regulatory space for medical devices.

Examples of high-quality registries:

- Transcatheter Valve Therapy Registry (TVT-R), American College of Cardiology and the Society of Thoracic Surgeons
- National Cardiovascular Disease Registries, American College of Cardiology
- Vascular Quality Initiative (VQI), Society of Vascular Surgeons (SVS)
- International Consortium of Orthopedic Registries (ICOR)



New developments in **Coordinated Registries Networks** linking existing registries with claims data, EHRs have started, including international registries



Source: MDTRF Task Force Report, August 2015



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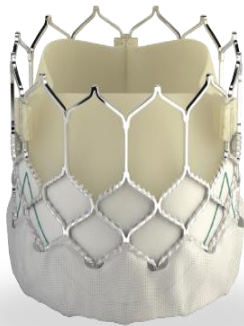


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USE OF REGISTRIES FOR EVIDENCE GENERATION

Use of RWD/RWE in device registries has already demonstrated success.

- ✓ Provide high-quality, fit-for-purpose data
- ✓ Support observational and randomized interventions at lower costs (e.g., TASTE trial)
- ✓ Deploy algorithms for automated safety surveillance (e.g., DELTA study)



Source: TASTE Trial, Fröbert, NEJM 2013; DELTA, Resnic NEJM 2017

Registries are currently the main source of RWE decisions by FDA-CDRH:

National Registries in CDRH “RWE” decisions (2017):

- 15 Post-Approval Studies
- 1 Continued Access Study
- 8 Pre-Market Studies (including labeling expansion)
- 7 Post-Market Surveillance Studies (522)

International Registries are being leveraged for:

- 3 Post-Approval Studies

Source: FDA-CDRH Staff

SAFE-STEMI

OVERVIEW

Objective An International CRN-based Prospective Randomized IDE Study of Labelling for Diagnostic and Therapeutic Devices Used in Seniors Suffering Heart Attack

Study Design

- Randomized study using the ACC-NCDR Cath-PCI Registry and Medicare Claims Data
- SAFE-STEMI for Seniors entails a three year prospective registry study of STEMI patients over 64 undergoing primary PCI via the radial artery access randomized to either infarct artery only or complete revascularization.

Participants

Principal Investigators:
David F. Kong (DCRI),
Roseann White (DCRI),
Mitchell W. Krucoff (DCRI)

IMPACT

Project Aims

- Assess major bleeding comparing the radial vs. femoral artery access
- Assess one-year outcome of infarct-target vessel failure and major adverse cardiovascular events (MACE) comparing a drug-eluting vs. bare metal stent
- Assess major adverse cardiovascular events (MACE) comparing infarct-artery PCI only vs. complete revascularization

Intended Impact for NESTcc

- **NESTcc Use-Case:** Pre-market / Investigational device exemption (IDE) study for DES and IFR devices
- **Significance:** Use of RWD in an IDE study to increase efficiency and lower cost of traditional clinical trial

Device-Specific Challenges

- ✗ High cost of developing and maintaining registries
- ✗ Registries cannot be developed for all devices and all disease areas
- ✗ Limited availability of Unique Device Identifier in EHRs or claims
- ✗ Impact of operator characteristics and learning curve

Ecosystem-Wide Challenges

- ✗ Data quality issues and lack of standard data capture
- ✗ Methods issues
- ✗ Data linkage issues
- ✗ Administrative issues
- ✗ Privacy and security concerns

WHAT DOES THE FUTURE HOLD?

Pragmatic trials using electronic health data for e-identification, e-consent, e-randomization and e-follow-up should be possible in the device space.



Embedded RCTs in registries are possible but not the norm



Registries are:

- not available for all devices
- do not have all relevant outcomes (including LT F/U)
- expensive and use a parallel infrastructure
- may have complex governance



In the device space, we need proof-of-concept for **pragmatic trials** making use of **electronic health data** generated in the course of care



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Pragmatic Solutions to New Challenges



Kourtney Davis, PhD MSPH
Head, Real World Data and Analytics
GSK



Objectives

- **What is the Salford Lung Study and why a pRCT?**
- **What major hurdles did the team face?**
- **Solutions proposed**
- **Lessons learned and new questions raised**



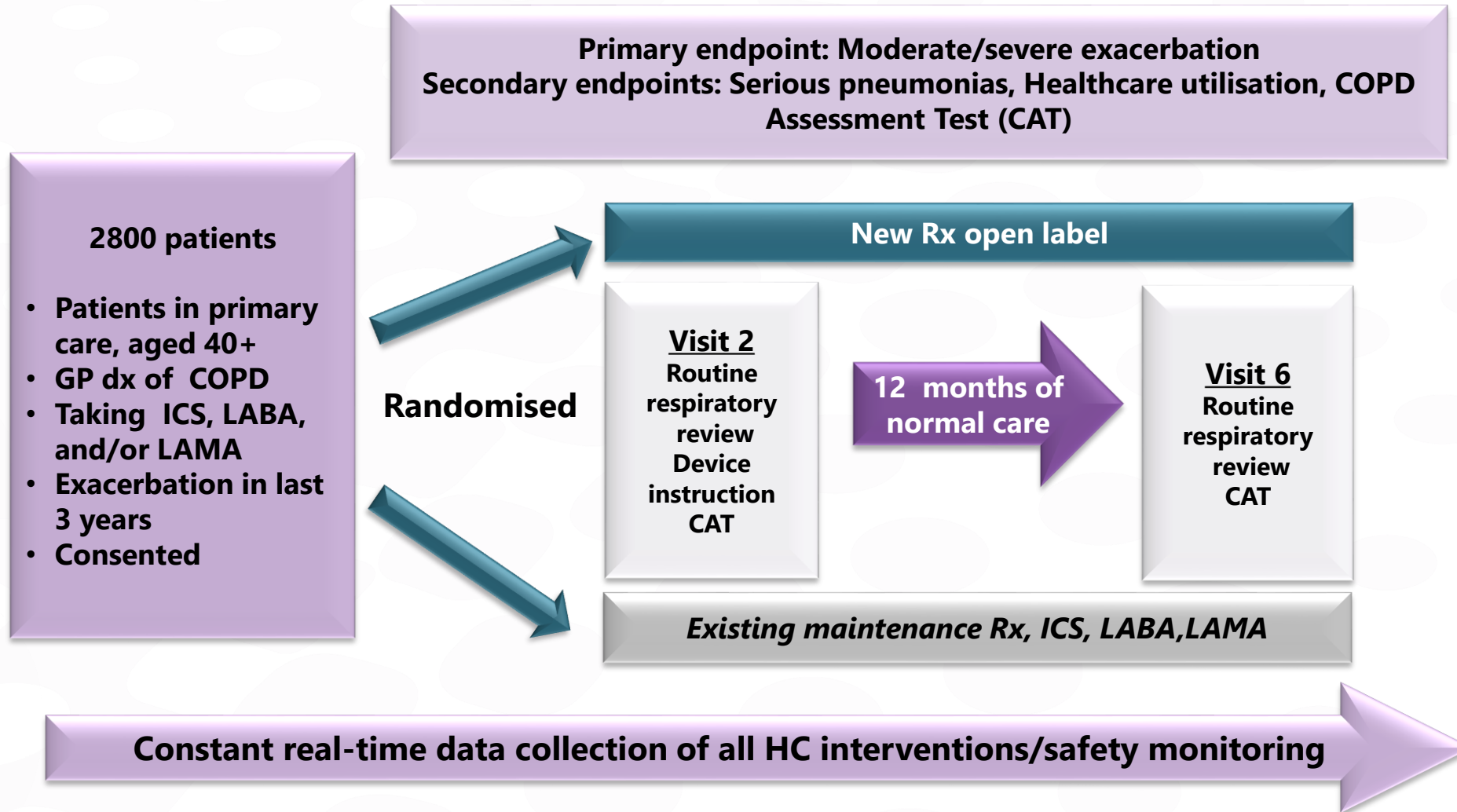
Salford Lung Study: Research question

- Evaluate benefit:risk profile of new combination ICS/LABA (one inhalation daily) versus usual care in a typical environment for prescribers and COPD patients using a pre-license medicine
- Pragmatic design which can address limitations of standard RCT
 - Reflect medicine taking behaviors and care seeking in clinical practice
- Provide relevant information for clinicians, healthcare providers, payers and patients

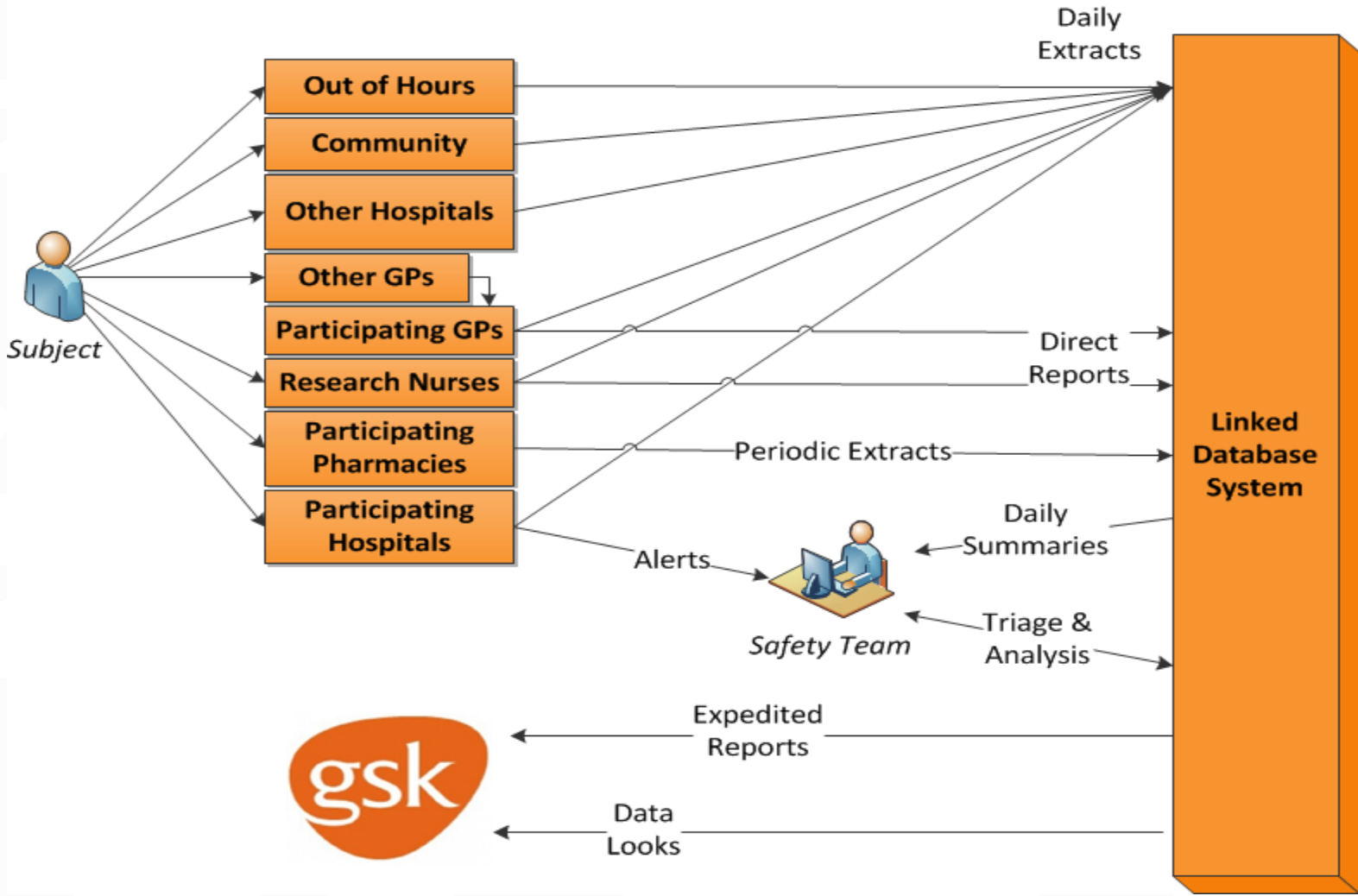
Challenges of EMR-enabled RCT in Phase III

- Time and clinician workload
- Monitoring and safety reporting with minimal impact to #1
- Ethical and regulatory approval
- Fixed population of EMR systems and pharmacy involvement
 - less flexibility to add additional sites/ patients
 - Generalizability
- Endpoints may not be routinely or systematically collected
 - Trade-offs between routine care and meaningful, differentiating endpoint
- Impact on “usual care” (potential Hawthorne effect)

SLS Study outline for COPD



How the data were gathered



Challenge #1: Recruitment

- Where to find extra subjects to reach when all eligible subjects in Salford were not sufficient?
 - Willing GP investigators?
 - Willing pharmacy partners?
 - Secondary Care Facilities able to provide robust safety monitoring?
 - Impact of workload for study staff and partners
 - Increasing complexity of project
- Solution found by **extending study to parts of Trafford and South Manchester**
- University Hospital South Manchester able to provide robust inpatient monitoring in line with Salford Royal

How to encourage GPs and patients new to research to participate?

- GPs
 - Grassroots approach
 - Local clinical research network
 - Enthusiastic local clinicians
 - Ensure excellent set-up, training and ongoing support of sites
- Patients
 - Letter to every eligible patient directly from their own GP
 - Follow-up telephone calls
 - Local advertising
 - Detailed F2F explanation of study by staff to allow informed consent

Eccles: working together against COPD

Recruiting here



If you have COPD, are over 40 years old and live in Eccles

You could take part in research, here in Eccles, into how this condition is treated



REGISTER TODAY!
 Speak to your GP or practice nurse
 Call 0951 245 9884
 Text Study to 83366
(Texts will be charged at your standard message rates)

Please note:
 Please note the Salford Lung Study is only available to patients registered at participating GP sites in Salford, Trafford, Stockport or South Manchester.

The Salford Lung Study
 Investigating treatment of chronic obstructive pulmonary disease and asthma in Salford

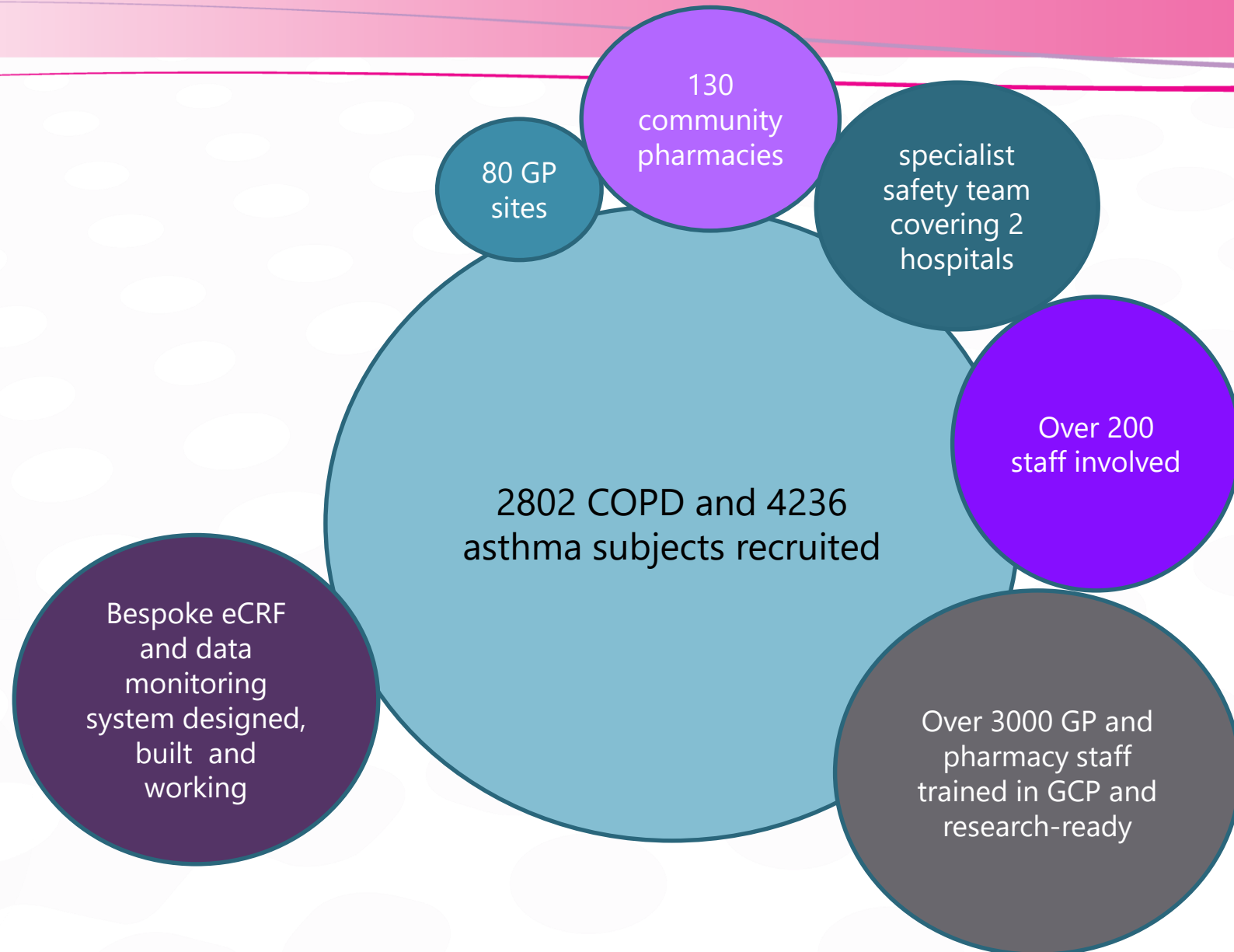
If you have COPD
 Recruitment is now closed

If you have asthma
 Please Click Here →

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Scale of the Project



SLS COPD Headline Results

- Relvar® Ellipta® 100/25mcg (fluticasone furoate 'FF'/vilanterol 'VI' or 'FF/VI') achieved a **superior reduction in exacerbations versus usual care**, in patients with COPD.
- For the primary effectiveness analysis, in patients treated with FF/VI 100/25mcg there was a **statistically significant reduction of 8.41% (CI 1.12,15.17)** in the rate of moderate or severe exacerbations compared with those receiving usual care (p=0.025).
- Within the intent-to-treat (ITT) population, the **incidence of serious adverse events (SAE) was similar between the groups (29% FF/VI, 27% usual care)**.
 - For **pneumonia**, an SAE of special interest, FF/VI demonstrated **non-inferiority** versus usual care (**7% FF/VI versus 6% usual care**).

Addressing interpretation challenge: Observational companion study

- **CHES: CPRD-COPD Hawthorne Effect Study in Salford:** A UK cohort study to characterise usual care patients enrolled in the Salford Lung Study and evaluate a potential Hawthorne effect using the Clinical Practice Research Database (CPRD) eMR
- CHES designed to answer 2 critical questions:
 - To what extent do subjects in SLS usual care arm represent the general population of COPD subjects eligible for RELVAR in England and in demographically similar areas?
 - To what extent have we influenced usual care (UC) in Salford by conducting SLS?
- Value of CHES evidence
 - Provides evidence regarding the external validity of SLS
 - Provides possible explanations for results; educates regulatory and scientific community on strengths/limitations of 'real world' studies based on electronic medical records.

Summary: SLS case study

- Increased use and quality of EHR can enable pragmatic studies
 - SLS enabled by data sharing agreements, simplified operational processes, QOF, validated data linkage and flows, and strong partnerships
- Trials and observational designs both provide useful information
 - Viewing both in light of strengths and limitations is critical
- To perform pRCT at scale requires increased linkages, availability and quality of eHR married with advanced methods improve design and conduct; this also benefits conduct of observational studies
- Better transparency, use and integration of a range of different types of evidence can help inform the benefit-risk profile throughout a medicine's lifecycle
 - Better evidence informs decision making by industry, regulators, HCPs, and patients

Challenges and Lessons Learned

- Research naive investigators need a lot of ongoing training and support
- EHR data quality varies
 - start early to evaluate; validation studies and augmented collection might be necessary for key variables (explore mobile solutions)
- Allowing “usual care” can create unforeseen challenges
- EHRs with alerts can provide robust safety monitoring
- Ordinary patients may be enthusiastic about taking part
- Good project management support is critical
- Flexibility and creativity are key skills
- Interpretation of final results may require more context

**Thanks to all the SLS study team, investigators,
pharmacy staff and patients!**

