SCYLLA: Large-scale characterization of COVID-19 treatment utilization

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CSM, University of Oxford
AGENDA

• Why SCYLLA (if we have trials)
• Aims & Methods
• Data source/s and Ns to date
• DUS – findings to date
• A call for participation!
Are we killing trials with RWE?

The Magic of Randomization versus the Myth of Real-World Evidence


Nonrandomized observational analyses of large electronic patient databases are being promoted as an alternative to randomized clinical trials as a source of “real-world evidence” about the efficacy and safety of new and existing treatments.¹⁶ Safety and efficacy because the potential biases with respect to both can be appreciable. For example, the treatment that is being assessed may well have been provided more or less often to patients who had an increased or decreased risk.
I’m afraid we are... there’s only 2,342 covid-19 trials ongoing...
So, why do we need Scylla?

2. We have tones of data available, without incurring additional risks

Together, OHDSI has studied (to date):

- >7m patients tested for SAR-COV-2
- >1.6m patients diagnosed or tested positive for COVID-19
- >300k hospitalized for COVID-19
• Many trials ongoing
• 25 published, 10 preprints
• All study treatment/s vs placebo or ‘standard care’

But …
– Are all corticosteroids equally safe?
– Are all IL-inhibitors equally effective?
– Are IL-inh safer than corticosteroids?
– …

So, why do we need Scylla?
3. Comparative effects (risks and benefits) DO matter
AGENDA

• Why SCYLLA (if we have trials)
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Study Aims

• To assess the comparative effectiveness and safety among treatments administered during hospitalization and prior to intensive services

• To assess comparative effectiveness and safety among treatments administered after COVID-19 positive testing or diagnosis in outpatient setting without prior hospitalization

FULL STUDY PROTOCOL REGISTERED AT http://www.encepp.eu/encepp/viewResource.htm?id=37226
METHODS

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

Population-level estimation
CohortMethod package
Study drugs/exposures

• Antivirals/repurposed therapies
• Immune-based therapies (GCs, biologic rx, etc)
• Antithrombotic therapies (heparin, oral anticoagulants, etc)
• Concomitant
  – Antibiotic therapy
  – CV prevention therapy (statins, ACEi, etc)
  – Other concomitant therapies
New user cohorts in Scylla - OUTPATIENT

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'

-365d to -1d

>=1 COVID diagnosis OR positive test result

=0 inpatient visit start (no end)

-30d to 0d

Pre-index characteristics for confounding adjustment:
- Age - year (cohort start date) - year of birth
- Age group (5-year strata)
- Sex
- Concept-based:
  - Condition groups (SNOMED + descendants), >=1 occurrence during the interval
  - Drug era groups (ATC/ReNorm + descendants), >=1 day during the interval which overlaps with at least 1 drug era

Treatment Cohorts (can be used as target AND comparator)
- Antivirals
- Immune-based therapies
- Antithrombotics
- Antibiotics
- Anti-inflammatory
- Anti-diabetics
- Statins
- Concomitant therapies

Outcomes:
- Admission to Hospitalization
- Initiation of hospitalization intensive services (ventilation, tracheostomy, ECMO)
- Haemolysis
- Death (all-cause mortality, cardiovascular-related mortality)
- Pneumonia
- Acute kidney injury
- Sepsis
- Venous thromboembolism (Pulmonary embolism, Deep Vein Thrombosis)
- Arrhythmia
- Haemorrhage
- Anuria
- Asthma/COPD 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 (pops ratio on proportion having event in TAR)
- CoxPH (hazards ratio for time-to-event analysis)
New user cohorts in Scylla – INPATIENT (pre-ICU)

Estimation design for patients treated for COVID-19 on the date of admission of hospitalization and prior to intensive services, with >365d prior observation

>=365d prior continuous observation period

=0 prior exposure to ‘treatment’

>=1 COVID diagnosis OR positive test result

>=1 inpatient visit start (no end)

=0 intensive services

365d to -1d

Pre-index characteristics for confounding adjustment:
- Age = year(cohort start date) – year of birth
  - Age group (5-year strata)
- Sex
概念-based:
- Condition groups (SNOMED = descendants), >=1 occurrence during the interval
- Drug era groups (ATC/ReNorm = descendants), >=1 day during the interval which overlaps with at least 1 drug era

Cohort end date = end of ‘Treatment’ continuous use (7d persistence window)

1d to 7d

1d to 30d

1d to cohort end

Outcomes:
- Initiation of hospitalization intensive services (ventilation, tracheostomy, ECMO)
- Hemodialysis
- Discharge from Hospitalization (or Death)
- Death (all-cause mortality, cardiovascular-related mortality)
- Pneumonia
- Acute kidney injury
- Sepsis
- Venous thromboembolism (Pulmonary embolism, Deep Vein Thromboembolism)
- Arrhythmia
- Haemorrhage
- Angina
- Asthma/COPO 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 TAR)
- Cox PH (hazards ratio for time-to-event analysis)

Treatment” Cohorts: (can be used as target AND comparator)
- Antibiotics
- Immune-based therapies
- Antithrombotics
- Antibiotics
- Anti-hypertensives
- Anti-diabetics
- Statins
- Concomitant therapies
AGENDA

• Why SCYLLA (if we have trials)
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  • DUS – findings to date
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DATA SOURCES to date

**Hospital EMR**
- No lookback
  - HM ES
  - Premier US
- 1y lookback
  - Optum EHR
  - CUIMC

**GP/Amb EMR**
- SIDIAP ES, CPRD UK, IPCI NL, IQVIA LPD IT, FR, DA Germany

**Claims**
- HIRA SK
- IQVIA Open Claims
- Optum SES

**Inpatient rx**

**Outpatient rx**
# N to date – Outpatient new user cohorts

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<th>OPTUM M SES</th>
<th>OPTUM EHR</th>
<th>SIDIAP</th>
<th>LPD-IT</th>
<th>CPRD</th>
<th>Health Verity</th>
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</table>
AGENDA

• Why SCYLLA (if we have trials)
• Aims & Methods
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Pop-level Drug Utilisation – inpatient data
Antivirals/repurposed therapies
Great heterogeneity in the use of concomitant therapies

- Antithrombotics/anticoagulants
- Antibiotics
- Immune-based rx (mostly corticosteroids)
DUS in Pregnant women hospitalized with COVID19

- Charybdis - drug utilization in 2,031 pregnant women hospitalized with COVID19
- Substantial use of corticosteroids, antithrombotics, antibiotics, vitamins ...
DUS in children/adolescents hospitalized with COVID19

- Antivirals (<10%), systemic steroids (6.8% to 37.6%), famotidine (9.0% to 28.1%), and antithrombotics eg heparin (2.2% to 18.1%)

- Antibiotics, vitamin supplements and immunoglobulins were also used.
Patient-level DUS – 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](#)
- All analytic code is available at GitHub

Cohort Diagnostics:
- TBD
Setting-specific characterization - demographics

ACE inhibitors with Persons with a COVID-19 diagnosis record or a SARS-CoV-2 positive test prior to inpatient visit or intensive services and 365d prior observation

OUTPATIENT

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Setting-specific characterization – BY SETTING

OUTPATIENT

INPATIENT

INTENSIVE SERVICES
Drug and setting-specific, across data source characterisation

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DB and drug-specific, across setting ...

Premier, DEXA, **inpatient pre vs post-ICU initiators**

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<th>Mean Comparator</th>
<th>SD Comparator</th>
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<td>0.29</td>
<td>11.7%</td>
<td>0.32</td>
<td>0.05</td>
</tr>
<tr>
<td>age group: 60-64</td>
<td>9.7%</td>
<td>0.30</td>
<td>12.5%</td>
<td>0.33</td>
<td>0.06</td>
</tr>
<tr>
<td>age group: 65-69</td>
<td>9.9%</td>
<td>0.30</td>
<td>15.1%</td>
<td>0.36</td>
<td>0.11</td>
</tr>
<tr>
<td>age group: 70-74</td>
<td>8.1%</td>
<td>0.27</td>
<td>11.8%</td>
<td>0.32</td>
<td>0.09</td>
</tr>
<tr>
<td>age group: 75-79</td>
<td>8.0%</td>
<td>0.27</td>
<td>7.9%</td>
<td>0.27</td>
<td>0.00</td>
</tr>
<tr>
<td>age group: 80-84</td>
<td>7.4%</td>
<td>0.26</td>
<td>6.3%</td>
<td>0.24</td>
<td>-0.03</td>
</tr>
<tr>
<td>age group: 85-89</td>
<td>6.6%</td>
<td>0.25</td>
<td>3.7%</td>
<td>0.19</td>
<td>-0.09</td>
</tr>
<tr>
<td>age group: 90-94</td>
<td>2.3%</td>
<td>0.15</td>
<td>0.9%</td>
<td>0.09</td>
<td>-0.08</td>
</tr>
<tr>
<td>gender = female</td>
<td>49.5%</td>
<td>0.50</td>
<td>43.8%</td>
<td>0.50</td>
<td>-0.08</td>
</tr>
<tr>
<td>gender = male</td>
<td>50.5%</td>
<td>0.50</td>
<td>56.2%</td>
<td>0.50</td>
<td>0.08</td>
</tr>
</tbody>
</table>
Antivirals – Premier

HCQ + AZM

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

• Why SCYLLA (if we have trials)
• Aims & Methods
• Data source/s and Ns to date
• DUS – findings to date
• A call for participation!
JOIN the SCYLLA team

“She has twelve feet, all dangling in the air, and six long scrawny necks, each ending in a grisly head with triple row of fangs, set thick and close, and darkly menacing death...”

( Odyssey, 12:87-95)

We can’t fight this monster without you!
daniel.prietoalhambra@ndorms.ox.ac.uk