Insights from the large-scale evidence generation and evaluation across a network of databases for type 2 diabetes mellitus (LEGEND-T2DM)

Marc A Suchard, MD, PhD
on behalf of the LEGEND investigators

VA Informatics and Computing Infrastructure (VINCI)
US Department of Veterans Affairs and UCLA

2023 OHDSI Global Symposium
20 October 2023
Diabetes treatment and some open questions

- Are patients with cardiovascular disease (CVD) preferentially starting GLP1RA/SGLT2Is?
- Are GLP1RA/SGLT2Is more effective (or safer) than DPP4I/SUs?

Type 2 diabetes mellitus (T2DM) → Metformin → 1st line agent

- Elevated blood sugar
- Blood sugar still elevated

2nd line agents:
- DPP4 inhibitors (DPP4I)
- Sulfonylureas (SU)
- GLP-1 receptor agonists (GLP1RA)
- SGLT2 inhibitors (SGLT2I)

Cardiovascular outcome RCTs:
- Neutral effect
- Not evaluated
- Reduced cardiovascular risk
  - MI, Death
  - MI, Death, Heart failure

9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023


Disclosure information for each author is available at https://doi.org/10.2337/dc23-SDIS.

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Reduced cardiovascular risk

Downloaded from http://diabetesjournals.org/care/article-pdf/46/Supplement_1/S140/693669/dc23s009.pdf by guest on 02 October 2023
LEGEND philosophy

LEGEND is a **guiding principle**-driven enterprise to deliver verified and open evidence at scale

- **VERIFIED**
  - Employ only previously validated methods
  - Advanced, systematic methods to control bias
  - Extensive diagnostics and large-scale controls
  - Test many hypotheses to assess operating characteristics
  - Study many databases, locations, practice types

- **OPEN**
  - Fully pre-specified public protocol
  - All software open-source with public parameters
  - All diagnostics made public with results initially blinded
  - All results made publicly available
  - Results paired with detailed attestation and characterization of populations studied

- rich, rigorous, and reliable
Second-line initiators across a global network

Inclusion: adult diabetics, + metformin, − other glycemic agents, ± CVD

- US National Databases
  - IBM MarketScan® Commercial Claim and Encounters Data (CCAE)
  - IBM Health MarketScan® Multistate Medicaid Database (Medicaid)
  - IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database (Medicare)
  - Optum Clinformatics Extended Data Mart - Date of Death (Optum CEDM)
  - Optum® de-identified Electronic Health Record Dataset (Optum EHR)
  - US Open Claims

- US Health System Databases
  - Columbia University Irving Medical Center
  - Johns Hopkins Medicine
  - Stanford Medicine
  - Department of Veterans Affairs Healthcare System

- Australia Longitudinal Patient Database (Australia)
- Germany Disease Analyser (Germany)
- France Longitudinal Patient Database (France)
- HIC, University of Dundee (Scotland)
- UK-IQVIA Medical Research Data (UK)
- Information System for Research in Primary Care (Spain)
- Hong Kong Hospital Authority (Hong Kong)
- Taipei Medical University Clinical Research Database (Taiwan)
- Yinzhou Health Commission (China)
- Optum© de-identified Electronic Health Record Dataset (Optum EHR)

- 19 administrative claims and EHR data partners around the world
Serial cross-sectional initiation (2011-2021)

Large variation in use of SGLT2I/GLP1RAs across CVD populations (less surprising)

Uptake is lower in US relative to other country sources, particularly for CVD patients (more surprising)

Leading ECRs:
- Lovedeep Dhingra
- Arya Aminorroaya
Risk of major cardiovascular events (MACE)

Via systematic best-practices:

- New-user cohort design (emulate target trial)
- LSPS adjustment (measured, unmeasured confounding)
- 100 negative controls (empirical calibration)
- Rigorous diagnostics (improved reliability)

- SGLT2I \approx GLP1RA (moderately unexpected)
- GLP1RA > DPP4I > SU (RWE fills in for missing RCTs)
LEGEND-T2DM is a rich, open resource

32 outcomes: CV, safety, patient-centered (PC)

Multiple populations: gender, age, race, CVD, renal disease

Leading ECR (first PC manuscript):
- Carlen Reyes (SIDIAP)

Comparative GI symptoms: GLP1RAs > others (but no ↑ acute pancreatitis)
Thyroid tumor relative risk under multiple sensitivity analyses

<table>
<thead>
<tr>
<th></th>
<th>Calibrated HR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP1RA vs SGLT2I</td>
<td></td>
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</tr>
<tr>
<td>PS matching on-treatment</td>
<td>0.83 (0.57 – 1.27)</td>
<td>0.33</td>
</tr>
<tr>
<td>PS stratification on-treatment</td>
<td>0.88 (0.75 – 1.03)</td>
<td>0.13</td>
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<tr>
<td>PS matching ITT</td>
<td>0.89 (0.74 – 1.07)</td>
<td>0.22</td>
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<tr>
<td>PS stratification ITT</td>
<td>0.95 (0.85 – 1.06)</td>
<td>0.35</td>
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<tr>
<td>GLP1RA vs Sulfonylureas</td>
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<tr>
<td>PS matching on-treatment</td>
<td>0.95 (0.75 - 1.20)</td>
<td>0.68</td>
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<tr>
<td>PS stratification on-treatment</td>
<td>0.94 (0.73 - 1.21)</td>
<td>0.64</td>
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<tr>
<td>PS matching ITT</td>
<td>1.03 (0.87 - 1.23)</td>
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<td>PS stratification ITT</td>
<td>1.02 (0.84 - 1.24)</td>
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<td>GLP1RA vs DPP4I</td>
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<tr>
<td>PS matching on-treatment</td>
<td>0.78 (0.60 - 1.01)</td>
<td>0.06</td>
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<tr>
<td>PS stratification on-treatment</td>
<td>0.83 (0.67 - 1.03)</td>
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<td>PS matching ITT</td>
<td>0.92 (0.79 - 1.06)</td>
<td>0.24</td>
</tr>
<tr>
<td>PS stratification ITT</td>
<td>0.93 (0.83 - 1.04)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Case-control study (Bezin et al, Diabetes Care, 2023) alerts EMA to potential thyroid cancer / GLP1RA association

We delivered a short report to EMA’s Pharmacovigilance Risk Assessment Committee

Leading MCR:
- Daniel Morales (Dundee)
Emerging directions in LEGEND-T2DM

- Patients with renal disease
- Patients with heart failure
- Older adults
- Risk differences in women
- Ingredient (drug-level) comparisons

- Open opportunities for all interested parties ... and that means you!

Treatment guidelines vary across populations, but need RWE support and refinement

- ASCVD
  - Defined differently across CVTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

- Indicators of high risk
  - While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

- HF
  - Current or prior symptoms of HF with documented HFrEF or HFpEF

- CKD
  - eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

- CKD (on maximally tolerated dose of ACEi/ARB)
  - PREFERABLY SGLT2i with primary evidence of reducing CKD progression
  - Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation
  - GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

- If A1C above target
  - For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
  - TZD

- If additional cardiorenal risk reduction or glycemic lowering needed
Acknowledgments

Current legendary members: … and you? please join us!

Arya Aminorroaya, Faaizah Arshad, Clair Blacketer, Mary Bowring, Fan Bu, Michael Cook, Lovedeep Dhingra, David Dorr, Talita Duarte-Salles, Scott DuVall, Thomas Falconer, Tina French, Elizabeth Hanchrow, Scott Horban, George Hripcsak, Jason Hsu, Rohan Khera, Harlan Krumholz, Wallis Lau, Jing Li, Kelly Li, Yuntian Liu, Yuan Lu, Kenneth Man, Michael Matheny, Nestoras Mathioudakis, Michael McLemore, Evan Minty, Daniel Morales, Paul Nagy, Akihiko Nishimura, Anna Ostropolets, Thanh Phan, Andrea Pistillo, Jose Posada, Nicole Pratt, Patrick Ryan, Carlen Reyes, Joseph Ross, Martijn Schuemie, Sarah Seager, Nigam Shah, Katherine Simon, Marc Suchard Eric Wan, Jianxiao Yang, Can Yin, Seng Chan You, Jin Zhou

Funding:

- NIH K32 HL153775, R01 HL169954, R01 LM006910
- IPA agreement with the US Department of Veterans Affairs
Lessons Learned from OHDSI Network Studies

Sarah Seager, Marc Suchard, Cindy Cai, Seng Chan You, Anthony Sena
Intravitreal anti-VEGF and risk of kidney failure: A Sisyphus Challenge Study

Cindy X. Cai, MD, MS
The Jonathan and Marcia Javitt Rising Professor
Assistant Professor of Ophthalmology
Retina Division, The Wilmer Eye Institute
Johns Hopkins University School of Medicine

10/20/2023
Lessons Learned From Two Perspectives

A Clinician’s Perspective…

A Newbie’s Perspective…

Demystify the process of network studies: you can do it!
Background: anti-VEGF medications

- Systemic administration of anti-VEGF agents have known adverse kidney side effects
  - Acute kidney injury
  - Proteinuria
  - Hypertension
  - Vascular clotting events
  - Glomerular disease
  - Risk factors for: kidney failure (need for renal replacement therapy with dialysis or kidney transplant, aka end stage kidney disease or end stage renal disease)


Intravitreal Anti-VEGF and Systemic Absorption

<table>
<thead>
<tr>
<th>Drug</th>
<th>Size</th>
<th>Systemic Elimination (half-life)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab</td>
<td>48 kDa</td>
<td>2 hours</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>115 kDa</td>
<td>5-6 days</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>149 kDa</td>
<td>20 days</td>
</tr>
</tbody>
</table>

Detectable/elevated serum drug levels
Decreased plasma concentrations of free-VEGF

Bevacizumab > aflibercept >> ranibizumab

**Question**: Is there evidence for preferentially choosing ranibizumab to lower the risk of kidney failure?

**Hypothesis**: in pairwise comparisons, lower risk of kidney failure in patients with blinding diseases who are exposed to ranibizumab
<table>
<thead>
<tr>
<th>Date</th>
<th>Times</th>
<th>Topic</th>
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<tbody>
<tr>
<td>Mar. 28</td>
<td>11 am / 7 pm ET</td>
<td>SOS Week 1 Tutorial: Initiating A Network Study</td>
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<tr>
<td>Apr. 4</td>
<td>11 am / 7 pm ET</td>
<td>SOS Week 2 Tutorial: Data Diagnostics</td>
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<tr>
<td>Apr. 11</td>
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<td>SOS Week 3 Tutorial: Phenotype Development</td>
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<td>Apr. 18</td>
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<td>SOS Week 4 Tutorial: Phenotype Evaluation</td>
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<td>Apr. 25</td>
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<td>SOS Week 5 Tutorial: Creating Analysis Specifications</td>
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<td>May 2</td>
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<td>SOS Week 6 Tutorial: Network Execution</td>
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<td>May 9</td>
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<td>SOS Week 7 Tutorial: Study Diagnostics</td>
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<td>May 16</td>
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<td>SOS Week 8 Tutorial: Evidence Synthesis</td>
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<td>May 23</td>
<td>11 am / 7 pm ET</td>
<td>SOS Week 9 Tutorial: Interpreting The Results</td>
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</tbody>
</table>
Anti-VEGF OHDSI Study: Process

**OHDSI Tools Used**

- ATLAS
- PheValuator
- Strategus execution pipeline to call Hades Packages (CohortGenerator, Characterization, Cohort Incidence, Cohort Method, PatientLevelPrediction)
- EvidenceSynthesis

**Data Sources**

<table>
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<td>IBM Health MarketScan Multi-State Medicaid Database (MDCD)</td>
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<tr>
<td>Optum(R) de-identified Electronic Health Record Dataset (OptumEHR)</td>
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<tr>
<td>Optum’s Clininformatics Extended Data Mart - Socio-economic Status (SES)</td>
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<tr>
<td>Japan Medical Data Center (JMDC)</td>
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<tr>
<td>Johns Hopkins Medical Enterprise (JHME)</td>
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<td>Department of Veterans Affairs (VA)</td>
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<td>PharMetrics Plus (NEU)</td>
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<tr>
<td>Columbia University Medical Center (CUMC)</td>
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<td>Stanford (STARR)</td>
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<tr>
<td>University of Southern California (USC)</td>
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</tbody>
</table>

- 12 databases:
  - 6 administrative claims and 6 EHR
- Collectively: 485 million patients
Anti-VEGF OHDSI Study: Results

• 6.1 million patients with blinding diseases
  – 240,247 anti-VEGF
    • 37,189 received ranibizumab
    • 39,447 aflibercept
    • 163,611 bevacizumab
  – 1209 kidney failure outcomes

• Standardized incidence proportion of kidney failure: 680 per 100,000 persons

• In all pairwise comparison, the hazard ratio was around 1.0

For retina colleagues: can choose between any of these 3 anti-VEGF medications for those at risk for kidney failure
Components of an OHDSI Network Study
From a Clinician / Newbie’s Perspective

1) Prep Work:
- Learn about the OMOP CDM
- Learn about the OHDSI tools
- Look at “classical” OHDSI Network studies

Frame the appropriate clinical question
Components of an OHDSI Network Study
From a Clinician / Newbie’s Perspective

2) Pre-Execution:
• Find core team (e.g., clinician, epidemiologist, biostatistician)
• Consult with OHDSI experts

• Phenotype development
• Cohort definitions
• Study design choices

Develop study protocol
Components of an OHDSI Network Study
From a Clinician / Newbie’s Perspective

3) Execution:
• Promote project across the OHDSI community: SOS Challenge
• Project management
  • Who is doing what
  • What needs to be done
  • Data partner restrictions

Perform study across the network
Components of an OHDSI Network Study
From a Clinician / Newbie’s Perspective

4) Wrap Up:
• Summarize/translate work
• Disseminate knowledge gained

Publish
Not for the faint of heart...but you can do it too!

Network studies can answer important clinical questions
Come to poster #306 to chat more
Save Our Sisyphus: Is fluoroquinolone use associated with the development of aortic aneurysms and aortic dissections?

An international distributed network study of 390 million patients with urinary tract infection

Seng Chan You

Dep. of Biomedical Systems Informatics, Yonsei University College of Medicine

Chief investigators: Jack Janetzki, Nicole Pratt – University of South Australia
Seng Chan You, Seonji Kim, Jung Ho Kim, Jung Ah Lee – Yonsei University

On Courtesy of Jack Janetzki
Background and context of study

- Fluoroquinolones are broad spectrum antibiotics

- Indicated for many infections including pneumonia, bone and joint infections, and **Urinary Tract Infections (UTIs)**

- Use is rising internationally [1]

- Generally well tolerated:
  - Common side effects: vomiting, diarrhoea, abdominal pain
  - Serious adverse events (e.g. tendon ruptures)

Timeline of warnings

- Warnings based on findings from epidemiologic studies
- Pharmacological mechanism not well understood

2008
- FDA black box warning (tendinitis and tendon rupture)

2016
- FDA enhanced label warnings (joint pain, tendon rupture, tendinitis, altered mental status)

2018
- FDA warning: increased risk of aortic aneurysms or dissections

2019-2023
- SOS Challenge March 2023
- 2022 Study from Taiwan shows no increased risk of AA/AD among 1.2M people with UTIs

Chen YY, Yang SF, Yeh HW, Yeh YT, Huang JF, Tsao SL, Yeh CB. Association Between Aortic Aneurysm and Aortic Dissection With Fluoroquinolones Use in Patients With Urinary Tract Infections: A Population-Based Cohort Study. J Am Heart Assoc. 2022 Mar 15;11(6):e023267. doi: 10.1161/JAHA.121.023267. PMID: 35229623
Background and context of study

- Prior warnings based on epidemiologic studies

- **2020 Meta-analysis** of 5 observational studies described quality of evidence as moderate
  - 2.8M patients
  - **Comparators:** non-users or users of other antibiotics
  - **Primary outcome:** first occurrence of aortic diseases
  - OR 2.23 (95%CI 1.80-2.77) (range 1.66-2.78)
  - Inconsistencies in study designs
    - Patient age ranges, follow-up duration
    - Potential for unmeasured confounding (by indication and surveillance bias)

## Prior observational studies

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<tbody>
<tr>
<td></td>
<td>Nested case-control</td>
<td>Nested cohort</td>
<td>Cohort study</td>
<td>Case-crossover</td>
<td>Nested case-control</td>
<td>Cohort study</td>
<td>Cohort study</td>
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<tr>
<td>Data sources</td>
<td>Taiwan NHIRD</td>
<td>Ontario Registered Persons, Drug Benefits database</td>
<td>Swedish National Prescribed Drug, Patient Register, Statistics Sweden</td>
<td>Taiwan NHIRD</td>
<td>Taiwan NHIRD</td>
<td>US (IBM MarketScan)</td>
<td>US (IBM MarketScan)</td>
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<tr>
<td>Indication</td>
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<td>Lower RTI, Genitourinary tract infection, Skin, soft tissue, or bone infections, Intra-abdominal infections, Mixed infections, Septicemia</td>
<td>Pneumonia, UTI</td>
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<tr>
<td>Active comparators</td>
<td></td>
<td>Amoxicillin</td>
<td></td>
<td>Amoxicillin-clavulanate, Ampicillin-sulbactam, Extended-spectrum cephalosporins</td>
<td>Azithromycin for pneumonia Trim and sulf for UTI Amoxicillin without indication</td>
<td>Amox-clav, Azithromycin, Cephalexin Clindamycin, Trim and sulf</td>
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<tr>
<td>Rationale for selecting comparators</td>
<td>Approved indications largely overlap with FQ</td>
<td>Based on the recommendations of the treatment guidelines in Taiwan</td>
<td>Clinically appropriate</td>
<td>Based on commonly prescribed antibiotics for similar indications</td>
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- Different study designs
- Predominantly single country studies
- Indication of FQ not specified or multiple indications of varying severity
- Unspecified or different active comparators
- Covariate Balance: mostly PS matching however no assessment of clinical equipoise
- Some studies addressed systematic error (usually single positive or negative control)
How do we build trust in real-world evidence?

- Open science system to build trust and confidence:

  **Sysiphus:** mythological figure; represents repetitive and laborious task of pushing a boulder uphill
  
  - Ensure that we have the right information
  - Stop pushing boulder up the hill when conditions aren't right; study doesn't pass diagnostics at any step
SOS challenge

- Pitched topic given:
  - ongoing regulatory monitoring
  - inconsistencies of prior methodologies
  - recent evidence of no association

- Over 9 weeks (with help of OHDSI team):
  - Planned and executed study

- Sharing results today
## Treatment, Comparator & Outcome

### Exposure Cohorts

**Indication: Urinary Tract Infection**
- Within 7 days prior
- No hospitalisation within 7 days prior; taking antibiotic in outpatient setting

#### Fluoroquinolones | Active comparators
---|---
All | 1. Trimethoprim +/- sulfamethoxazole (TMP)  
2. Cephalosporins (CPH)  
Chosen based on treatment guidelines and usual clinical care

### Outcomes

**Outcome of interest**
1. Aortic aneurysm or aortic dissection during 60 days  
2. Aortic aneurysm (+/- rupture)  
3. Aortic dissection  
4. TAR of 30, 90, 365 days

**Negative controls**
As recommended by CommonEvidenceModel (N~50)  
(Used to test for systematic bias)
Note on phenotyping of outcome cohorts

- See SOS Challenge tutorial by Evan Minty: defining outcome cohorts
- Prior studies inconsistent on definition of outcome
- ICD codes used interchangeably
- Requiring primary position diagnosis decreases observed counts that would contribute to estimate by 75% - carefully define inclusion criteria to ensure acceptable specificity of cases captured
Data partners

- 17 data partners across the OHDSI network
Results
Covariate balance: Optum EHR

- Can check **covariate balance** before and after PS matching by plotting **standardised mean differences**
  - Determine whether baseline characteristics are sufficiently similar between target and comparator cohorts
  - If SMD < 0.1 (10%) for all covariates = sufficient balance
  - All < 0.1 for all cohort comparisons in Optum EHR

**FQ v TMP-SMX**

**FQ v CEF**
Propensity score: Optum EHR

- Check **empirical equipoise** by observing **preference score distribution**:
  - Transformation of propensity score
  - Aims for overlap between 0.3 and 0.7
  - Higher overlap ensures that results will be generalisable
  - Good equipoise = large PS model could not discriminate between two treatments
Propensity score: Optum EHR

- Having achieved covariate balance between matched cohorts, is our result generalisable back to original population?
- Check empirical equipoise by observing preference score distribution:
  - Transformation of propensity score
  - Aims for overlap between 0.3 and 0.7
  - Higher overlap ensures that results will be generalisable
  - Good equipoise = large PS model could not discriminate between two treatments
Preference Score distributions across several databases
FQ v TMP

<table>
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<tr>
<th>US</th>
<th>Taiwan</th>
<th>Korea</th>
<th>Japan</th>
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<tr>
<td>CUMC</td>
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</table>

• Similar patterns across US databases
• PS distribution was almost identical

• Different pattern in Non-US databases
  (Less preference of TMP versus FQ)
Preference Score distributions across several databases
FQ v CPH

• Again similar patterns across US databases
• Lower PS overlap compared with FQ vs TMP

• Different patterns in Non-US databases
• Higher PS overlap in FQ vs CPH than FQ vs TMP
**Systematic error**

- **50 negative controls**
- Estimates below the line in graphs are statistically different from the true effect size
- Negative control outcomes should return estimate of 1 (95% CIs should contain 1 95% of the time)
  - In both cases 95% of negative control estimates had HR with CI that included 1 after empirical calibration, which indicates low systematic error
<table>
<thead>
<tr>
<th>Source</th>
<th>Matched(n)</th>
<th>FQ</th>
<th>TMP</th>
<th>HR (95% CI)</th>
<th>Max SDM</th>
<th>PS overlap</th>
<th>EASE</th>
<th>Diagnostics</th>
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<tr>
<td>CUMC(US)</td>
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<td>&lt;7.69</td>
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<td>0.45(0.08-2.58)</td>
<td>0.12</td>
<td>0.92</td>
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<td>IBM CCAE(US)</td>
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<td>0.58</td>
<td>0.53</td>
<td>1.07(0.70-1.63)</td>
<td>0.03</td>
<td>0.94</td>
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<td>IBM MDCD(US)</td>
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<td>2.87</td>
<td>2.09</td>
<td>1.36(0.84-2.19)</td>
<td>0.03</td>
<td>0.88</td>
<td>0.03</td>
<td>PASS</td>
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<td>Optum DOD(US)</td>
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<td>3.75</td>
<td>4.53</td>
<td>0.83(0.68-1.01)</td>
<td>0.05</td>
<td>0.93</td>
<td>0.04</td>
<td>PASS</td>
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<tr>
<td>Optum EHR(US)</td>
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<td>2.23</td>
<td>2.34</td>
<td>0.92(0.73-1.15)</td>
<td>0.05</td>
<td>0.91</td>
<td>0.06</td>
<td>PASS</td>
</tr>
<tr>
<td>PharMetrics(US)</td>
<td>358621</td>
<td>1.12</td>
<td>0.96</td>
<td>1.15(0.80-1.66)</td>
<td>0.03</td>
<td>0.93</td>
<td>0.03</td>
<td>PASS</td>
</tr>
<tr>
<td>VA(US)</td>
<td>108202</td>
<td>4.46</td>
<td>6.40</td>
<td>0.67(0.50-0.91)</td>
<td>0.04</td>
<td>0.86</td>
<td>0.05</td>
<td>PASS</td>
</tr>
<tr>
<td>TMUDB(TW)</td>
<td>2328</td>
<td>&lt;13.60</td>
<td>0.00</td>
<td>NA</td>
<td>NA- NA</td>
<td>0.14</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>AUSOM(KR)</td>
<td>61</td>
<td>0.00</td>
<td>0.00</td>
<td>NA</td>
<td>NA- NA</td>
<td>0.57</td>
<td>0.62</td>
<td>NA- FAIL</td>
</tr>
<tr>
<td>NHIS-NSC(KR)</td>
<td>442</td>
<td>0.00</td>
<td>0.00</td>
<td>NA</td>
<td>NA- NA</td>
<td>0.30</td>
<td>0.77</td>
<td>NA- FAIL</td>
</tr>
<tr>
<td>Yonsei(KR)</td>
<td>251</td>
<td>0.00</td>
<td>0.00</td>
<td>NA</td>
<td>NA- NA</td>
<td>0.33</td>
<td>0.40</td>
<td>NA- FAIL</td>
</tr>
<tr>
<td>JMDJ(JP)</td>
<td>722</td>
<td>0.00</td>
<td>0.00</td>
<td>NA</td>
<td>NA- NA</td>
<td>0.21</td>
<td>0.48</td>
<td>NA- FAIL</td>
</tr>
<tr>
<td>Japan Claims(JP)</td>
<td>1106</td>
<td>0.00</td>
<td>0.00</td>
<td>NA</td>
<td>NA- NA</td>
<td>0.20</td>
<td>0.36</td>
<td>NA- FAIL</td>
</tr>
<tr>
<td>LPD Australia(AU)</td>
<td>947</td>
<td>0.00</td>
<td>0.00</td>
<td>NA</td>
<td>NA- NA</td>
<td>0.16</td>
<td>0.55</td>
<td>NA- FAIL</td>
</tr>
</tbody>
</table>

Shades proportional to PS overlap
Summary:
• **Objective diagnostics** helped us to objectively interpret **reliability** and **validity** of evidence we produced
• At each point in SOS journey we were willing to **STOP** if failed diagnostics
• Meta-analysis only includes databases that **passed** diagnostic checks

- **Statistical power**: minimum detectable relative risk
- **Target-comparator similarity**: empirical equipoise
- **Between-person confounding**: covariate balance
- **Generalizability**: attrition fraction
- **Residual bias**: expected absolute systematic error (calibration)
## Meta-analysis: 60 day risk window, AA AD

### Comparator Meta-analysis

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Hazard Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP-SMX</td>
<td>0.92 (0.74-1.16)</td>
</tr>
<tr>
<td>CEF</td>
<td>1.02 (0.83-1.25)</td>
</tr>
</tbody>
</table>

### Hazard Ratio (95% CI)

#### TMP

<table>
<thead>
<tr>
<th>Source</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUMC</td>
<td>0.45 (0.08 - 2.58)</td>
</tr>
<tr>
<td>IBM MDCD</td>
<td>1.36 (0.84 - 2.19)</td>
</tr>
<tr>
<td>Optum DoD</td>
<td>0.83 (0.68 - 1.01)</td>
</tr>
<tr>
<td>Optum EHR</td>
<td>0.92 (0.73 - 1.15)</td>
</tr>
<tr>
<td>PharMetrics</td>
<td>1.15 (0.80 - 1.66)</td>
</tr>
<tr>
<td>VA-OMOP</td>
<td>0.67 (0.50 - 0.91)</td>
</tr>
<tr>
<td>Summary</td>
<td>0.92 (0.74 - 1.16)</td>
</tr>
</tbody>
</table>

#### CEF

<table>
<thead>
<tr>
<th>Source</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUMC</td>
<td>0.73 (0.22 - 2.42)</td>
</tr>
<tr>
<td>IBM MDCD</td>
<td>1.45 (0.96 - 2.21)</td>
</tr>
<tr>
<td>Optum DoD</td>
<td>0.90 (0.72 - 1.13)</td>
</tr>
<tr>
<td>Optum EHR</td>
<td>0.89 (0.73 - 1.09)</td>
</tr>
<tr>
<td>PharMetrics</td>
<td>1.29 (0.92 - 1.81)</td>
</tr>
<tr>
<td>TMUDB</td>
<td>0.77 (0.19 - 3.08)</td>
</tr>
<tr>
<td>VA-OMOP</td>
<td>0.86 (0.65 - 1.13)</td>
</tr>
<tr>
<td>Summary</td>
<td>1.02 (0.83 - 1.25)</td>
</tr>
</tbody>
</table>
Sensitivity analyses

![Graph showing sensitivity analyses with hazard ratio and confidence interval for different outcomes and time periods.]

- **Outcome:** TAR, 30d, 60d, 90d, 365d
- **Significance:** P<.05, Not significant

**OHDSI Symposium 2023**
Distribution of possible results for one single question
Distribution of possible results for one single question

JAMA IM  JACC

Our study:
AD risk at 90days
Distribution of possible results for one single question
Assessing strength of evidence for regulatory decision making in licensing: What proof do we need for observational studies of effectiveness?

Jim Slattery | Xavier Kurz

European Medicines Agency, Amsterdam, The Netherlands
Correspondence
Jim Slattery, European Medicines Agency, Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands. Email: jim.slattery@ema.europa.eu

Abstract
Before a medicine can be recommended for a marketing authorization research must be provided to regulators that convincingly supports the benefit-risk of the product in the claimed indication. The established criteria for such research are usually expressed in terms of evidence from randomized controlled trials (RCT). If studies in real-world data (RWD) are to be accepted as all or part of the package of evidence, it is necessary to understand the relationship between information from studies of RWD and that from RCTs. The aim of this review is to consider how the strength of such evidence can be quantified in a manner that relates to the decision-making process, what research is currently available to further this understanding and what additional information will be required.

Key points
- Availability of large quantities of observational data from clinical practice and health insurance systems has prompted suggestions of a potential role in supporting regulatory assessment of drug effectiveness.
- In order to protect public health, regulators must understand the reliability of the evidence underlying their decisions.
- Analyses of observational data are prone to biases that necessitate empirical evaluation.
- Large-scale experiments to measure errors in observational studies are already under way and will inform decisions on how the results of such studies can be used by regulators.
- Additional work will be required to ensure that the design of future studies conform to validated standards and that their conduct can be verified by regulators.
Summary of findings

- We observed considerable heterogeneity in the characteristics of patients and comparative preference of antibiotics across various databases.
- No consistent evidence was found to suggest an increased risk of aortic aneurysm or dissection following the use of fluoroquinolones in patients with UTI.
- Generalizability of our findings cannot be guaranteed to non-US countries.
Final remarks

- Our findings suggest that relying on a singular database without proper diagnostics can potentially lead to unreliable evidence.
- To provide globally generalizable evidence, there’s an urgent need for more analysis-ready standardized healthcare data worldwide.
Lessons learned applying the Strategus framework across the OHDSI Evidence Network

Anthony G. Sena
Johnson & Johnson
Department of Medical Informatics, Erasmus University
20 October 2023
What is the Strategus framework?

- **Characterization**
  - Cohort diagnostics
  - Cohort features
  - Incidence rates
  - Time-to-event
  - Dechallenge / rechallenge

- **Patient-level prediction**

- **Population-level effect estimation**
  - Comparative cohort
  - Self-controlled case-series (SCCS)
What is the Strategus framework?

Building up standardized analytics one lego at a time.
What is the Strategus framework?

• Strategus modules can be combined to accommodate various study designs.
Save our Sisyphus Challenge

• OHDSI Community came together for 9 weeks in March – May 2023 for the Save Our Sisyphus (SOS) Challenge

• Educated the OHDSI community on the process of leading or participating in an OHDSI network study
Save our Sisyphus Challenge

- Analysis design used Strategus for both studies:
  1. Intravitreal anti-VEGF and kidney failure risk (Anti-VEGF)
  2. Fluoroquinolone and aortic aneurysm risk (FQ)
- Strategus provided standardized executing environment in R
- Allows for re-use of execution environments for each study
Save our Sisyphus Challenge

• OHDSI Community learned the process for running the SOS Challenge studies Strategus during 2 online sessions

Week 6: Network Execution

Download project → Configure local settings → Execute → Review CSV files → Share Results

Session 1: Jenna Reps, Jack Brewster (slides)

Session 2: Anthony Sena, Chungsoo Kim
Save our Sisyphus Challenge

• OHDSI Community came together for “office hours” to share questions/issues that arose when running the studies.
• OHDSI Community members shared learnings and patches that enabled others in the community to run Strategus and complete the study at their site
• Many of the lessons learned are shared as GitHub issues and are planned for future releases of Strategus
Lessons Learned

• Standardization of your R environment matters, and it is not easy
  – Result: HADES has declared an official R version that everyone should use

• Use of tools such as renv are necessary to control the R execution environment
  – Result: Strategus makes use of renv to control the execution environment and R dependencies

• Collaboration is critical in network studies
  – Office hours and HADES working group calls helped to improve the quality of the Strategus software
## Results

<table>
<thead>
<tr>
<th>OHDSI Data Partner</th>
<th>Study Status (Number of Databases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-VEGF (12)</td>
</tr>
<tr>
<td>Ajou University Medical Center</td>
<td>FQ (17)</td>
</tr>
<tr>
<td>Columbia University Medical Center</td>
<td></td>
</tr>
<tr>
<td>IQVIA</td>
<td></td>
</tr>
<tr>
<td>Janssen R&amp;D</td>
<td>Completed (1)</td>
</tr>
<tr>
<td>Johns Hopkins University</td>
<td>Completed (1)</td>
</tr>
<tr>
<td>Northeastern University</td>
<td>Completed (1)</td>
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<tr>
<td>Stanford University</td>
<td>Completed (1)</td>
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<tr>
<td>Taipei Medical University</td>
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<tr>
<td>University of Southern California</td>
<td>Completed (1)</td>
</tr>
<tr>
<td>Department of Veterans Affairs</td>
<td>Completed (1)</td>
</tr>
<tr>
<td>Yonsei University College of Medicine</td>
<td></td>
</tr>
</tbody>
</table>

- Completed (2)  
- Completed (1)  
- Completed (5)  
- Completed (6)  
- Completed (6)  
- Completed (1)  
- Completed (1)  
- Completed (1)  
- Completed (1)