SARS-Cov-2 Large-scale Longitudinal Analyses on the comparative safety and effectiveness of treatments under evaluation for COVID-19 across an international observational data network:

The SCYLLA STUDY
Complementary evidence to inform the patient journey

Clinical characterization:
What happened to them?

Patient-level prediction:
What will happen to me?

Population-level effect estimation:
What are the causal effects?
Head-2-head comparisons - Rationale

• Guidelines (eg NIH) and clinicians have divided COVID-19 therapies into **Anti-viral**, and ‘**Adjunctive**’ therapies

• The latter are divided further into:
  – Anti-thrombotics
  – Immune-based therapy
  – Antibiotics
  – Concomitant (antihypertensive, statin, antidiabetic, others)
Many trials ongoing
Many already published
Most in some ‘living’ meta-analysis of RCTs
All study treatment/s vs placebo or ‘standard care’

But ...
- Are all corticosteroids equally safe?
- Are anticoagulants better than antithrombotics?
- Are IL-inh safer than corticosteroids?
- …
METHODS

Full protocol available at
http://www.encepp.eu/encepp/viewResource.htm?id=37226
New user cohorts in Scylla - OUTPATIENT

To assess comparative effectiveness and safety among treatments administered after COVID positive testing and prior to hospitalization

- Estimation design for patients treated PRIOR to hospital for COVID-19
  - Cohort start date = 'Treatment' new use
  - Cohort end date = end of 'Treatment' continuous use (7d persistence window)

- >=365d prior continuous observation period
- <0 prior exposure to 'treatment'
- >=1 COVID diagnosis OR positive test result
- 0 inpatient visit start (no end)

- Pre-index characterizes for confounding adjustment:
  - Age - year (cohort start date) - year of birth
  - Agegroup (5-year strata)
  - Sex
- Concept-based
  - Condition groups (SNOWED + descendants), >=1 occurrence during the interval
  - Drug era groups (A/C/Br Norm + descendants), >=1 day during the interval which overlaps with at least 1 drug era

- Treatment Cohorts (can be used as target AHR comparator):
  - Antibiotics
  - Immune-based therapies
  - Antiplateletics
  - Antibiotics
  - Anti-hypertensives
  - Anti-diabetics
  - Status
  - Concomitant Therapies

- Outcomes:
  - Admission to hospitalization
  - Initiation of hospitalization intensive services (ventilation, ECLS, Inotropes, ECMO)
  - Hemodialysis
  - Death (all-cause mortality, cardiovascular related mortality)
  - Pneumonia
  - Acute kidney injury
  - Sepsis
  - Various thromboembolism (Pulmonary embolism, Deep Vein Thrombosis)
  - Arrhythmia
  - Hemorrhagic
  - Anemia
  - Asthma/CHD exacerbation
  - Hepatic failure
  - Acute pancreatitis
  - Cardiovascular disease events (stroke, heart failure, acute myocardial infarction, sudden cardiac death)
  - Transient ischemic attack
  - Gastrointestinal bleeding

- Analysis:
  - Logistic regression (odds ratio on proportion having event in TAD)
  - Cox PH (hazard ratio for time-to-event analysis)
New user cohorts in Scylla – INPATIENT (pre-ICU)

To assess comparative effectiveness and safety among treatments administered on the date of admission of hospitalization and prior to intensive services.

Outcomes:
- Initiation of hospitalization intensive services (ventilation, tracheostomy, ECMO)
- Renal dialysis
- Discharge from hospitalization (or Death)
- Death (all-cause mortality, cardiovascular-related mortality)
- Frecenoma
- Acute kidney injury
- SIRS
- Venous thromboembolism (Pulmonary embolism, Deep Vein Thrombosis)
- Arrhythmia
- Brain death
- Stroke
- Asthma/COPD exacerbation
- Respiratory failure
- Acute myocardial infarction
- Cardiovascular disease events (stroke, heart failure, acute myocardial infarction, sudden cardiac death)
- Transient ischemic attack
- Cerebrovascular bleeding

Analysis:
- Logistic regression (with ratio proportion having event in TAM)
- Cox PH (hazard rate for time to event analysis)
DESIGN AND ANALYTICS

• New user, active comparator, cohort designs
• Large-scale propensity scores - observed confounding
• Negative control outcomes and empirical calibration – unobserved confounding
• Diagnostics

1. Power/sample size for each drug-outcome-setting
2. Propensity score models and overlap
3. Covariate imbalance <0.1 SD
4. Systematic error = negative control outcomes
RESULTS
Somewhat predictable challenges...
• Instrumental variables ‘sneaking’ into our PS models. Eg ‘chemotherapy or iv administration’

• 2-step SOLUTION:
  1. Look at correlation between concepts and T/C cohorts
  2. Exclude those with a high correlation coefficient
DIAGNOSTICS FAILED FOR MANY T-C

• Plethora of medicines used for COVID-19
• Relatively rarely find ‘clean’ new user cohorts

• OUTCOME:
  1. Mostly inpatient treatments pass diagnostics
  2. Only large cohorts make it to the analysis
SCYLLA Patient-level Drug User Characterisation
Preliminary findings – web app

data.ohdsi.org/ScyllaCharacterization/

Project Sc(y)lla Characterization: SARS-Cov-2 Large-scale Longitudinal Analyses on the comparative safety and effectiveness of treatments under evaluation for COVID-19 across an international observational data network

PLEASE NOTE: All results are preliminary and subject to change

Terms of Use:
These results are being shared as part of OHDSI’s open science community efforts to characterize disease natural history of COVID-19, for the purposes of enabling collaborative research within the community. Synthesis of the results and interpretation of the findings is underway and manuscripts are being prepared. All manuscripts must be reviewed and approved by all co-authors and data partner contributors prior to submission. Until final publication, all results are to be considered preliminary and subject to change, and may only be used under the terms of use of the respective data partner contributors.

Objectives:
The aim of this study is to characterize all emerging drug therapies used in COVID-19 treatment.

Specifically, the study aims to characterize:

1. Treatments administered during hospitalization and prior to intensive services
2. Treatments administered during hospitalization after initiating intensive services
3. Treatments administered after COVID-19 positive testing or diagnosis in outpatient setting without prior hospitalization

Resources:
- The study protocol is available [here](link)
- All analytic code is available at [GitHub](link)

Cohort Diagnostics:
- TBD
Drug and setting-specific, across data source characterisation

<table>
<thead>
<tr>
<th>Covariate Name</th>
<th>CDM_OPTUM_EHR_COVID_v1239</th>
<th>cdm_premier_covid_v1260</th>
<th>HM</th>
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<td>(n = 1,020)</td>
<td>(n = 216)</td>
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<td>&lt;0.5%</td>
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<td>age group: 20-24</td>
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<td>1.7%</td>
<td>&lt;2.3%</td>
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<td>age group: 25-29</td>
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<td>age group: 80-84</td>
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<td>7.4%</td>
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<tr>
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<td>&lt;2.3%</td>
</tr>
<tr>
<td>gender = female</td>
<td>59.5%</td>
<td>49.5%</td>
<td>31.0%</td>
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<tr>
<td>gender = male</td>
<td>40.5%</td>
<td>50.5%</td>
<td>69.0%</td>
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</tbody>
</table>
Eg Antivirals – Premier

HCQ + AZM

HCQ
Immune-based therapies in HM (L) and Optum EHR (R)

- DEXAM
- PREDNIS
- TOCI
- PREDNIS

- DEXAM
- PREDNIS
- TOCI
- PREDNIS
PRELIMINARY FINDINGS – Heparin vs Aspirin
• Is anticoagulation worth it (beneficial, not too risky) in patients with COVID-19?
### Public health impact?

% of heparin/AAS users in Charybdis

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Heparin Use</th>
<th>Aspirin Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUIMC</td>
<td>38%</td>
<td>28%</td>
</tr>
<tr>
<td>HIRA</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>HM Hospitals</td>
<td>2%</td>
<td>13%</td>
</tr>
<tr>
<td>IQVIAHospitalCDM</td>
<td>29%</td>
<td>21%</td>
</tr>
<tr>
<td>OptumEhr Hospitalized</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td>Premier Hospitalized</td>
<td>8%</td>
<td>27%</td>
</tr>
<tr>
<td>STARR-OMOP Hospitalized</td>
<td>51%</td>
<td>29%</td>
</tr>
<tr>
<td>TRDW Hospitalized</td>
<td>51%</td>
<td>24%</td>
</tr>
<tr>
<td>VA-OMOP Hospitalized</td>
<td>34%</td>
<td>41%</td>
</tr>
</tbody>
</table>
Are we using anticoagulants?

Trends in % of heparin users
Trends in % of AAS users

- Are we using anticoagulants?
What’s the evidence?

- Large multi-platform RCT ATTACC/REMAP-CAP/ACTIV-4a (still a preprint) suggests reduction in morbidity and mortality in COVID wards but not in ICU/severe patients.

- An analysis of VA in BMJ suggests 30% reduction in mortality.

- [https://www.bmj.com/content/372/bmj.n311](https://www.bmj.com/content/372/bmj.n311)

- **Question** is: would platelet aggregation safer? And would it do the trick?
Scylla findings (to date) – Heparin vs Aspirin Diagnostics
IQVIA Hospital CDM

- PS overlap -> PS matching to ‘common support’ area should enable ATT estimation

- No relevant (SMD>0.1) observable imbalance after PS matching
## Scylla findings (to date) – Heparin vs Aspirin

### Outcomes - effectiveness

**PRELIMINARY FINDINGS:** Do not interpret as yet 😊

<table>
<thead>
<tr>
<th>Rx initiation (index)</th>
<th>ARDS HR [95CI]</th>
<th>Total CVE HR [95CI]</th>
<th>ICU HR [95CI]</th>
<th>Death HR [95CI]</th>
<th>Discharge HR [95CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>On admission</td>
<td>0.96 [0.87-1.06]</td>
<td><strong>0.75 [0.63-0.89]</strong></td>
<td>1.12 [0.97-1.29]</td>
<td>1.28 [1.08-1.53]</td>
<td>0.89 [0.81-0.98]</td>
</tr>
<tr>
<td>During admission</td>
<td>0.97 [0.89-1.05]</td>
<td><strong>0.77 [0.66-0.89]</strong></td>
<td>1.20 [1.06-1.36]</td>
<td>1.35 [1.15-1.58]</td>
<td>0.83 [0.76-0.90]</td>
</tr>
</tbody>
</table>
### Scylla findings (to date) – Heparin vs Aspirin

#### Outcomes - safety

<table>
<thead>
<tr>
<th>Rx initiation (index)</th>
<th>GI Bleed HR [95CI]</th>
<th>Haemorrh Stroke HR [95CI]</th>
<th>AKI HR [95CI]</th>
<th>Liver failure HR [95CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>On admission</td>
<td>1.09 [0.65-1.85]</td>
<td>2.24 [0.69-10.03]</td>
<td>1.51 [1.32-1.73]</td>
<td>0.92 [0.47-1.80]</td>
</tr>
<tr>
<td>During admission</td>
<td>1.09 [0.72-1.65]</td>
<td>1.38 [0.54-4.01]</td>
<td>1.50 [1.34-1.68]</td>
<td>1.43 [0.85-2.48]</td>
</tr>
</tbody>
</table>

**PRELIMINARY FINDINGS:** Do not interpret as yet 😊
## Scylla findings (to date) – Heparin vs Aspirin “Positive” and Neg Control Outcomes

**PRELIMINARY FINDINGS:** Do not interpret as yet 😊

<table>
<thead>
<tr>
<th>Rx initiation (index)</th>
<th>Isch stroke HR [95CI]</th>
<th>Acute MI HR [95CI]</th>
<th>VTE HR [95CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission day</td>
<td>0.59 [0.35-0.99]</td>
<td>0.61 [0.48-0.77]</td>
<td>2.33 [1.70-3.22]</td>
</tr>
<tr>
<td>During admission</td>
<td>0.36 [0.19-0.65]</td>
<td>0.73 [0.60-0.89]</td>
<td>2.27 [1.72-3.05]</td>
</tr>
</tbody>
</table>
What do well-powered NCOs look like?

From Lane J et al. HCQ safety.
Lancet Rheum 2020
So what next?

1. Look into index date misclassification w VTE (luckily we are working on this as part of AESI rates work)
2. Look for additional/alternative negative control outcomes
3. Run the Scylla estimation package in additional databases (e-mail me prietoalhambra@ohdsi.org)
4. Wait for more data to accrue in the same data sources ...
So what next?

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4. Wait for more data to accrue in the same data sources ...
5. All of the above 😊
Questions?