E-CORE: European COVID-19 Observational Research Exchange

Multicentre collaboration for COVID-19 observational studies

18 November 2021 – ENCePP meeting

Project background

- COVID-19 is spreading rapidly throughout the world, creating immense burden on the healthcare community
- Few established treatments were available at the start of the project, and little was known about their safety
- RCTs are limited in sample size and challenging to conduct, posing additional burden on sites. They have to be complemented by parallel rigorous real-world studies
- Study aim EMA: In the context of the COVID-19 pandemic, the Agency considered that it required a framework that would support collaborations for conducting multicentre observational studies related to the utilisation, safety and effectiveness of medicines used by COVID-19 patients
- In June 2020, At the initiative of EMA, the E-CORE network was created with the aim to conduct multicentre cohort studies on the use of medicines for the treatment of COVID-19, accelerating the generation of robust real-world evidence of therapies for COVID-19 treatment.

Timeline for network creation and output

Six milestones (with deliverables) were met between June 20-September 21

1) Creation of a European network of at least 7 databases

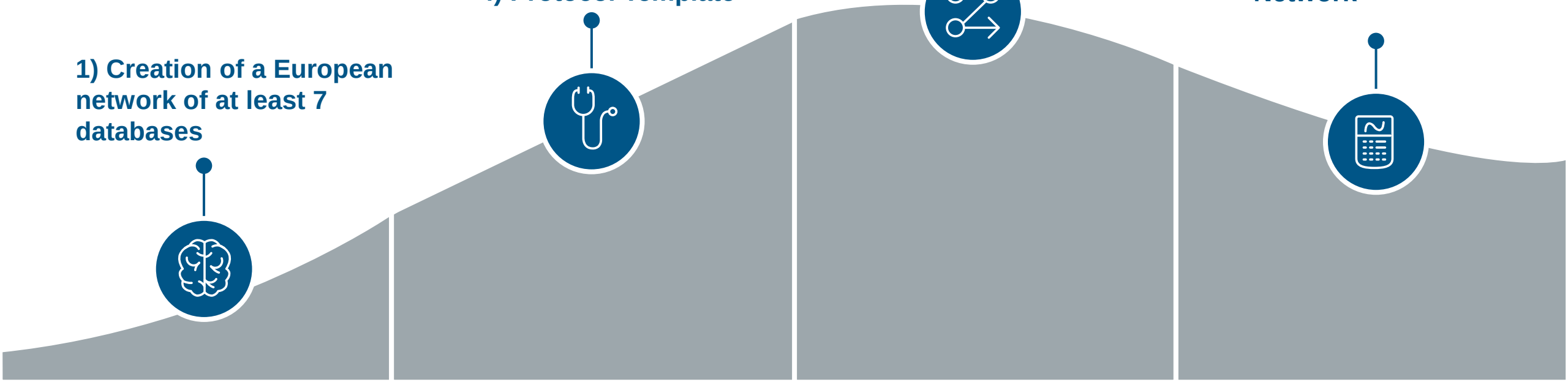
2) Proof of concept study protocol and database characterization

3) Governance model of the network

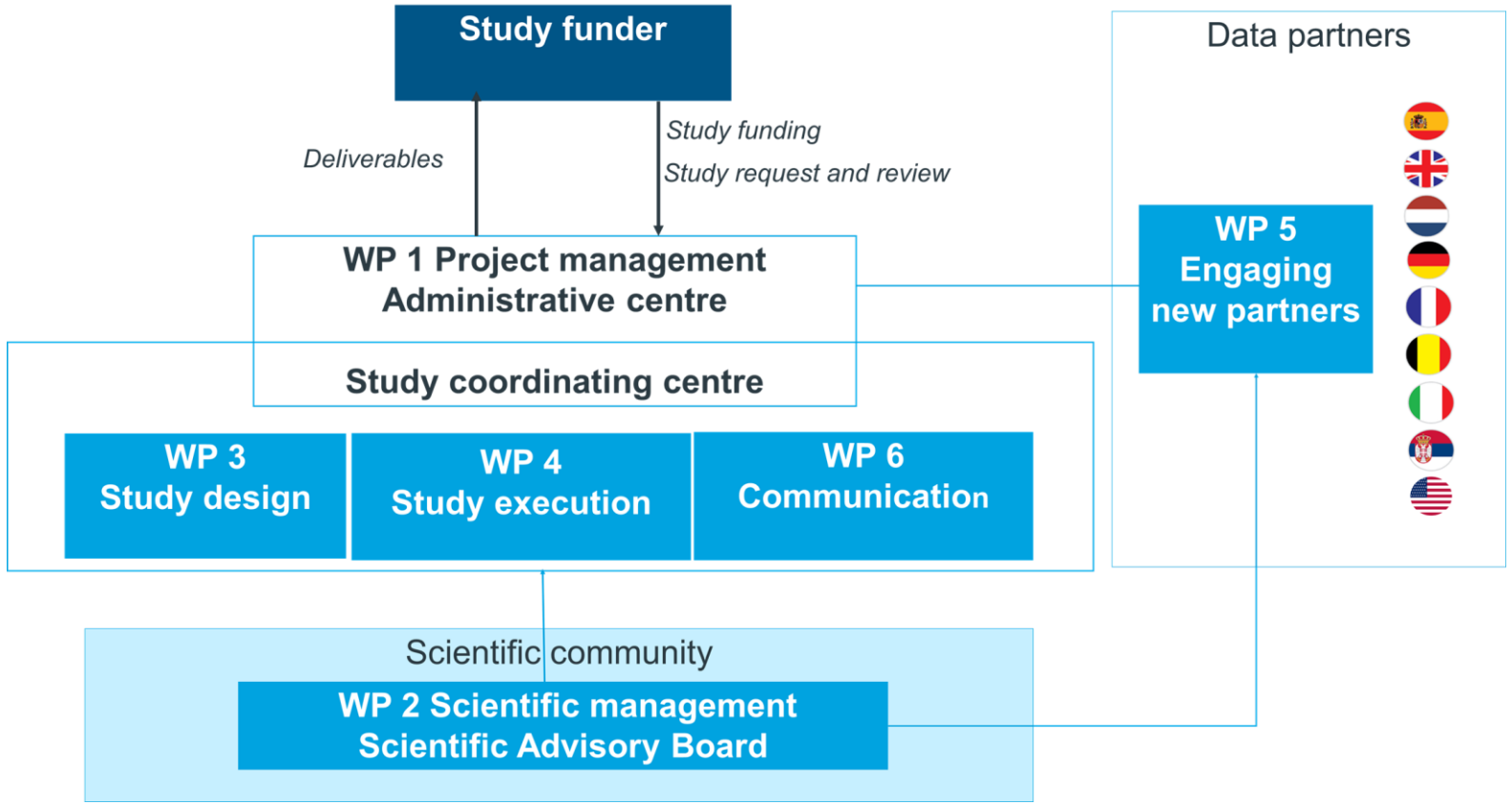
4) Protocol Template

5) Study results

6) Review of the efficiency of the collaboration Sustainability of the Network



E-CORE infrastructure and governance model

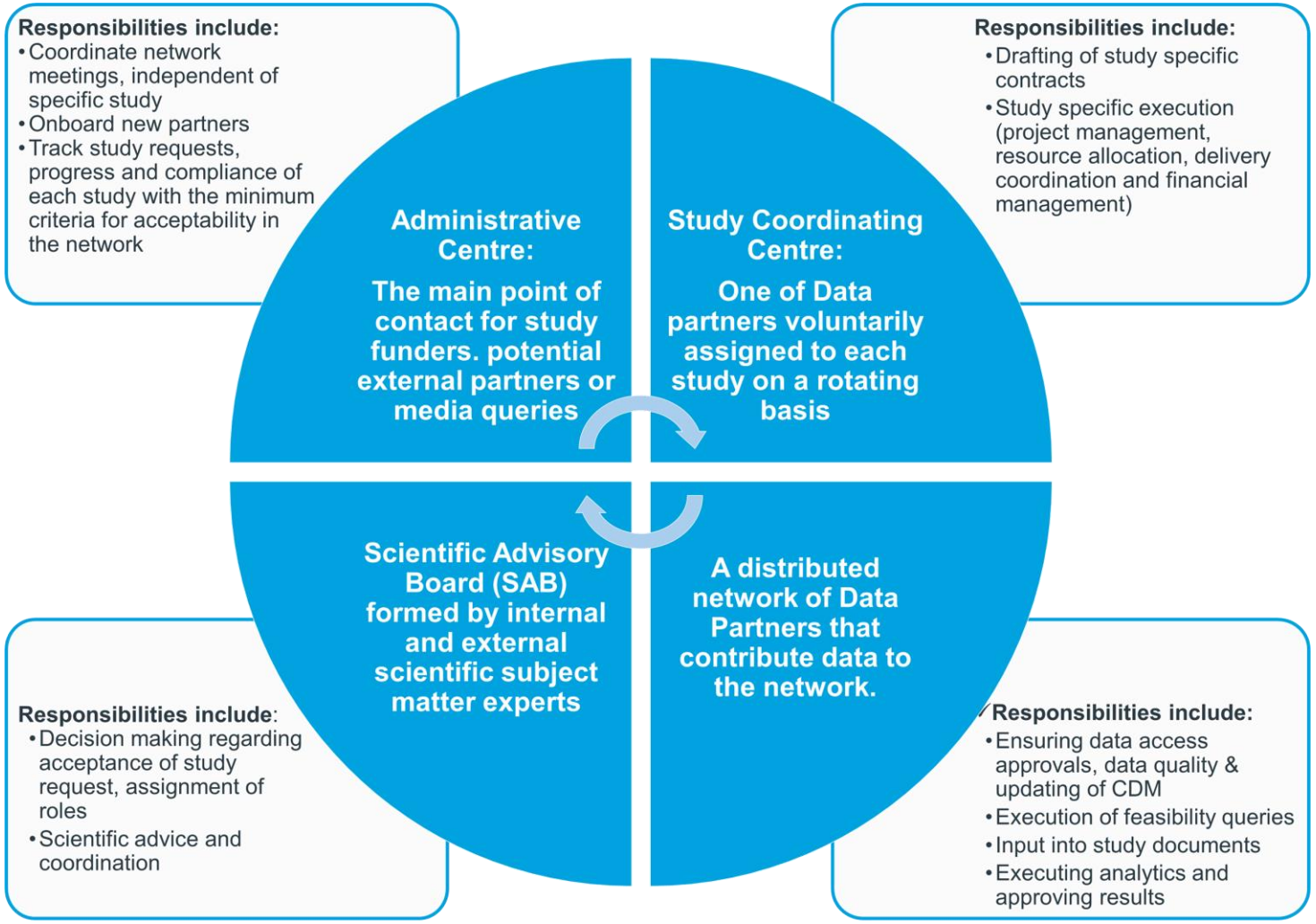


Fourteen databases from 9 countries (**Germany**: IQVIA DA and a University hospital; **France**: IQVIA LDP and APHM; **Belgium**: IQVIA LPD, **Italy**: IQVIA LDP; **UK**: IMRD and HIC; **Spain**: SIDIAP, HM Hospitales and Parc Salut Mar Barcelona (IMASIS); **the Netherlands**: IPCI, **Serbia**: Clinerion/Heliant and **US**: Hospital Charge Data Master).
Of these, 8 encompass the primary/ambulatory care setting and 6 encompass the hospital care setting

Governance model characteristics

E-CORE is:

- A federated network with data sources mapped to the OMOP common data model (CDM) to enable common analytics.
- A collaboration between multiple institutions: academics, contract research organizations and data partners with expertise in conducting pharmaco-epidemiological studies and access to health databases.
- A structure based on a series of work packages (WP) that cover project and scientific management, study design, and execution, engaging new data partners and communication



Proof of concept study

Proof of concept study

Overall aim

EMA wish to generate real world evidence to describe the **utilisation patterns of systemic glucocorticoids** in patients with COVID-19 and investigate the **risks of adverse outcomes** including non-fatal complications and deaths occurring within the first 6 months following COVID-19 diagnosis in patients treated with systemic glucocorticoids, as observed **in ambulatory and hospital inpatient** care settings of **seven European countries** during the first year of the pandemic until latest data availability.

- The POC study was conducted in a network of databases mapped to a common data model (OMOP CDM)
- A common protocol has been developed[1] to test the network capability to conduct similar studies in the future in a very fast paced manner.
- Cohorts of COVID-19 patients have been created in nine European countries
- Descriptive outputs encompas: demographics, comorbidities, number of cases per month, total of hospital admissions (ambulatory) and deaths, and incidence of steroid use before and after the RECOVERY trial.

[1] ENCEPP Pas register:http://www.encepp.eu/encepp/viewResource.htm?id=41699

Proof of concept study

Primary objective

To describe **utilization of systemic glucocorticoids** for treatment of COVID-19 in two settings: hospitalized and ambulatory within 90 days after COVID-19 diagnosis.

Secondary objectives

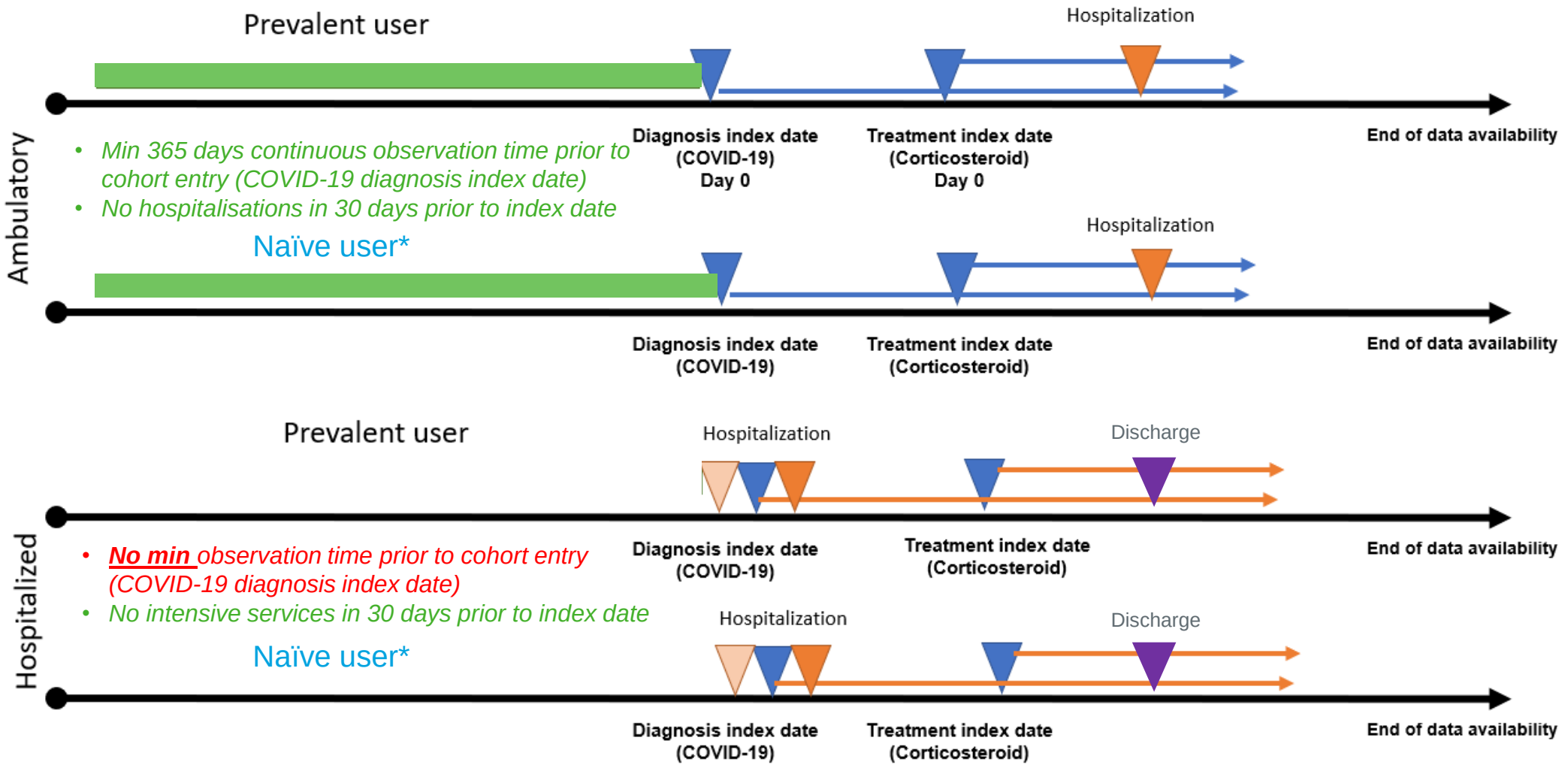
1.To **describe demographic, health and clinical patient characteristics** at COVID-19 diagnosis date and at treatment index date.

2.To **quantify the crude and adjusted incidence rates** and time to onset of **adverse events** in various treatment groups, stratified by setting and glucocorticoid exposure type (naive, prevalent).

3. To quantify the **crude and adjusted incidence rates of mortality and other outcomes** in various treatment groups stratified by setting, glucocorticoid exposure type (naive, prevalent).

4. To explore the **performance of different coding definitions** for COVID-19.

Proof of concept study design



* No glucocorticoid exposure between 3 and 120 days prior to index date

Study methods

Case and outcome definitions

COVID-19 definitions

- Main analysis: Catch-all definition based on the earliest of a first diagnosis confirmed for COVID-19 or first SARS-CoV-2 positive PCR test
- Alternative definitions: Diagnosis confirmed (diagCOVID-19), laboratory confirmed (labCOVID-19), symptomatic COVID-19 and suspected COVID-19 cases

Exposure (based on prescription data)

- Glucocorticoids used in COVID-19 indication (dexamethasone, prednisolone, prednisone, methylprednisolone or hydrocortisone)
- Glucocorticoid for pre-existing conditions based on prescription records.
- Other COVID-19 treatments (e.g., antiviral, antibiotic, statin therapy)
- Respiratory support

Outcomes (Secondary objectives 2 and 3)

- Adverse events such as composite cardiovascular events, hypertension, arrhythmia, gastritis, psychosis, myopathy, hyperglycaemia and infections (composite)
- Disease outcomes:
  - Ambulatory: Hospital admission, venous thromboembolism, disseminated intravascular coagulation, death of any cause
  - Hospital: Intensive services, venous thromboembolism, disseminated intravascular coagulation, discharge from hospital, death of any cause

Results

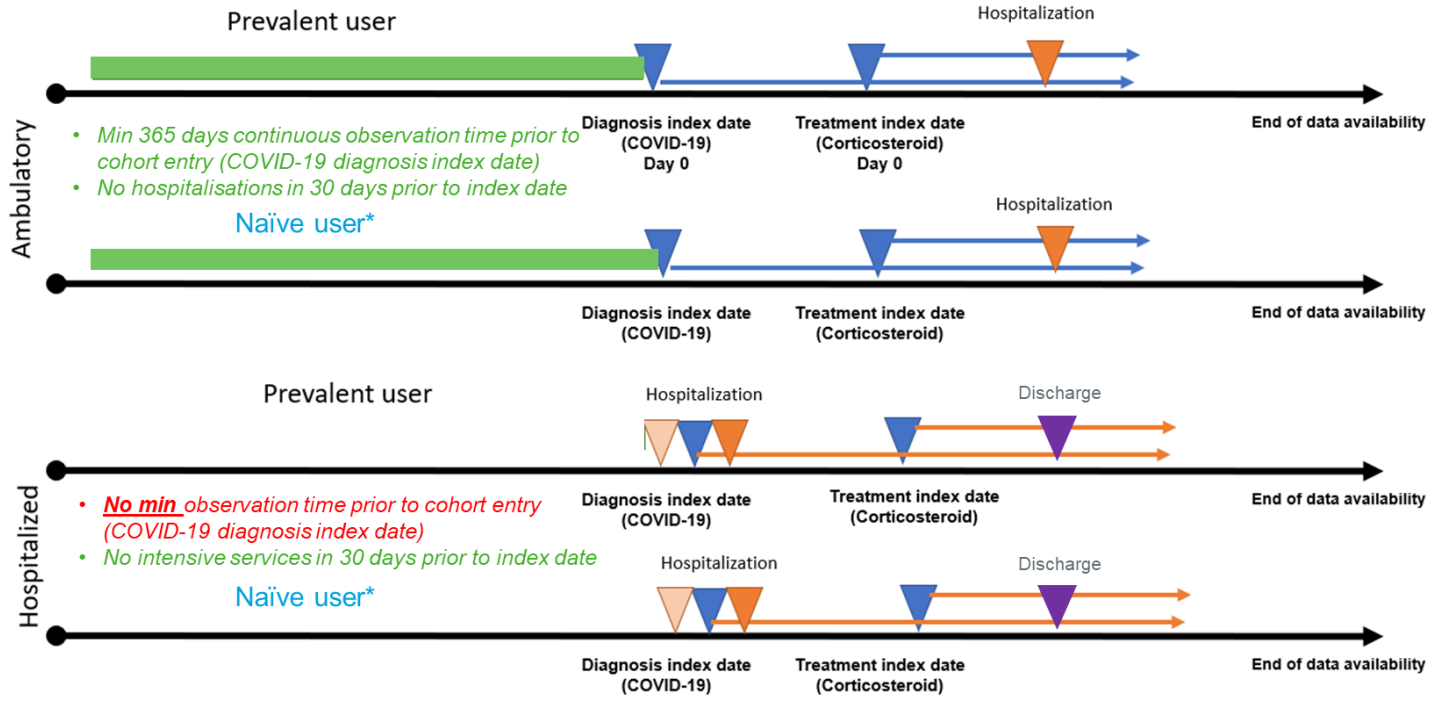
Results

Descriptive characteristics

Fourteen databases from 9 countries (**Germany**: IQVIA DA and a University hospital; **France**: IQVIA LDP and APHM; **Belgium**: IQVIA LPD, **Italy**: IQVIA LDP; **UK**: IMRD and HIC; **Spain**: SIDIAP, HM Hospitales and Parc Salut Mar Barcelona (IMASIS); **the Netherlands**: IPCI, **Serbia**: Clinerion/Heliant and **US**: Hospital Charge Data Master).

Of these, 8 encompass the primary/ambulatory care setting and 6 encompass the hospital care setting

Study period: 01/01/2020- latest available data; data extraction 27/08/2021



9,719 patients (7 countries)

497,723 patients (7 countries)

14,026 patients (3 countries)

94,916 patients (6 countries)

* No glucocorticoid exposure between 3 and 120 days prior to index date

https://ecorecoviddashboard.shinyapps.io/e-core-shiny-app

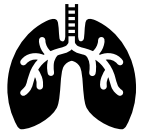
Results

Descriptive characteristics of the included cohorts, across all databases

- The majority of patients were adults, with the **hospital cohorts having a slightly older population** than the ambulatory cohorts (range across all databases 64.0-74.0 vs 49.0-76.0 years in the prevalent cohort and 53.0-71.0 vs 43.0-71.0 in the naïve cohort).
- The number of **children** was very small, **less than 5% of the included population**.

- The **percentage of women** was **slightly higher** in the **ambulatory prevalent** cohorts (range across all databases 51.1% -67.4%) than in the hospital prevalent cohorts (40.9%- 47.8%), while the naïve cohorts have similar percentages for both ambulatory (46.9%-58.6%) and the hospital cohorts (50.0%-59.8%)

- The most frequent **co-morbidities** in the ambulatory prevalent cohorts were **hypertension, COPD, T2DM** [and CKD for hospitalized cohorts only]. Comorbidities were more frequent among hospitalized patients.



- **Recording of symptoms was variable** between cohorts and databases. Between 1-37% of patients had one or more COVID-19 symptoms. Cough, dyspnoea, and fever were the most frequent symptoms

Results

Utilization of systemic glucocorticoids for treatment of COVID-19 across databases

Ambulatory setting

- The percentage of patients treated with steroids: 8,627 (1.7%) ranging from 0.6% to 3.3% across databases
- The treatment duration of corticosteroids 4.0 to 25.0 days
- The number of patients receiving other COVID-19 Rx: 0.6% to 3.3% across databases
- No respiratory support

Hospital setting

- The percentage of patients treated with steroids: 30,483 (32.1%) ranging from 2.4% to 45.6% across databases
- The treatment duration of corticosteroids 4.0 days to 10.0 days
- The number of patients receiving other COVID-19 Rx: 43.7% to 99.5% across databases
- No respiratory support

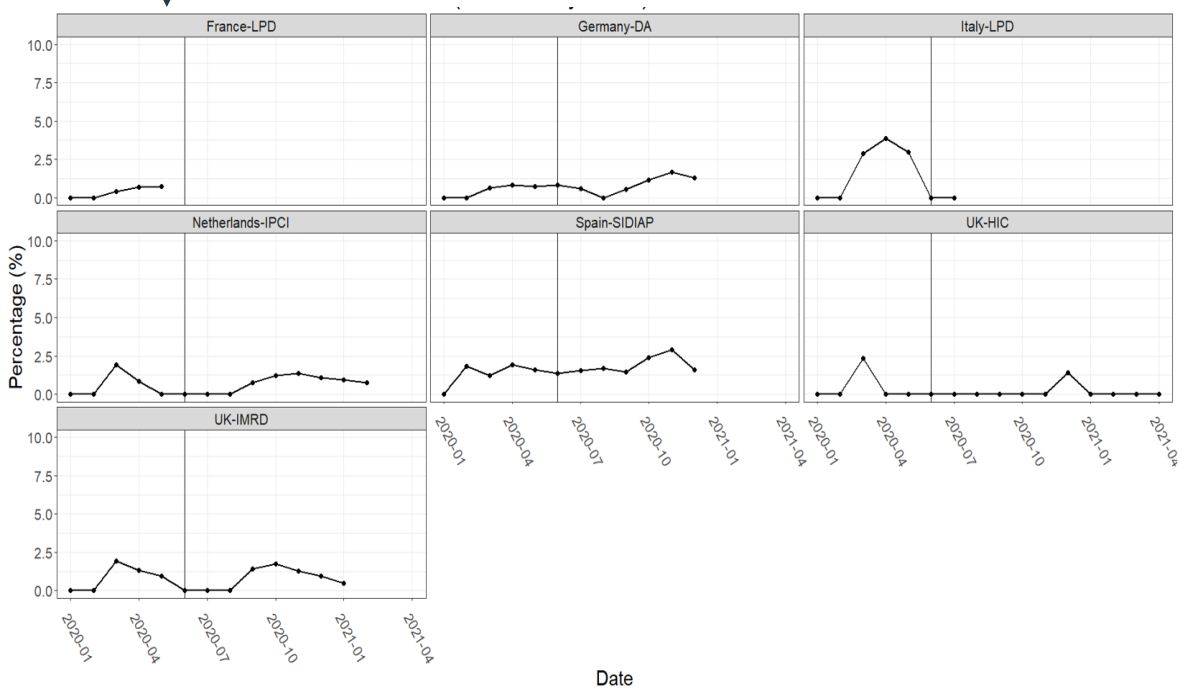
The study did not identify any prevalent users treated with corticosteroids specifically for COVID-19.

Results

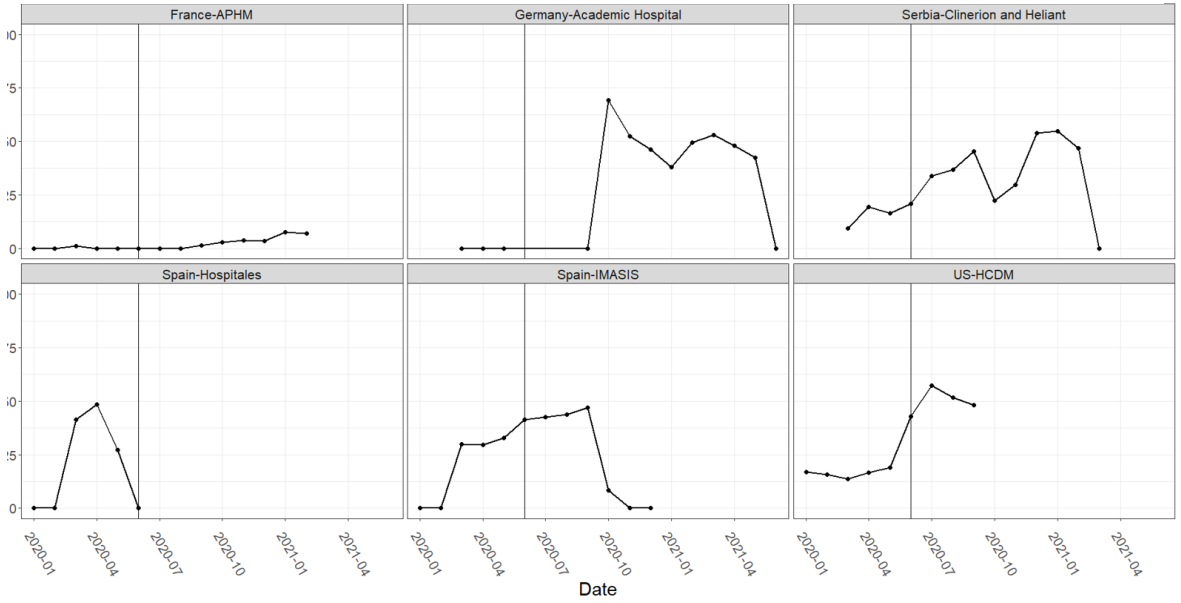
Changes in prescribing patterns over calendar time

Recovery trial results published

Ambulatory naive



Hospital naive



Vertical line represents the date when the RECOVERY trial results were made public

Results

Adverse events of interest

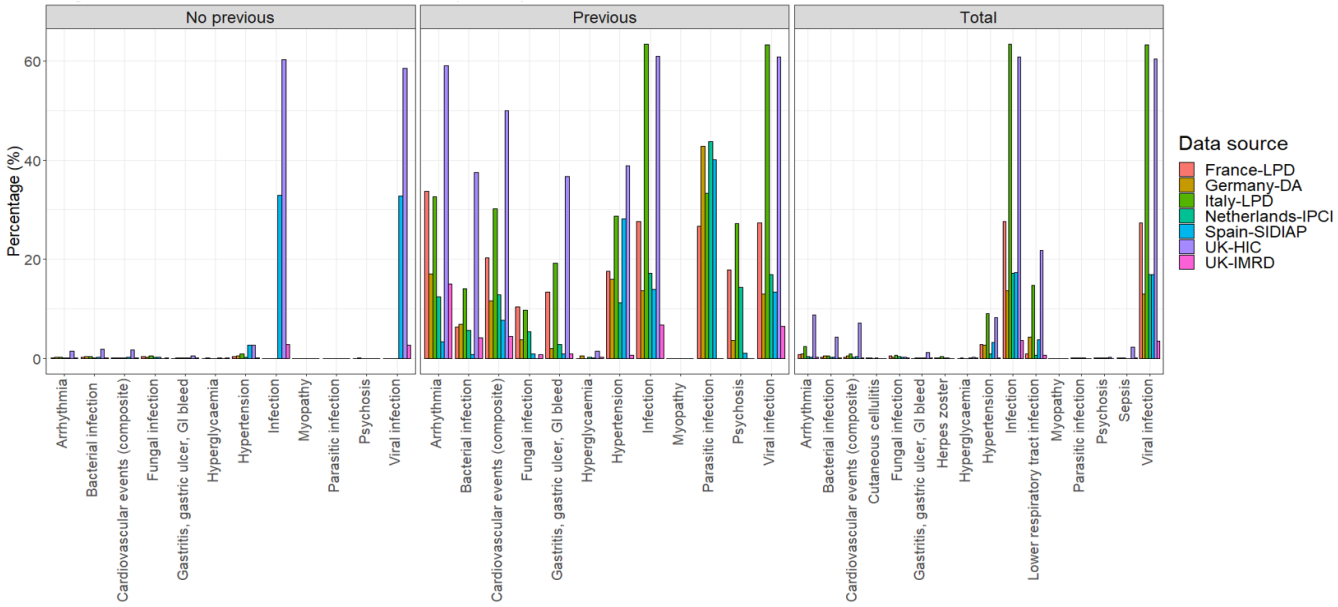
- Eight main events: Composite cardiovascular events, hypertension, arrhythmia, gastritis, psychosis, myopathy, hyperglycaemia and infections (composite)
- The most frequent AEs, reported in over 10% of the patients in any cohort and at least one treatment group were infection (composite), viral infection, LRTI and hypertension; this finding being constant across databases and both at 30- and 90-days follow-up
- AE profile differed by setting. Hospital cohorts had higher frequency of AEs but also some AEs such as psychosis, myopathy, hyperglycaemia, parasitic infection, herpes and cutaneous cellulitis appeared predominantly in the hospital cohorts.
- The majority of patients had a follow up consistently lower than 30 days, mainly associated with censoring due to end of treatment.
- In the naïve cohorts, higher rates appeared in the ‘other COVID-19 treatments only’ or ‘glucocorticoid and other COVID-19 treatments’ groups suggesting patients that require multiple COVID treatments may have a higher burden of subsequent AEs than those that require only steroid treatment.

! *The results were not formally compared across treatments taking into account factors such as disease severity therefore caution should be applied when interpreting these results.*

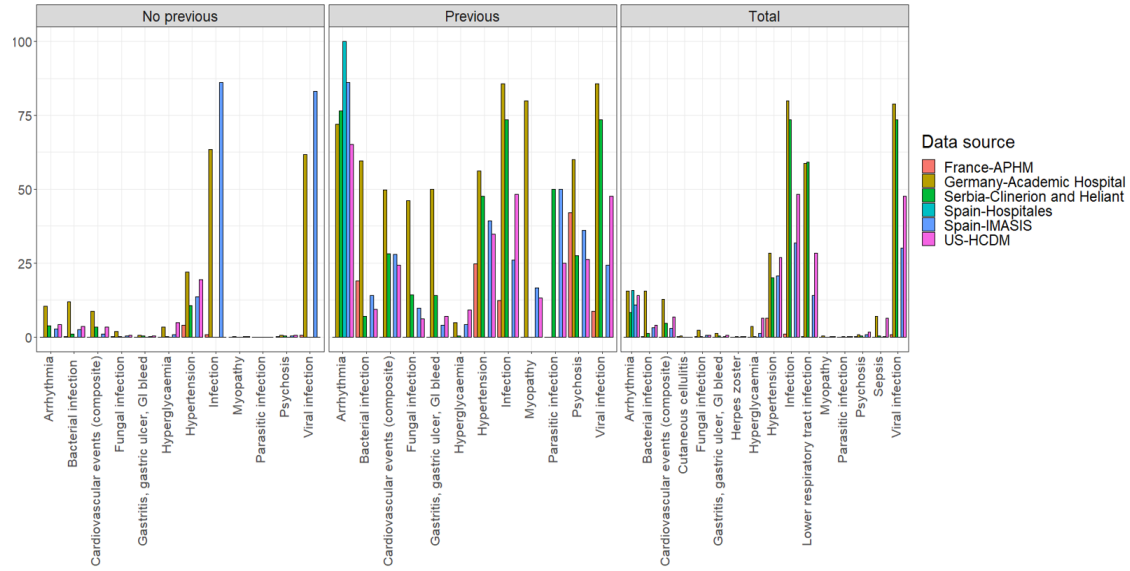
Results

Adverse events of interest in the naïve cohorts at 30 days

Ambulatory



Hospital



The frequency of all AEs decreased substantially to almost zero when restricting to people with no medical history of the event, suggesting strong confounding by prior medical history of the AE of interest.

Results

Disease outcome events of interest

Disease outcomes investigated were : death (all cause), hospital admission (ambulatory cohort only), VTE, DIC, intensive care admission and hospital discharge (hospital cohort only).

- Death as an outcome ranged from 0% to 50.0% in the ambulatory cohort and from 11% to 53.8% in the hospital cohorts.

- Hospitalization rates were between 0% to 20.2% in the prevalent ambulatory cohort and 0% to 50% in the naïve ambulatory cohort; this being possibly highest in the ‘other COVID-19 treatment group’.
- DIC was not reported in any of the databases
- VTE was reported in all databases
- No formal comparisons between treatment groups were done.

Pooled incidence rates of outcomes in ambulatory naïve cohort

	Glucocorticoid Only					Other COVID treatments Only				
	Databases					Databases				
Outcome	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)
Death	5	1	3	1	NA*	5	0	1	4	NA*
Hospitalisation	5	3	1	1	1.43 (95% CI 0.96-2.13)	5	2	0	3	NA*
VTE/PTE	6	3	3	0	0.24 (95% CI 0.08-0.70)	6	1	5	0	NA*
DIC	6	6	0	0	NR^	6	6	0	0	NR^

	Glucocorticoid and other COVID treatments					No COVID related treatments				
	Databases					Databases				
Outcome	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)
Death	5	2	2	1	NA*	5	0	0	5	NA*
Hospitalisation	5	3	1	1	3.44 (95% CI 2.29-5.16)	5	2	0	3	NA*
VTE/PTE	6	5	1	0	0.2 (95% CI 0.04-0.98)	6	0	0	6	NA*
DIC	6	6	0	0	NR^	6	6	0	0	NR^

Pooled incidence rates of outcomes in hospital naïve cohort

	Glucocorticoid Only					Other COVID treatments Only				
	Databases					Databases				
Outcome	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)
Death	6	0	4	2	NA*	6	0	0	6	NA*
Hospital discharge	6	6	0	0	NR^	6	6	0	0	NR^
VTE/PTE	6	4	1	1	2.45 (95% CI 1.29-4.64)	6	2	0	4	NA*
DIC	6	5	1	0	0.43 (95% CI 0.09-2.13)	6	3	2	1	0.17 (95%CI 0.11-0.26)
Intensive Care	6	3	2	1	2.68 (95% CI 1.50-4.80)	6	3	0	3	NA*

	Glucocorticoid and other COVID treatments					No COVID related treatments				
	Databases					Databases				
Outcome	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)
Death	6	0	1	5	NA*	6	0	0	6	NA*
Hospital discharge	6	6	0	0	NR^	6	6	0	0	NR^
VTE/PTE	6	2	0	4	NA*	6	2	0	4	NA*
DIC	6	3	1	2	0.34 (95% CI 0.23-0.51)	6	3	2	1	NA*
Intensive Care	6	3	1	2	NA*	6	3	0	3	NA*

Discussion

The network indicated large heterogeneity in COVID-19 management across the countries

- This study provides a good understanding of the utilisation patterns of systemic glucocorticoids in COVID-19 patients in a selection of both ambulatory and hospital settings in Europe and the US
- In line with usual clinical practice, more patients are treated with steroids in hospital than in the ambulatory setting, while the dose and the treatment duration are largely in line with recommendations.
- The most common AEs were infection related, which may be due confounding by the COVID-19 diagnosis. Patients in the hospital settings had generally more AEs than those in ambulatory settings.
- The death rates were higher than reported in other studies, which may be due to inclusion of a population with more severe disease.
- However, for most part there was a high heterogeneity of results across the different databases, which precluded meta-analyses of many AEs and disease outcomes.
- The E-CORE project included 6 additional databases than initially envisaged in the technical specification, with a balanced mix of ambulatory and hospital databases.

Conclusion

A successful collaboration between EMA, IQVIA and academic partners across Europe

- To our knowledge this is the first study on COVID-19 treatments in real world setting, based on a considerable number of data sources providing a large number of patients from across different countries.

- Despite the many databases included, small sample size was still an issue for some rare outcomes. Expanding the network to include further data sources is therefore recommended.

We conclude that E-CORE network can be successfully used for studying effects of COVID-19 therapies in an international setting.

Thank you!

More details:
Deborah Layton debaroah.layton@iqvia.com