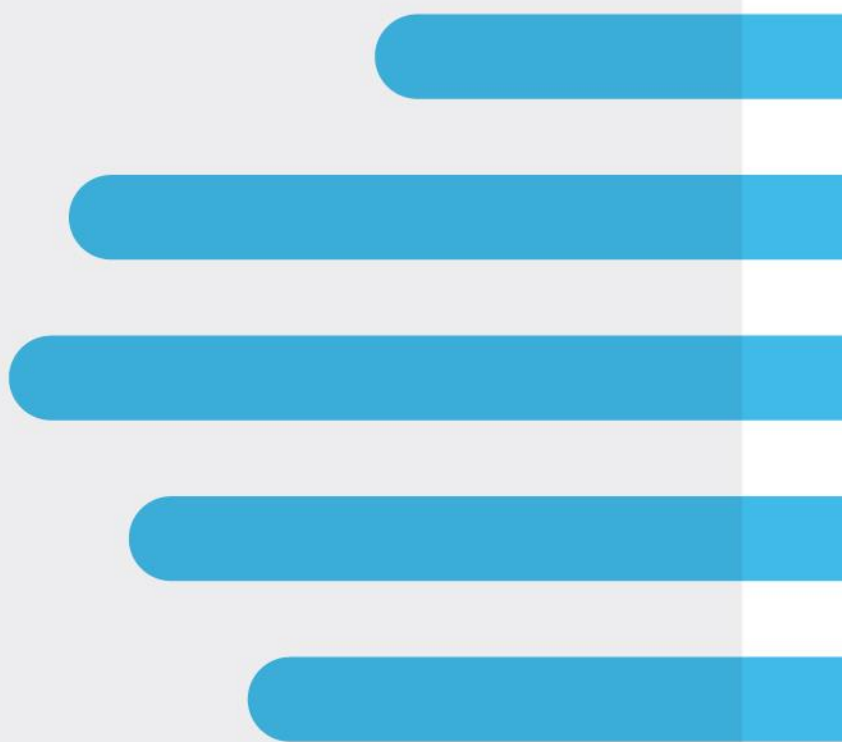# Study protocol: Systemic glucocorticoids in the treatment of COVID-19 and risks of adverse outcomes in COVID-19 patients in the primary and secondary care setting

European Medicines Agency

4th December 2020

IQVIA

Protocol Approval and Sign-off
I confirm that I have read the contents of this protocol and its attachments. I approve the protocol in its current form.

Epidemiologist & author	Alexandra Pacurariu		
	Senior Consultant, EMEA Data Science Hub, IQVIA Ltd.	Signature	Date
Principal Investigator	Deborah Layton		
	Director of Drug Safety, EMEA Data Science Hub, IQVIA Ltd.	Signature	Date
Senior QC	Deborah Layton		
	Director of Drug Safety, EMEA Data Science Hub, IQVIA Ltd.	Signature	Date

PASS Information

Section	Description
Title	Systemic glucocorticoids use in the treatment of COVID-19 and risks of adverse outcomes in COVID-19 patients in the primary and secondary care setting
Protocol version identifier	Version 4.0
Date of last version of protocol	NA
EU PAS register number	To be registered
Active substance	Steroids (H02AB)
Procedure number	EMA/198302/2020
Research questions and objectives	Primary objective
	To describe utilization of systemic glucocorticoids (e.g., dexamethasone, prednisolone, methylprednisolone or hydrocortisone) for treatment of COVID-19 in two types of setting: hospitalized (in hospital care) and ambulatory (any care received outside the hospital) within 90 days following COVID-19 diagnosis.
	Secondary objectives
	1. To describe at COVID-19 diagnosis date the demographic, health and clinical patient characteristics (stratified by setting and systemic glucocorticoid user type (naive, prevalent).
	2. To quantify the crude and adjusted incidence rates and time to onset of adverse events of interest (i.e., infections, hyperglycaemia, hypertension, gastrointestinal bleeding and composite cardiovascular disease events) within 30 and 90 days post treatment index date, by setting, in various treatment groups, systemic glucocorticoid user type (naive, prevalent) and sub-populations of special interest.
	3. To quantify the crude and adjusted incidence rates of mortality and other disease outcomes within 30- and 90-days post treatment index date, by setting, in various treatment groups, systemic glucocorticoid

	user type (naive, prevalent) and sub-populations of special interest.
	4. To explore the performance of different coding definitions for COVID-19 and how they influence the size of the cohort
Country(-ies) of study	Belgium, France, Germany, UK, Italy, Netherlands, Spain
Author	E-CORE Network

List of Tables

List of Figures

Table of contents

List of Abbreviations

Abbreviation	Definition
ARDS	Acute respiratory distress syndrome
ATC	Anatomical Therapeutic Chemical Classification System
CDM	Common Data Model
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
DDD	Defined daily dose
DIC	Disseminated intravascular coagulation
ECMO	Extracorporeal membrane oxygenation
ECMO	Extracorporeal membrane oxygenation
EHDEN	European Health Data and Evidence Network
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GI	gastrointestinal
GP	General Practitioner
IMRD	IQVIA Medical Research Data
IPCI	Integrated Primary Care Information
LPD	Longitudinal Patient Database
MAS	macrophage activation syndrome
OMOP	Observational Medical Outcomes Partnership
PASS	Post-authorization safety study
PCR	Polymerase chain reaction
PDC	Proportion of days covered
PE	Pulmonary embolism
SARS Cov 2	severe acute respiratory syndrome coronavirus 2
SIDIAP	Information System for Research in Primary Care
VTE	Venous thromboembolism
WHO	World Health Organization

Responsible Parties

Principal Investigator
Prof Deborah Layton
Director of Drug Safety, IQVIA
United Kingdom
Tel: +447472121332
Email: deborah.layton@iqvia.com

Data Steward IQVIA
Christian Reich MD
IQVIA
Real World Solutions
201 Broadway
Cambridge, MA 02139, USA
Tel: +49 172 804 4129
E-mail: christian.reich@iqvia.com

Data Steward SIDIAP and HM Hospitales
Talita Duarte Salles, PhD
IDIAPJGol
Gran Via de les Corts Catalanes 587, àtic
08007, Barcelona, Spain
Tel.: +34934824243
E-mail: tduarte@idiapjgol.org

Data Steward IPCI
Katia Verhamme, MD, PhD
Erasmus MC
Department of Medical Informatics
POBOX 2040
3000 CA Rotterdam
The Netherlands
Tel: +31-10 704 4152
E-mail: k.verhamme@erasmusmc.nl

Subject matter expertise
Dani Prieto-Alhambra, MD, PhD
Pharmaco- and Device Epidemiology
University of Oxford
United Kingdom
Tel: +44 7447 916 537
E-mail: daniel.prietoalhambra@ndorms.ox.ac.uk

Subject matter expertise
Prof Sam Salek
University of Hertfordshire
United Kingdom
Email: m.s.salek@herts.ac.uk

Abstract

Section	Description
Title Section 2.0	Systemic glucocorticoids in the treatment of COVID-19 and risks of adverse outcomes in COVID-19 patients, within primary and secondary care settings
Rationale and background	Approximately 10-20% of COVID-19 positive patients, many of whom are older or have co-morbidities, suffer from pneumonia and acute respiratory distress syndrome (ARDS), requiring hospitalization and ventilatory support. It has been suggested that this population is also at higher risk of inflammatory immune system disorders. As a result, current treatment recommendations are to combine anti-viral therapy with immunosuppressive or immunomodulatory drugs to mitigate these immunologic complications, reducing COVID-19 associated morbidity and mortality. While the search for appropriate anti-viral therapy is ongoing, there have been some positive results with respect to systemic glucocorticoid use, such as dexamethasone, which has been associated with reduced mortality in ventilated patients and those on supplemental oxygen therapy. This has mobilised efforts to repurpose some of these steroids for the treatment of severe COVID-19 cases. That said, a lot of information on steroid use in COVID-19 patients is currently missing. Treatment type, dosage, timing of administration, as well as identification of patient risk groups that will benefit most from the treatments, is inadequately explored. To partially address these research gaps, this protocol describes a non-comparative study to explore patterns of systemic glucocorticoid use and administration in patients with either a first confirmed diagnosis for COVID-19 (diagCOVID-19) or a first positive PCR test for SARS-CoV-2 (labCOVID-19) using healthcare databases from seven European countries.
Research question and objectives	The aim of this study is to describe patterns of systemic glucocorticoid use, as well as the risks of adverse events associated with these medications, in diagCOVID-19 or labCOVID-19 patients across seven European countries in ambulatory and hospital inpatient care settings. **Primary Objective**: To describe utilization of systemic glucocorticoids (e.g., dexamethasone, prednisolone, methylprednisolone or hydrocortisone) for treatment of COVID-19 in two settings: hospitalized (in hospital care) and ambulatory (any care received outside of hospital) within 90 days following COVID-19 diagnosis. The following variables will be described:

- Prevalent use or naïve (incident) use of systemic glucocorticoids at date of diagnosis of COVID-19
- Concomitant use of other medications (number and type) and invasive/non-invasive respiratory support during follow up
- Type of systemic glucocorticoid received
- Time to systemic glucocorticoid initiation from COVID-19 diagnosis
- Route of administration
- Systemic glucocorticoid daily dose at initiation (treatment index date), cumulative duration, distribution of duration of use and cumulative dose of systemic glucocorticoid received
- For prevalent users: proximity of previous glucocorticoid use to COVID-19 diagnosis (current use (concomitant on date of COVID-19 diagnosis, recent use (between 15-30 days before date of COVID-19 diagnosis) or remote use (use ended more than 30 days before date of COVID-19 diagnosis))

Secondary Objectives:

1. To describe **at COVID-19 diagnosis date and at treatment index date** the demographic, health and clinical patient characteristics). The following variables will be described:

   – demographics

   – comorbidities (number and type)

   – symptoms (number and type) preceding and/or on the date of diagnosis the diagnosis if captured

   – time from onset of COVID-19 illness symptoms to confirmed diagnosis date

Some of these characteristics will be stratified by setting, glucocorticoid exposure type (naive, prevalent) and subgroups of special interest (e.g., chronic cardiac and pulmonary disease, diabetes, renal insufficiency).

2. To quantify the crude and adjusted incidence rates and time to onset of adverse events of interest (e.g., infections, hyperglycaemia, GI bleeding, composite of cardiovascular disease events) within **30 and 90 days post treatment index date**, in various treatment groups, stratified by setting, glucocorticoid exposure type (naive, prevalent) and subgroups of special interest.

3. To quantify the crude and adjusted incidence rates of mortality and other disease outcomes within **30 and 90 days post treatment index date**, in **various treatment**

groups, stratified by setting glucocorticoid exposure type (naive, prevalent)   and subgroups of special interest.

4. To explore the performance of **different coding definitions** for COVID-19 and how they influence the size of the cohort

Study design	This is a PASS study using a descriptive cohort study design using secondary data sources (electronic medical records).
Setting	COVID-19 diagnosed patients across primary and secondary care settings in seven European Countries (Belgium, France, Italy, Netherlands, Germany, United Kingdom, Spain), with the study time period from 1st January 2020 to 1st January 2021 (at the latest), will be considered for analysis. Cut-off dates for data inclusion i.e. data lock points will vary based on the country and database used. Four different cohorts based on healthcare setting (ambulatory or hospital setting) and systemic glucocorticoid user type (naïve or prevalent) will be created. Index dates, outcomes and follow-up censoring vary per objective and will be appropriately applied in the analyses.
Variables	**COVID-19 Case Definition**

- 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

  > Secondary Objective 4 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 glucocorticoid (dexamethasone, prednisolone, prednisone, methylprednisolone or hydrocortisone)
- Glucocorticoid for pre-existing conditions, described by metrics such as proportion of days covered in lookback period and recent use of medication based on prescription records.
- Other COVID-19 treatments (e.g., antiviral, antibiotic, statin therapy)
- Respiratory support

These will be further characterized using specific criteria and formula for dose and duration.

For secondary objectives 2 and 3 where the index date is based on treatment, the treatment exposure groups will be categorized as follows:

- Use of systemic glucocorticoids without other treatments for COVID-19
- Use of systemic glucocorticoids plus other treatments for COVID-19
- Only other treatments and respiratory support with no systemic glucocorticoids
- No specific treatments for COVID-19 infection

Outcomes (Secondary objectives 2 and 3)

- Adverse events: composite cardiovascular events, hypertension, arrhythmia, gastritis, gastric ulcer, GI bleed, psychosis, myopathy, hyperglycaemia and any bacterial viral, fungal and parasitic infection

- Disease severity:
  - Ambulatory: Hospital admission, venous thromboembolism or pulmonary embolism, disseminated intravascular coagulation, death of any cause
  - Hospital: Intensive services as an outcome in inpatient cohorts (including mechanical ventilation and Extracorporeal membrane oxygenation (ECMO)), venous thromboembolism or pulmonary embolism, disseminated intravascular coagulation, discharge from hospital, death of any cause

	Demographic and clinical variables: age, sex, month of diagnosis, comorbidities
Data sources	*Ambulatory*: - Belgium, France, Italy – Longitudinal Patient Database (IQVIA) - Germany – Disease Analyser (IQVIA) - United Kingdom – IQVIA Medical Research Data (IMRD) UK - The Netherlands – Integrated Primary Care Information (IPCI) - Spain – Information System for Research in Primary Care (SIDIAP) as primary care databases *Hospital:* - Hospital de Madrid Hospitales
Data analysis	Continuous variables will be described using mean, standard deviation, median, first and third quartiles, minimum, and maximum. Categorical variables will be described by the number and percentage of patients in each category. Patterns of missingness will be reported and 95% confidence Intervals will be presented. The

results for each country and where available, each setting will be presented separately.

Primary Objective:

- Descriptive analysis for systemic glucocorticoid use patterns will be carried and stratified by setting, glucocorticoid exposure type (naive, prevalent) and subgroups of special interest.
- Kaplan-Meier methods will be used to estimate time to systemic glucocorticoid initiation from COVID-19 diagnosis, stratified by route of administration (oral vs intravenous).

Secondary Objective 1:

- Cohort-specific descriptive statistics summarizing demographic, health and clinical patient characteristics, stratified by setting, glucocorticoid exposure type glucocorticoid (naive, prevalent), and subgroups of special interest will be presented.

Secondary Objectives 2 and 3:

- Crude incidence (presented as both proportions and rates) for the relevant outcomes for each of the treatment exposure groups will be calculated.
- The cumulative incidence rates will be reported at the end of follow-up (30 and 90 days).
- Data will be stratified by setting, glucocorticoid exposure type (naive, prevalent), and subgroups of special interest
- Cox regression models (using multivariable models and using PS adjustment) will be used to compute the adjusted incidence rates.

Secondary Objective 4:

- The performance of different COVID-19 disease definitions based on rule-based phenotype algorithms will be explored using diagnostic predictive modelling

Plans for Disseminating and Communicating Study Results	IQVIA will produce a study report in accordance with the GVP guidelines VIII (EMA/813938/2011). Study information (including protocol and final report) will be added in the EU PAS register.

Amendments and Updates

Major and Minor Amendments	
Major Amendments Section 3.0	**Minor Amendments**
• None	• Abstract section • Appendix 3 • Misspellings and editorial checks across the entire document

Number	Date	Section of the Protocol	Amendment or update	Reason
1	30th October 2020	Throughout document	Amended drug name from corticosteroids to glucocorticoids	Recommendation from reviewer to capture narrower term
2	30th October 2020	2.0	Re-aligned with the updated protocol. Editorial checks	
3	30th October 2020	6.2 and 6.3	Rewording of objective 4 Editorial checks Clarification of the stratifications performed	Clarification
4	30th October 2020	7.0	Editorial checks	
5	30th October 2020	7.2.2	Removal of ≥18 criteria, pediatric patients allowed	Comment from reviewer
6	30th October 2020	7.2.2	Change of 365 to 120 days prior exposure to corticosteroids for determining naïve and prevalent users and also removed from hospital cohort in figure 1 hospitalization cohorts	
7	30th October 2020	7.2.3	Follow up period has been changed from 180 days to 90	Error corrected

8	30th October 2020	7.3.1	Update of alternative COVID-19 definitions using CDC and WHO guidelines	In line with the amended objective 4 and alternative methodology
9	30th October 2020	7.7.5	Further information of use of propensity score adjustment strategy.	Further details requested
10	30th October 2020	7.7.6	A new method is proposed to assess the performance of various COVID-19 definitions probabilistic diagnostic predictive model	Comment from the reviewer
11	30th October 2020	7.7.7	New section on Meta-analysis added	Comment from the reviewer
12	16th November 2020	7.2.2	Hospitalization 30 days after diagnosis allowed	Comment from the reviewer
13	16th November 2020	7.1	Figure 1 updated with the new inclusion criteria	Comment from the reviewer
14	16th November 2020	7.2.4	Starting dose of steroids was added as a subgroup	Comment from the reviewer
15	16th November 2020	7.3.2	Define the low and high dose categories	Comment from the reviewer
16	16th November 2020	7.7.8	A sensitivity analysis to exclude short term use corticosteroid users was added	Comment from the reviewer
17	16th November 2020	7.9.1	Some limitations were added	
18	4th December 2020		Abstract amended to align with the protocol Misspellings and editorial checks across the entire protocol	
19	16th March 2021	7.2.2	Inclusion criteria for hospitalized cohort were modified to include patients who have diagnosis mentioned only at discharge (known to be the case for US Hospital database) Also, the window for the prevalent user was specified (3 to 120 days)	From SAP review
20	16th March 2021	7.2.4	Heart failure added to the list of cardiovascular diseases	From SAP review

21	16th March 2021	7.3.1	For the main definition, reference was made to the code lists in the Annex as the mentioned code list was not complete. Two unspecific codes were removed from the suspected COVID definition as were considered too unspecific during feasibility tests. Added the word 'distinct' in the symptomatic definition.	
22	16th March 2021	7.3.2	Categories of prevalent glucocorticoids exposures changed to current very recent and recent	After medical QC, alignment the with SAP
23	16th March 2021	7.3.2.3	Switch to another glucocorticoid is not considered a censoring event anymore (they are perceived as interchangeable)	After medical QC, alignment with SAP
24	16th March 2021	7.3.4	VTE contains PE therefore the specification of PE was removed	After medical QC, alignment with SAP
25	16th March 2021	7.3.5	Renal and hepatic impairment added to the comorbidities list.	After medical QC, alignment with SAP
26	16th March 2021	7.7.4 and 7.7.5	PS adjustment was removed since there is no formal comparator, the results will be hard to interpret	SAP review
27	16th March 2021	7.7.4	For the AE analysis, a stratification by medical history of that specific event was introduced in order to distinguish safety signals from reoccurrence of chronic/previous disease	SAP review
28	16th March 2021	7.7.4	Adjustment for age and sex mentioned	SAP review
29	16th March 2021	7.8	Quality control section aligned with E-CORE specifications.	SAP review

Milestones

Milestone	Planned date
Milestone Section 4.0	Planned date
Study protocol submitted	20th September 2020
Approval Study Protocol by EMA	23th November 2020
Registration in the EU PAS register	October 2020
Start of data collection	NA. Data extraction start date is 1st January 2020
End of data collection	NA. Data extraction last end date will be the latest available date in each database up to maximum 1st January 2021
Final study report provided to EMA	July 2021

Milestones

Rationale and Background

Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2) originated in China in December 2019 and was accepted as a global pandemic March 2020. (1) The majority of COVID-19 infections are either asymptomatic or have mild symptoms, however, progression to pneumonia and acute respiratory distress syndrome (ARDS) is reported in 10-20% cases, especially in those of older age or with co-morbidities who are subsequently more likely to be hospitalized and require ventilatory support. (2,3) The overall case fatality rate is hard to estimate in view of rapidly changing data and serious underestimation of cases, however, it is considered to be around 3%. (4) Amongst COVID-19 patients admitted to UK hospitals, the case fatality rate is over 26% overall, and over 37% in patients requiring invasive mechanical ventilation. (5)

According to the current literature, older age and co-morbidities are associated with higher risk of immunologic complications such as macrophage activation syndrome (MAS) and cytokine storm syndrome secondary to, and disproportionate to the severity of Covid-19 infection. (6) Accordingly, there are recommendations that anti-viral treatment should be combined with appropriate immunosuppressive and immunomodulatory drugs since it is hypothesized that early recognition and appropriate treatment of immunologic complications will decrease the morbidity and mortality in COVID-19 patients. (7)

With regards to treatment options, there are many immunosuppressive and immunomodulatory drugs which may be repurposed. Initially antimalarial drugs (chloroquine and hydroxychloroquine) were reported to have immunomodulatory effects and antiviral activity and beneficial effects among patients with COVID-19 (8), however, serious concerns have been raised about the results of clinical trials on these products.(9) Other classes of drugs that show potential include interleukin (IL)-6R antagonists, IL-1 antagonists, TNF-alpha inhibitors, and Janus kinase inhibitors. (10,11) Systemic glucocorticoid use in ARDS is controversial, however, some positive results have been reported for dexamethasone. (12–14). Until March 2020 systemic glucocorticoid use was not recommended for routine use by the WHO except in patients with lethal complications, because of a lack of positive evidence from randomized controlled trial (RCTs). (15) More recently, the RECOVERY RCT has shown a significant reduction of death in COVID-19 patients treated with dexamethasone by 35% in ventilated patients and by 20% amongst patients on supplemental oxygen therapy, however no benefit was observed in mild cases.(13,16)

Several literature reviews have attempted to summarize existing evidence. Lu et al. performed a review addressing use of steroids in critically ill COVID-19 patients to explore whether these drugs may reduce mortality, however for patients with severe COVID-19 without ARDS the evidence remains inconsistent. (17) Another systematic review (11) found 5 studies on the role of steroids for COVID-19 reporting inconsistent outcomes. Of the 5 studies (4 retrospective studies and 1 quasi-prospective study) conducted for evaluating the role of glucocorticoids, 3 studies have shown benefit, while 2 studies showed no benefit and there was a suggestion of significant harm in critical cases in one sub-study.

A lot of questions remain unanswered, especially which patients might benefit from glucocorticoids use, what is the best substance and dose (7) and timing of administration. (18) Some US and UK guidelines now recommend to low-dose glucocorticoid therapy ("shock-reversal"), over no glucocorticoid therapy and only in severe patients, however the evidence is considered weak. (19)

The current study aims to partially answer some of the remaining questions as detailed in the following sections.

Research Questions and Objectives

6.1 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.

6.2 Primary Objective

To describe utilization of systemic glucocorticoids (e.g., dexamethasone, prednisolone, methylprednisolone or hydrocortisone) for treatment of COVID-19 in two settings: hospitalized (in hospital care) and ambulatory (any care received outside of hospital) within 90 days following COVID-19 diagnosis. The following variables will be described:

- Prevalent use or naïve (incident) use of systemic glucocorticoid at date of diagnosis of COVID-19
- Concomitant use of other medications (number and type) and invasive/non-invasive respiratory support during follow up
- Type of systemic glucocorticoid received
- Time to systemic glucocorticoid initiation from COVID-19 diagnosis
- Route of administration
- Systemic glucocorticoid daily dose at initiation (treatment index date), cumulative duration, distribution of duration of use and cumulative dose of systemic glucocorticoid received
- For prevalent users: proximity of previous glucocorticoid use to COVID-19 diagnosis (current use (concomitant on date of COVID-19 diagnosis, very recent use (end date within 30 days before date of COVID-19 diagnosis) or recent use (use ended more than 30 days before date of COVID-19 diagnosis))

6.3 Secondary Objectives

1. To describe **at COVID-19 diagnosis date and at treatment index date** the demographic, health and clinical patient characteristics. The following variables will be described:

   - demographics

   - comorbidities (number and type)

   - symptoms (number and type) preceding and/or on the date of diagnosis the diagnosis if captured time from onset of COVID-19 illness symptoms to confirmed diagnosis date.

Some of these characteristics will be stratified by setting, glucocorticoid exposure type (naive, prevalent) and subgroups of special interest. (e.g., chronic cardiac and pulmonary disease, diabetes, renal insufficiency, see Section 7.2.4 Subgroups).

2.To quantify the crude and adjusted (selected confounders tbc) incidence rates and time to onset of adverse events of interest (e.g., infections, hyperglycaemia, hypertension, GI bleeding, composite of cardiovascular events) within **30 and 90 days post treatment index date**, in **various treatment groups**, stratified by setting, glucocorticoid exposure type (naive, prevalent) and subgroups of special interest.

3. To quantify the crude and adjusted incidence rates of mortality and other disease outcomes within **30- and 90-days post treatment index date**, in **various treatment groups**, stratified by setting, glucocorticoid exposure type (naive, prevalent) and subgroups of special interest.

4. To explore the performance of **different coding definitions** for COVID-19 and how they influence the size of the cohort

Out of scope:

To assess comparative effectiveness and safety between individual treatments administered for COVID-19 infection or between treated and untreated patients.

To validate definition for COVID-19 using clinical adjudication of individual patient medical records sampled from the study population

Research Methods

7.1   Study Design

This is a descriptive cohort study using secondary data sources (electronic medical records) from eight databases in seven European countries reflecting either hospital or ambulatory care setting. The study population will be comprised of a cohort of diagCOVID-19 or labCOVID-19 patients in the database within the study time period.

Patients may be either diagnosed and followed-up in an outpatient or in an inpatient setting (according to the database) and they might be new users or prevalent users of systemic glucocorticoids. Based on these 2 characteristics, four mutually exclusive cohorts will be created overall. Not all cohorts can be constructed in each database. They will be used differently depending the objective as mentioned in the analysis section. An overview of the study design is provided in Figure 1 below.

Patients will be followed during the study period from COVID-19 diagnosis date to assess the utilization of systemic glucocorticoids specifically indicated for the treatment of COVID-19 and from treatment index date for the occurrence of outcomes of interest.

2. Ambulatory cohort
Naive user

Diagnosis index date
(COVID-19)
Day 0

Treatment index date
(Corticosteroid)
Day 0

INCLUSION Assessment Window
(continuous observation time in the database);
Days [-365, -1]

INCLUSION Assessment Window
(COVID-19 diagnosis by lab test or diagnostic code);
Days [01-12-2019, -1]

Exclusion Assessment Window
(corticosteroid use);
Days [-120, -1]

FOLLOW-UP Assessment Window
([0, 90 or Censor [d])

Exclusion Assessment Window
(Hospital admission);
Days [-30, -1]

FOLLOW-UP Assessment Window
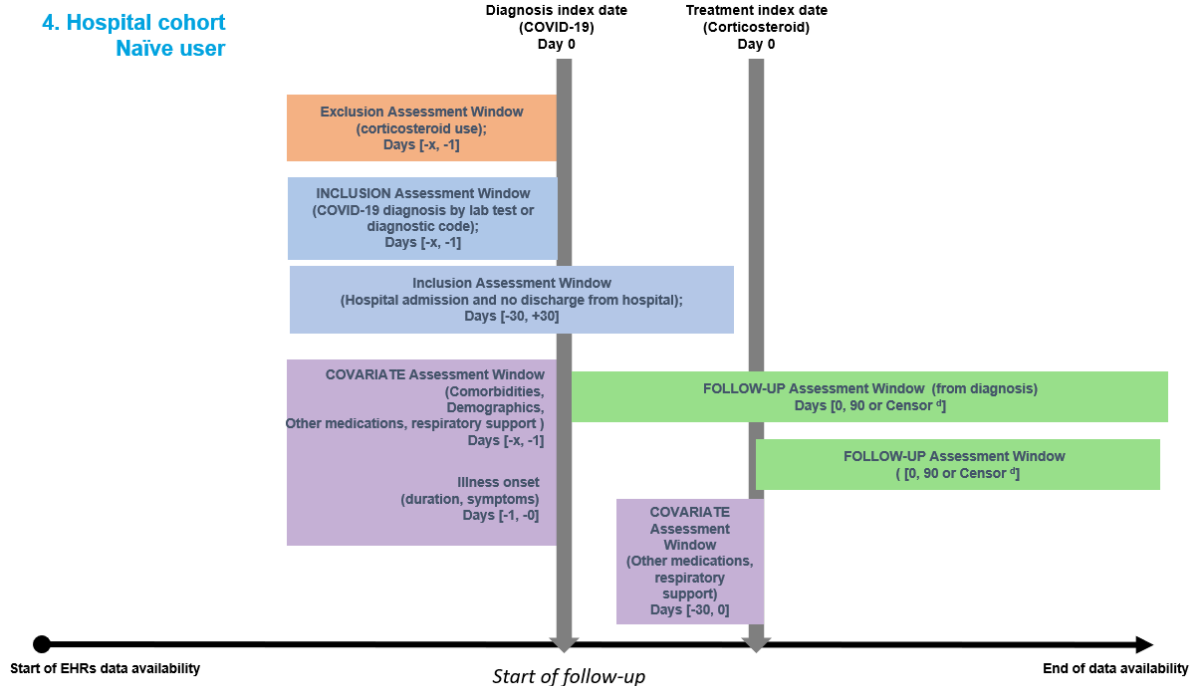Days [0, 90 or Censor [d]

COVARIATE Assessment Window
(Comorbidities)
Days [-365, 0]

Illness onset
(duration, symptoms)
Days [01-12-2019, -1]

COVARIATE Assessment Window
(Other medications, respiratory support)
Days [-30, 0]

COVARIATE
Assessment
Window
(Other medications,
respiratory support)
Days [-30, 0]

COVARIATE Assessment Window
(Demographics)
Days [0, 0]

Start of EHRs data availability   *look-back*   *Start of follow-up*   End of data availability

3. Hospital cohort
Prevalent user

Diagnosis index date
(COVID-19)
Day 0

Treatment index date
(Corticosteroid)
Day 0

INCLUSION Assessment Window
(Have a corticosteroid exposure at
admission);
Days [-x, -1]

INCLUSION Assessment Window
(COVID-19 diagnosis by lab test or
diagnostic code);
Days [-x, -1]

Inclusion Assessment Window
(Hospital admission and no discharge from hospital);
Days [-30, +30]

COVARIATE Assessment Window
(Comorbidities,
Demographics,
Other medications, respiratory support)
Days [-x, -1]

FOLLOW-UP Assessment Window (from diagnosis)
Days [0, 90 or Censor [d]

FOLLOW-UP Assessment Window
([0, 90 or Censor [d])

Illness onset
(duration, symptoms)
Days [-1, -0]

COVARIATE
Assessment
Window
(Other medications,
respiratory
support)
Days [-30, 0]

Start of EHRs data availability   *Start of follow-up*   End of data availability

Figure 1 Study design

7.2 Setting

The proposed setting for this study will be within seven European countries (Belgium [general practice EHR], Netherlands [general practice EHR], Germany [general practice EHR], France [general practice EHR], Italy [general practice EHR], Spain [general practice EHR, hospital EHR], and the United Kingdom [general practice EHR].

The study will be conducted using data from multiple real-world data (RWD) sources previously mapped to the OMOP CDM in collaboration with the OHDSI and European Health Data and Evidence Network (EHDEN) initiatives.

Each cohort is defined in a separate setting (either hospital or primary care) based on the data source type and will be described at diagnosis of diagCOVID-19 or labCOVID-19 accordingly. The follow up will take place in the same setting and switch of setting (hospitalization for ambulatory cohorts or discharge for hospital cohorts) during follow up will be captured as an outcome.

7.2.1 Study Time Period

The study period, when index events and outcomes of interest can be observed, will start from 1st January 2020 and end at the latest available date for all data sources in 2020 (Table 1) which can be 1st January 2021, at the latest. Before the final extraction and analysis, data will be updated as frequently as possible, in collaboration with local data partners. The results will not be refreshed after the data extraction which will take place on 1st February 2021 at the latest.

Table 1 Data lock point for each available database

Database	Actual/Future data lock points
LPD Belgium	December 2020
LPD France	November 2020
DA Germany	December 2020
UK IMRD	June 2020
LPD Italy	December 2020
IPCI	December 2020
SIDIAP	December 2020
HM Hospitales	April 2020

7.2.2   Patient Selection

Inclusion Criteria

7.2.2.1 Four cohorts will be created based on healthcare setting and type of steroid use. Their eligibility criteria being described below (using Covid-19 catch-all definition Section 7.3.1):

Ambulatory prevalent user

– Have at least 365 days of continuous observation time prior to cohort entry (COVID-19 diagnosis)

– Have a glucocorticoid (oral or parenteral) exposure in the 3 to 120 days prior to diagnosis date (unrelated to COVID-19 diagnosis)

– Have a positive PCR test for SARS-CoV-2 (labCOVID-19) or a confirmed COVID-19 diagnosis (diagCOVID-19)

– Have no hospitalizations in the 30 days prior to or on index

Ambulatory naive user

– Have at least 365 days of continuous observation time prior to cohort entry (COVID-19 diagnosis)

– Have no glucocorticoid (oral or parenteral) exposure in the 3 to 120 days prior to index (unrelated to COVID-19 diagnosis)

– Have a positive PCR test for SARS-CoV-2 (labCOVID-19) or a confirmed COVID-19 diagnosis (diagCOVID-19)

– Have no hospitalizations in the 30 days prior to or on index

Hospitalized prevalent user

– Have a glucocorticoid (oral or parenteral) exposure in the 120 days prior to index (unrelated to COVID-19 diagnosis)

– Have a positive PCR test for SARS-CoV-2 (labCOVID-19) or a confirmed COVID-19 diagnosis (diagCOVID-19) (index date)

– Diagnosis for COVID-19 during a hospitalisation where the start date of hospitalisation is <30 days before diagnosis or hospitalised within 30 days after diagnosisHave no intensive services in the 30 days prior to or on index

Hospitalized naïve user

– Have no prior exposures to glucocorticoids in the 3 to 120 days prior to index

– Have a positive PCR test for SARS-CoV-2 (labCOVID-19) or a confirmed COVID-19 diagnosis (diagCOVID-19)

– Diagnosis for COVID-19 during a hospitalisation where the start date of hospitalisation is <30 days before diagnosis or hospitalised within 30 days after diagnosisHave no intensive services in the 30 days prior to or on index

7.2.2.2   **Exclusion Criteria**

Missing age or sex

7.2.3   Follow-up

Two index date definitions will be applied as appropriate for each objective.

- Diagnosis index date is defined as a positive PCR test for SARS-CoV-2 (labCOVID-19) or a confirmed COVID-19 diagnosis(diagCOVID-19) whichever is the earliest.
- Treatment index date is defined as start of first systemic glucocorticoid treatment episode specifically for the treatment of COVID-19, irrespective of whether the patient is a prevalent or naïve user.

Follow up for all patients will begin from the index date until they experience the outcome of interest (endpoint, depending on the objective) or until cohort exit (date of censoring). The patients will be followed up for maximum 90 days or until censoring occurs, censoring criteria are:

- death
- patient exit (deregister) from a contributing data provider (GP practice)
- end of the database's data collection
- end of study period (latest data cut-off)

The lookback window for evaluating risk factors, medical history is 365 days and will be applied only to outpatient cohorts.

7.2.4   Subgroups

The following subgroups will be used to stratify the descriptive tables in Primary objective 1 and secondary objective 1-3. These are a mix of contraindications (e.g. heart failure, myocardial infarction, ischaemic stroke, hypertension, diabetes) and underrepresented groups in clinical trials (e.g. renal impairment, hepatic impairment) as well as conditions for which glucocorticoids are indicated (COPD and asthma).

Comorbidities

- Cardiovascular diseases[1] (e.g., hypertension, arrhythmia, valve disorders, stroke, acute myocardial infarction, heart failure)

- Type 2 diabetes mellitus

- Respiratory diseases: asthma, COPD

- Renal impairment

- Hepatic impairment

- Autoimmune diseases (e.g., type 1 diabetes mellitus, rheumatoid arthritis, psoriasis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, Addison's, Graves, Sjogrens, Hashimoto, myasthenia gravis, autoimmune vasculitis, pernicious anaemia, celiac disease, scleroderma, sarcoid, ulcerative colitis, Crohn disease)

- Starting dose of steroids: low dose and high dose (use the cut off defined by WHO)

Speciality of the healthcare practitioner (GPs vs specialists) in databases that record this information

The subgroups are not mutually exclusive, and patients can contribute to more than one subgroup, The above subgroups will be used for descriptive purposes and will not be used for statistical comparisons.

7.3   Variables

Each treatment/variable definition will be based on standard concepts in the OMOP Standardized Vocabularies. Variables will be identified using pre-specified concept sets reviewed by a core team of clinicians, epidemiologists, vocabulary experts, and health data scientists with extensive expertise in the use of the OMOP CDM and the OHDSI tools. Some of the codes used and validated before will be reused in this project.

7.3.1. COVID-19 diagnosis

The definitions used for COVID-19 diagnosis will depend on the data source, for example, the primary care data sources usually do not contain the laboratory values. All the analyses will be run on the

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[1] Cardiovascular disease as a subgroup variable has a different definition from the composite cardiovascular event as an adverse event which is focused on acute and severe outcomes.

main definition while the alternative definitions will be used for secondary objective 4 - to explore how COVID-19 is captured across different databases. (see Appendix 1 for code lists)

1. Catch-all (main definition, the most sensitive)

Defined either as the first confirmed diagnosis for COVID-19 **OR** the first SARS-CoV-2 positive PCR test, if both present the earliest date will be considered.

Alternative definitions

2. Diagnosis confirmed (diagCOVID-19)

Defined as one of the following medical codes for COVID-19 at any time (first occurrence considered), as detailed in Appendix 1

3. Laboratory confirmed (labCOVID-19)

Defined as a record of SARS-CoV-2 positive PCR as performed on nasopharyngeal swabs and/or on respiratory tract secretions and aspirates.

We will not include the testing for the presence of antibodies due to the issue of not knowing the point of infection via antibody testing. If patient has more than one test, first occurrence will be considered

4. Symptomatic COVID-19.

At least two distinct symptoms of the following
- Cough
- Dyspnoea
- Fever, unspecified
- Malaise and fatigue
- Myalgia
- Anosmia,Hyposmia or Dysgeusia episodes

5. Suspected COVID-19
- Coronavirus as the cause of diseases classified to other chapters
- Coronavirus infection, unspecified site
- Other viral pneumonia
- Acute bronchitis due to other specified organisms
- Unspecified acute lower respiratory infection
- Bronchitis, not specified as acute or chronic
- Adult respiratory distress syndrome
- Other specified respiratory disorders

This classification is aligned with the ICD-10 International coding guidance on COVID-19 disease (20)

7.3.2 Exposures

The following exposures of interest are captured in this study

Table 2 Exposures of interest

	Cohort	When is measured
Glucocorticoids used in COVID-19 indication	All	At diagnosis index date and follow-up
Glucocorticoids for pre-existing conditions	Only in prevalent users' cohort	Before diagnosis index date
Other COVID-19 treatments: • antiviral therapy (AV) • antibiotic therapy (AB) • immune-based therapy (IB) • antithrombotic therapy (AT) • anti-hypertensives (AH) • statins (S) • anti-diabetic (AD) (see Appendix 3)	All	At diagnosis index date and during follow-up
Oxygen therapies	All	At diagnosis index date and during follow-up*

* During follow-up this will be considered as an outcome

7.3.2.1 Glucocorticoids

Glucocorticoids used in COVID-19 indication

The primary treatment group of interest is based on exposure to systemic glucocorticoids. The following drugs will be considered as being used for COVID-19 diagnosis:

- Dexamethasone (H02AB02)
- Prednisone (H02AB07)
- Prednisolone (H02AB06)
- Methylprednisolone (H02AB04)
- Hydrocortisone (H02AB09)

Only glucocorticoids which were investigated in clinical trials (13,21) or are recommended by clinical guidelines are included (22–24) to avoid misclassification of steroids used for other conditions. As indication is not captured in the available databases, a glucocorticoid treatment will be considered to have been initiated for COVID-19 treatment if:

For incident users
- The glucocorticoid treatment was initiated between 2 before and 30 days after COVID-19 diagnosis date (21)
- It is one of the five glucocorticoids recommended for COVID-19 as above

For prevalent users

- The glucocorticoid treatment was initiated between 2 before and 30 days after COVID-19 diagnosis date
- It is one of the five glucocorticoids recommended for COVID-19 as above
- The glucocorticoid started after COVID-19 diagnosis differs from the chronically used glucocorticoids OR there is a change in dose compared to the prevalent use, occurred after COVID-19 diagnosis.

Glucocorticoids for pre-existing conditions

For the prevalent users, any steroid in the ATC class H02 glucocorticoids for systemic use will be considered. A patient is defined as a systemic glucocorticoids prevalent user if it has at least one prior exposure to systemic[2] glucocorticoids in the 120 days prior to diagnosis index date.

For the description of prevalent users of glucocorticoids, categories of use will be created based on proportion of days covered (PDC) during the lookback period. PDC is calculated as the number of days in period covered by prescriptions divided by number of days in the period.

- PDC > 85% as heavy user
- PDC 50-85% as moderate user
- less than 50% PDC as light user

Another categorization of prevalent glucocorticoids user will be based on how recently in the past the last prescription was observed:

– current use (concomitant on date of COVID-19 diagnosis)
– very recent   (end date within 30 days before date of COVID-19 diagnosis)
– recent (use ended more than 30 days before date of COVID-19 diagnosis)

7.3.2.2 Other COVID-19 treatments

Additional distinct treatment cohorts will be created based on use of other drugs that might be used as treatment of COVID-19 according to various guidelines. Patients will be considered exposed to other pharmacotherapeutic treatments for COVID-19 if available prescription data are available and if the drugs are in the list below.

a) antiviral therapy (AV);
b) antibiotic therapy (AB)
c) immune-based therapy (IB)
d) antithrombotic therapy (AT)
e) anti-hypertensives (AH)
f) statins (S);
g) anti-diabetics (AD);

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[2] Systemic effects of inhaled and topical use of glucocorticoids is considered low and therefore use will not be considered for this study

These treatments were identified and classified through systematic review of CDC treatment guidelines, clinicaltrials.gov, or clinical guidelines, as part of another OHDSI project. (25) The full list of products is available in Appendix 3.

7.3.2.3 Operationalization of exposure metrics

Cumulative duration

For glucocorticoids used in COVID-19 indication

Exposure to a treatment will commence on the date of the first qualifying record, subject to satisfying all inclusion criteria listed in section 7.2.2. Each drug exposure record has a start date and inferred end date, which is either explicitly entered or derived from other available information, such as days' supply or refills. Duration of each episode will be calculated as end date minus start date or directly from days' supply variable, whatever available. For each patient, the cumulative duration of use will be calculated as the sum of the duration of treatment episodes.

Table 3 Calculation of duration of use and end of treatment across databases

	IPCI	UK IMRD	Germany DA	Belgium LPD	SIDIAP	France LPD
If days_supply is missing	Use amount and dose extracted from the sig	Use daily dosage along with prescribed quantity	Impute with the most frequent daily dosage or DDD at a therapy level	Use calculated quantity/ units_per_day.	Use the quantity, daily dosage and DDD of each drug	Use the quantity and daily dosage of each drug
If still missing	Use the DDD and prescribed quantity	Impute most frequent daily dose at the drug level	-	-	-	-
If still missing	Use the modal duration in the database					

DDD= defined daily dose; sig - the directions ('signetur') on the drug prescription as recorded in the original prescription (and printed on the container) or dispensing record from the physician.

Daily dose

For glucocorticoids used in COVID-19 indication, the prescribed daily dose at initiation of glucocorticoid (treatment index date) will be recorded and categorized in low and high dose. The definition of low dose and high dose will use the cut off defined by WHO in their prospective meta-

analysis from REACT subgroup (16), namely: 15 mg/d of dexamethasone, 400 mg/d of hydrocortisone, and 1 mg/kg/d of methylprednisolone.

The current recommendation is to use 10 mg or dexamethasone for maximum 10 days, administered orally or intravenously. In case glucocorticoids other than dexamethasone are administered, their dose will be converted in prednisolone equivalents as described:
https://emedicine.medscape.com/article/2172042-overview

Steroids often have adjusted dose regimens such that drug may be slowly increased or decreased over time and short acute treatment episodes are also possible. Such changes in dose over time will not be examined, however total cumulative dose will be examined in relation to outcomes of interest (see below).

Cumulative dose

For glucocorticoids used in COVID-19 indication, orally administered, if quantity is available, the formula to calculate the cumulative exposure in mg is described below:

$$Cumulative\ dose_{solid}[mg] = \sum_{all\ exposures} quantity \times amount\_value\ [mg]$$

If the **quantity is missing**, the number of units per day for solid formulations are extracted. The cumulative exposure in mg can then be calculated using the following formula:

$$Cumulative\ dose_{solid}[mg] = \sum_{exposures} units\ per\ day \times amount\_value\ [mg] \times duration$$

For intravenous administration (bolus administration), the dose administered each time will be counted.

$$Cumulative\ dose\ intravenous\ [mg] = \sum_{all\ exposures} amount\_value\ [mg]$$

Exposure groups for incidence calculation (secondary objective 2 and 3)

For the incidence rates calculation, an on-treatment exposure will be considered with mutually exclusive groups to allow calculation of incidence rates.

Each person will be classified as belonging to one of the following mutually exclusive exposure groups at treatment index date following COVID-19 diagnosis:

- Use of systemic glucocorticoids without other treatments for COVID-19 (drug and respiratory support)

- Use of systemic glucocorticoids plus other treatments for COVID-19 (drug and respiratory support)

- Only other treatments and respiratory support with no systemic glucocorticoids

- No specific treatments for COVID-19 infection (other concomitant treatments for indications other than for COVID-19 are allowed)

A single prescription would be enough to consider the patient as exposed. See section 7.3.2.1 for description of 'other treatment for COVID-19' that are included.

Only the first episode of exposure will be considered, patients being censored when they switch to another treatment or when follow up ends. Duration of follow-up for each treatment cohort will be summarized and will constitute the denominator for calculation of effect estimates. A persistence window of 7 days between drug utilization records for each study drug will be allowed considered as continuous exposure for the outcome's assessment.

In case that more than 70% of the patients are censored, a sensitivity approach will be applied for objectives 2 and 3 (see Section 7.7.8).

7.3.3 Adverse events

The following acute adverse events will be evaluated in the glucocorticoid treated patients and patients treated with alternative therapies:

- Composite cardiovascular events (composite of ischemic stroke, haemorrhagic stroke, heart failure, acute myocardial infarction or sudden cardiac death)

- Hypertension

- Arrhythmia

- Gastritis, gastric ulcer, GI bleed

- Psychosis

- Myopathy

- Hyperglycaemia

- Infections

- Any bacterial infection

- Any viral infection

- Any fungal infection

- Any parasitic infection

And if numbers allow, within infections, also separately look at:

- Sepsis

- Lower respiratory tract infections

- Herpes zoster

- Cutaneous cellulitis

7.3.4 Disease severity outcomes

In ambulatory care cohorts

–   Hospital admission

–   Venous thromboembolism (VTE)

–   Disseminated intravascular coagulation (DIC)

–   Death of any cause

In hospitalized cohorts

–   Intensive services as an outcome in inpatient cohorts (including mechanical ventilation and Extracorporeal membrane oxygenation (ECMO))

–   Discharge from hospital

–   Death of any cause

–   Venous thromboembolism (VTE)

–   Disseminated intravascular coagulation (DIC)

They will all be treated as time to event outcomes, see section 7.7 for details.

7.3.5 Other Variables

Age – measured both as continuous and categorical variable in years. The following categories will be created:
–   <18
–   ≥18 and <65
–   ≥ 65 and <75
–   ≥75

Sex
–   Male
–   Female

Index month of diagnosis

Comorbidities
–   Hypertension
–   Type 2 diabetes mellitus
–   Chronic obstructive pulmonary disease (COPD)
–   Asthma
–   Ischemic stroke or haemorrhagic stroke
–   Heart failure
–   Acute myocardial infarction
–   Arrhythmia
–   Venous thromboembolism (VTE)

- Obesity (using diagnosis codes)
- Smoker
- Alcohol/Drug abuse
- Autoimmune conditions (type 1 diabetes mellitus, rheumatoid arthritis, psoriasis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, Addisons, Graves, Sjogrens, Hashimoto, myasthenia gravis, autoimmune vasculitis, pernicious anaemia, celiac disease, scleroderma, sarcoid, ulcerative colitis, Crohn disease)
- Organ transplantation,
- Cancer
- Dementia,
- Major psychiatric disorder
- Renal impairment
- Hepatic impairment

These will be used to describe the cohorts at relevant index dates(s) and some of these will be selected as risk factors/confounders for the incidence rates analysis, see section 7.7 for details.

Respiratory support

Patients will be considered having adjunctive respiratory support if available medical records data are available for the following interventions on or post COVID-19 diagnosis:

- Any type of respiratory support
- Invasive mechanical ventilation (including ECMO)
- ECMO only

If no records are observed, then the patient will be considered as receiving no respiratory support.

7.4   Data Sources

Longitudinal Patient Database (LPD) Belgium (IQVIA)

LPD Belgium is a computerised network of general practitioners (GPs) who contribute to a centralised database of anonymised data of patients with ambulatory visits. Currently, around 300 GPs from 234 practices are contributing to the database covering 1.1M patients from a total of 11.5M Belgians (10.0%). The database covers a time period from 2005 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilisation studies.

Longitudinal Patient Database (LPD) France (IQVIA)

LPD France is a computerised network of physicians including GPs who contribute to a centralised database of anonymised patient EMR. Currently, >1200 GPs from 400 practices are contributing to the database covering 7.8M patients in France. The database covers a time period from 1994 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilisation studies.

Disease Analyser (DA) Germany (IQVIA)

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings. Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are not cross-identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to 28.8% General, 13.4% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilisation studies.

IQVIA Medical Research Data (IMRD) UK (IQVIA)

IMRD UK is a large database of anonymised electronic medical records collected at Primary Care clinics throughout the UK. Data coverage includes 15.2M patients, 5.6M providers, 793 care sites and more than 5 billion service records, covering 22.5% of a population of 67.5M. Dates of service include from 1996 through present. Quality indicators define the start date for that patient (e.g. each patient's observation period began at the latest of the patient's registration date, the acceptable mortality recording date of the practice, the Vision date). The end of the observation period is determined by the end date of registration in the database. Drug treatment is recorded as prescriptions. All protocols must be submitted to an independent Scientific Review Committee prior to study conduct.

Longitudinal Patient Database (LPD) Italy (IQVIA)

LPD Italy is comprised of anonymised patient records collected from software used by GPs during an office visit to document patients' clinical records. Data coverage includes over 2M patient records with at least one visit and 119.5M prescription orders across 900 GP practices. Dates of service include from 2004 through present. Observation time is defined by the first and last consultation dates. Drugs are captured as prescription records with product, quantity, dosing directions, strength, indication and date of consultation.

Integrated Primary Care Information (IPCI), The Netherlands

IPCI is collected from EHR records of patients registered with their GPs throughout the Netherlands. The selection of 391 GPs is representative of the entire country. The database contains records from 2.6 million patients out of a Dutch population of 17M (8.2%) starting in 1996. The median follow-up is 2.2 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g. exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance

Board. (5) The IPCI database is currently increasing the update frequency because of the COVID-19 pandemic (now updated till March 2020).

Information System for Research in Primary Care (SIDIAP), IDIAP Jordi Gol (Spain)

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff. The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee (9).

Hospital de Madrid (HM) Hospitales (Spain)

Hospital de Madrid (HM) Hospitales data are made available through partnership with SIDIAP. The HM Hospitales database covers in-patient care delivered across a network of private hospitals in Spain. HM Hospitales covers more than 17M patients, out of whom a subset will be catalogued and followed for acute care delivered for suspected COVID-19 onset. This database covers more than 2300 confirmed COVID-19 cases and all in-patient hospital care, including the data of admission, conditions, procedures and medicines dispensed in hospital, date of discharge, and date of known death or date of end of follow-up in the database. Studies using HM Hospitales data require review and approval from data custodians at SIDIAP authorised to execute observational network analyses. The number of newly diagnosed patients in each database per month since the outbreak of COVID-19 can be derived from the databases.

None of the databases, except SIDIAP have linkage between primary and secondary care setting.

A database profiling, describing a range of variables in terms of data quality and completeness, as well as attrition tables for COVID-19 populations can be found at the following link: https://dqdashboard.iqvia.com/ema_report1/ .

7.5   Sample Size

Based on database characterization conducted prior to this protocol, the eight databases mentioned above include between 1,417 to 124,221 diagCOVID-19 and labCOVID-19 patients per database, and o total of 153,759 patients, only one database observing hospitalized patients (around 2,000 patients).

The number of patients in each of the proposed EU countries is projected to be modest, but it is difficult to confirm and likely to vary between data sources. As the primary objective is a descriptive one, the aim is to observe a sufficient number of patients in order to estimate the frequency of drug utilization measures with an acceptable level of precision. The 95% CI width will provide an indication of precisions of the point estimate; the upper and lower limit will provide a range of credible values consistent with observed data.

7.6   Data Management

Data management for this study will be conducted using standard IQVIA processes. Further details on the data handling procedures will be provided to the EMA in the SAP and/or in the Data Management Plan. The process would take into consideration any data governance imposed on the data source including any plans to handle the data outside of the institution or country of origin. IQVIA will adhere to all local and regional laws on data protection and privacy.

7.7   Data Analysis

Continuous variables will be described using mean, standard deviation, median, first and third quartiles, minimum, and maximum. Categorical variables will be described by the number and percentage of patients in each category. The number of patients with missing data for each variable will be reported. Confidence intervals (CIs) of 95% will be presented for means using a normal approximation and for proportions using a binomial approximation. Only available data will be summarized.

In all regression analyses, guidelines for appropriate fitting of any logistic or Cox regression model recommend a minimum of 10 outcome events per term (where term may be any linear covariate, non-linear predictor, or interaction term). If sensitivity analyses are to be conducted, fully adjusted regression analysis will only be undertaken if sufficient outcome events are observed. In any scenario where the fully adjusted regression model does not have sufficient events, but a minimally adjusted regression model including only the exposure, age, and sex in the linear predictor does have sufficient events, the minimally adjusted regression model will be carried out instead.

Additionally, in all analyses where Cox regression modelling is used, the hazard rate (HR) can be used to represent the incidence rate.

The results for each country and database will be presented separately.

7.7.1   General considerations

An initial exploratory descriptive analysis will be conducted for each country specific cohort post data extraction to provide insight into general patterns, functional form and any outliers of exposure and covariates. These initial data will be further summarized using descriptive statistics as outlined in the previous section. Additionally, variable distribution will be explored visually using bar charts, boxplots or histograms where relevant.

From the study population, country specific cohorts will be created as detailed in section 7.2.2. Not all cohorts will be possible to be constructed in all databases as they depend on the healthcare setting present in a database. The proportion and summary characteristics of patients excluded from each sub-cohort analysis will be summarized in a STROBE diagram.

7.7.2   Glucocorticoid prescribing patterns (primary objective 1)

Prescribing patterns of systemic glucocorticoids for the treatment of COVID-19 will be summarized by the four cohorts (section 7.2.2) and by subgroups of special interest (section 7.2.4) and the

description will include time to initiation of glucocorticoid treatment (from COVID-19 diagnosis), duration of treatment, route of administration, daily dose at start, cumulative dose and duration of treatment received post COVID-19 diagnosis, see section 7.3.2 for details regarding calculation of exposure parameters.

Frequency of concomitant use of other medications and invasive/non-invasive respiratory support at COVID-19 diagnosis index date and during follow-up will also be presented.

The time to systemic glucocorticoid initiation from COVID-19 diagnosis will be modelled as a time-to-event outcome using the Kaplan-Meier (KM) estimator. The patient follow-up from COVID-19 diagnosis date until systemic glucocorticoid treatment index date will be included in the KM analysis, with start of systemic glucocorticoid therapy being considered a 'failure' event. This KM analysis will be stratified by route of systemic glucocorticoid administration (oral vs intravenous). The KM survival function curve (95% CI) and summary statistics of 25th percentile, median, 75th percentile of time to event (in days) will be provided. The survival function within each stratification will be compared using log-rank test.

A time series graph will be used to investigate changes in prescribing patterns over calendar time. Monthly and quarterly incidence steroid incident use will be plotted against time from January 2020 until study end. Key dates (such as Recovery trial) should be highlighted on this graph to allow differentiation between time periods. A formal before /after analysis is not proposed. Results will be stratified per country and per database.

7.7.3 Patient characteristics (secondary objective 1)

Summary descriptive statistics will be presented by the four cohorts (section 7.2.2) and *described both at diagnosis and treatment index dates in each cohort.* The following will be described at diagnosis date and also treatment index date: patient demographics and clinical characteristics. Where available, a description of COVID-19 illness onset (time to diagnosis), associated symptoms and time to hospitalization for COVID-19 infection will be presented.

Data will be further stratified by subgroups of special interest (see section 7.2.4).

7.7.4 Estimation of incidence of study adverse events of interest and disease outcomes (secondary objectives 2 and 3)

The crude incidence rate of the individual outcome relevant to each sub-cohort reported during person-time treated for each exposure group will be calculated. The crude person-time from relevant index date will be calculated for the following groups:

- Use of systemic glucocorticoids without other treatments for COVID-19 (drug and respiratory support)

- Use of systemic glucocorticoids plus other treatments for COVID-19 (drug and respiratory support)

- Only other treatments and respiratory support with no steroids

- No specific treatments for COVID-19 infection (other concomitant treatments are allowed are allowed)

Only the earliest eligible treatment is considered, and for patients who switch to another treatment, their follow-up is censored at date of switching. The number and reasons for patients censoring will be reported.

We will calculate both, the incidence proportion and the incidence rate. The numerator for both (risk and rate) will be comprised of counts of incident events of interest during the person-time as defined above recorded during each cumulative interval and summed to reflect the cumulative count for the interval.

The crude cumulative incidence rate will be calculated according to the formula:

$$\frac{\text{Total number of patients on Rx with first event during cumulative interval of interest} \times 100}{\text{Total person-time at risk (days)}}$$

The crude incidence proportion will be calculated according to the formula:

$$\frac{\text{Total number of patients on Rx with first event during cumulative interval of interest} \times 100}{\text{Total population at risk at start of study period}}$$

For each sub-cohort and type of person-time the numerator for each time frame will contain the number of patients for whom an outcome has been recorded in that time frame since the onset of that type of person-time. The crude incidence rate of each outcome within the relevant sub-cohort will be expressed as number of cases per 1,000 patient-days at risk.

The cumulative incidence rate will be reported at the end of follow-up (30 and 90 days).

The person-time estimation and the calculation of the crude incidence rate for secondary objectives 2 and 3 will be similar except for the outcomes being considered in each case. For secondary objective 2, adverse events of interest for glucocorticoids (listed in Section 7.3.3) will be the outcome, and for secondary objective 3 mortality and other disease outcomes (Section 7.3.4) will be the outcome.

Both stratification and adjustment will be used as a method to deal with confounders.

In order to examine risk factors of the outcomes of interest, data will also be stratified by subgroups of interest (7.2.4) and stratum-specific crude incidence rates will be calculated in each subgroup.

Each of the adverse event incidence rate and incidence proportion will be analysed overall and in the following subgroups:

- Cohort

- Comorbidity

- Starting dose of glucocorticoid (for relevant treatment groups)

- Medical history of that specific AEs (yes/no)

The stratification of medical history specific to each AE is detailed in the table below

Adverse event outcome	Medical history stratification
Composite cardiovascular events	Any of the composite cardiovascular events in 365 days prior to diagnosis index date: yes/no

Hypertension	Hypertension recorded in 365 days prior to diagnosis index date (as per comorbidities): yes/ no
Arrythmia	Arrythmia recorded in 365 days prior to diagnosis index date (as per comorbidities): yes/ no
Gastrointestinal events	Gastrointestinal events recorded in 365 days prior to diagnosis index date (as per comorbidities): yes/no
Psychosis	Any major psychiatric disorder (not specifically psychosis) recorded in the 365 days prior to and including diagnosis index date: yes/ no
Myopathy	Myopathy recorded in the 90 days prior to and including diagnosis index date: yes/ no
Hyperglycaemia	Any type 1 or type 2 diabetes (not specifically hyperglycaemia) recorded in the 365 days prior to and including diagnosis index date: yes/ no
Any infection	Any infection recorded in the 90 days prior to and including diagnosis index date: yes/ no
Any bacterial infection	Any bacterial infection recorded in the 90 days prior to and including diagnosis index date: yes/ no
Any viral infection	Any viral infection recorded in the 90 days prior to and including diagnosis index date: yes/ no
Any fungal infection	Any fungal infection recorded in the 90 days prior to and including diagnosis index date: yes/ no
Any parasitic infection	Any parasitic infection recorded in the 90 days prior to and including diagnosis index date: yes/ no

Separate Cox regression models will be used to estimate adjusted cause-specific HR[3] (in order to account for competing events) for each outcome **within** the following four treatment groups:

- Use of systemic glucocorticoids without other treatments for COVID-19 (drug and respiratory support)
- Use of systemic glucocorticoids plus other treatments for COVID-19 (drug and respiratory support)
- Only other treatments and respiratory support with no systemic glucocorticoids
- No specific treatments for COVID-19 infection (other concomitant treatments for indications other than for COVID-19 are allowed)

In addition to stratified analysis, for each of the above four treatment groups,
A Cox model that is adjusted for a list of predefined confounders (age and sex) will be run.

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[3] Cause-specific HR are to be interpreted as instantaneous risk estimates and not as cumulative risk estimates; cumulative risks estimates are subject to competing events https://pubmed.ncbi.nlm.nih.gov/30012114/

7.7.5   Explore the performance of different COVID-19 coding definitions (secondary objective 4)

The PheValuator is a tool that can be used to estimate the performance of rule-based coding definitions when validation by clinical adjudication of patient records is not possible. (29) This tool will be used to evaluate different COVID-19 definitions as described in section 7.3.1. The method involves three steps:

(1) Developing a probabilistic diagnostic predictive model for a rule-based case definition:

(2) Determine the probability for everyone in a large group of subjects to be a case.

(3) Evaluating the performance characteristics of the rule-based case definition.

This process can be repeated for each case definition constructed.

To construct the diagnosis predictive model, a very specific outcome cohort is needed (where cases have a high certainty to be true positives) which for this study will be the laboratory confirmed SARS-CoV-2 PCR test cases (cCOVID-19). This outcome cohort is nested in the target cohort which contains all subjects positive and a random selection of all subjects negative from the study population, to be used for the model.

This specific outcome cohort will be used to discriminate between positive and negative cases and to both 'train' and test the diagnostic prediction model. The PatientLevelPrediction R package (https://github.com/OHDSI/PatientLevelPrediction) will be used to create this model and all available data (except the code used to create the true positives) of a 75% random sample of each target cohort will be used.

Once the model is developed, internally validated on the remaining 25% of each target cohort dataset, calibrated and achieves good performance characteristics, this model will be applied to a larger study cohort (called the evaluation cohort, which is also sampled randomly from the study population), where each subject will have a predicted probability calculated for the case definition of interest. The probability of the case definition determined by the model is then used as the probabilistic gold standard with which to examine the following the performance characteristics of each case definition:

(1) Sensitivity defined as True Positives/ (True Positives + False Negatives)

(2) Specificity defined as True Negatives / (True Negatives + False Positives)

(3) Positive Predictive Value defined as True Positives/ (True Positives + False Positives)

(4) Negatives Predictive Value defined as True Negatives / (True Negatives + False Negatives)

In addition, the contribution of each patient to each of the five case definitions will be presented in aggregate in a 5 by 5 matrix. This will offer insight in the performance of each definition relative to each other and the potential gains of using a broader vs a narrower definition.

7.7.6   Meta-analysis

All the proposed analyses will be conducted for each database separately, with cumulative HR estimates (at 30 days follow-up) for each treatment group of interest combined using the DerSimonian-Lard random effects meta-analysis methods when I2 <=40%. The standard errors associated with the cumulative HRs will be used to weight individual database estimates using the

inverse variance weighting methods. No meta-analysis will be conducted when I2 for a given drug-outcome pair is >40%.

7.7.7   Sensitivity analysis

For objective 2 and 3, with regards to the reference group for incidence rates
As a sensitivity analysis, the reference group for incidence rates will be replaced with 'other immunotherapies' (see Appendix 3 for details).

For prevalent users' cohorts, the definition of remote users:
A sensitivity analysis to exclude those patients for whom short term duration of corticosteroid use (1 14 days) is identified prior to COVID-19 diagnosis.

For objectives 2 and 3, if the number of patients censored due to switching is higher than 70%
, a sensitivity analysis will be performed, namely an intention to treat approach (ITT), such that after initial exposure is defined to allocate patients to one of the four treatment groups, the denominator is then person-time observed (irrespective of treatment status), rather than person-time treated.

7.8   Quality Control

IQVIA Quality Management System (QMS)
The study will be conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (International Society for Pharmacoepidemiology 2008) and according to the ENCePP code of conduct (European Medicines Agency 2018).

Standard operating procedures or internal process guidance at each collaborating centre should be adhered to for the conduct of the study. These procedures should include rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for all aspects of the study from protocol development to the reporting of the results. This will include quality control on study methodology, statistical analysis plan, programming, data management and analysis, study results, conclusions and study report.

The study coordinating centre is responsible for the implementation of quality management procedures, supported by the technical support team. Each individual site is responsible for the execution of the study against their CDM, the interpretation of the study results and quality control sign-off. Final quality control is the responsibility of the Principal Investigators and study coordinating centre.

Data quality control is the responsibility of database owners.

OHDSI and EHDEN quality control mechanisms for the CDM will be applied. Each data source has to comply to the minimum threshold of the OHDSI recommendations and provide a summary report in form of a Data Quality Dashboard.

The Data Quality Dashboard (DQD) has been developed in the EHDEN project in close collaboration with OHDSI. and are described in high detail in Chapter 15 of The Book of OHDSI (http://book.ohdsi.org/DataQuality.html) and in the publication by Kahn et al., 2016.

In summary, this package runs a series of data quality checks against an OMOP CDM instance (currently supports v5.3.1 and v5.2.2). It systematically runs the checks, evaluates the checks against some pre-specified threshold, and then communicates what was done in a transparent and easily understandable way. The quality checks were organised according to the Kahn Framework, which uses a system of categories and contexts that represent strategies for assessing data quality (Kahn et al., 2016).

After systematically applying the 20 check types to an OMOP CDM version, approximately 3,351 individual data quality checks are resolved, run against the database, and evaluated based on a pre-specified threshold. The R package then creates a (JavaScript Object Notation) JSON object that is read into an RShiny application to view the results. Results from the DQD may be used to inform supplemental

7.9 Limitations of the Research Methods

7.9.1 Study design limitation

COVID-19 diagnosis misclassification – the diagnosis of COVID-19 in absence of confirmatory test has a high likelihood to be misclassified as the disease symptoms are unspecific. This misclassification is more likely for patients treated in primary case, e.g., those with milder symptoms. In addition, with regards to the availability of results of PCR test for SARS-CoV-2, this is currently available in only one database (SIDIAP).

- **Mitigation**: Different definitions will be explored and compared as part of objective 4. We will base the main definition on definite diagnosis not on symptoms only and supplement with confirmatory tests when available

Confounding by indication and severity may occur when the different treatments are prescribed depending upon the physician's assessment of the patient's health status in relation to the outcome of interest. The risk of this confounding is high due to glucocorticoids being indicated in severe COVID-19 cases only and therefore correlated with the increase in severity.

- **Mitigation**: No comparative analysis will be performed. This confounding needs to be considered when interpreting the incidence rates obtained.

Selection bias occurs when there is a selective recruitment into the study of subjects that are not representative of the population intended to be studied, so that the association between exposure and outcome of interest is different in the included and excluded population.

- **Mitigation**: Minimal exclusion criteria will be used. In addition, we have included data sources with large or whole national coverage and both ambulatory and hospital setting.

Exposure to glucocorticoids in hospital setting might be underrepresented as glucocorticoid might be captured only as ward stock and not as individual dispensation.

On-treatment exposure classification was considered suitable for this study in order to facilitate comparison with clinical trials results. However, this way of classifying exposure does not consider subsequent treatments and might miss a deterioration of disease.

The **short duration of follow-up** will allow only the capture of acute adverse events.

Prescribing patterns of corticosteroids over time
Due to the short study period (1 year)   any time series analysis cannot be undertaken, and the observed trends cannot be confirmed.

If exxposure to glucocorticoids as second or third treatment occurs very often, a large proportion of patients will be censored, leading to limited data to assess the outcomes of interest.

Mitigation – an ITT sensitivity analysis is proposed in case censoring is very large (>70%)

7.9.2 ***Databases related limitations***

Linkage between primary and secondary care

Seven out of eight databases will not have linkage between primary and secondary setting, and a consequence of this is that patient follow up time will be fragmented. Especially in the hospital setting, the access to medical history of the patient is limited and the patients who had prior exposure of glucocorticoids in primary care risk to be misclassified as naïve users.

Primary care databases

Severe outcomes that lead to hospitalization are less likely to be captured., although hospitalization is captured in some of the primary care databases.

If patients are free to change general practitioners and they are not tracked across different GPs or if they are treated. In private practice, their exposure will be underestimated and the follow up will be fragmented.

As the hospital and ambulatory settings are not linked, patients who had prior exposure of glucocorticoids in hospitals will be misclassified as naïve users.

Hospital setting databases

As the lookback period in the hospital setting is in general absent or reduced, there will be an under-ascertainment of baseline comorbidities.

Mortality data

The mortality information (vital status) is under-captured in some data sources. Three of them, DA Germany, LPD France and LPD Italy do not record vital status at all. For SIDIAP, the vital status comes from a regional mortality register while for HM Hospitales, the vital status comes directly from hospital records. For IMRD UK and IPCI, the vitals status information comes from GP recording.

Protection of Human Subjects

For this study, participants from various EU member states will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All the databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to.

In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results. The output files will not contain any data that allow identification of subjects included in the study. IQVIA has an internal set of rules and processes associated with Data quality assurance. Patient confidentiality will be protected according to the EU General Data Protection Regulation (GDPR)] on the protection of individuals. Security of the data will be maintained at all times. Access will be limited to authorized individuals.

Management and Reporting of Adverse Events/ Adverse Reactions

Section 9.0

Pursuant to the EMA requirements for reporting of adverse events for secondary data (GVP module VI, VI.C.1.2.1.2), adverse event reporting will not be conducted as part of this study given the study objectives will be met through the use of secondary data.

Plans for Disseminating and Communicating Study Results

The final study report will be written in accordance with the GVP guidelines module VIII, (EMA/813938/2011). In accordance with the 2010 EU pharmacovigilance legislation (Articles 10 or 10a of Regulation (EC) No 726/2004; Articles 21a or 22a of Directive 2001/83/EC), information about this PASS will be entered into the publicly available EU PAS register before the start of data collection. Updates to the study protocol in case of substantial amendments, progress reports where applicable, and the final study report will also be entered in the register.

The R script used for this analysis will be published to https://github.com/OHDSI/   (Observational Health Data Science and Informatics).

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Example of code lists

Appendix 1

This appendix provides an overview of the standard concepts and cohort set descriptions that are used to define each indication or risk group. The concept ID refers to the unique ID in the OMOP Common Data Model.

1. Covid-19 diagnosis

1.1. Covid-19 diagnosis

Concept ID	Concept name
37311061	Disease caused by 2019-nCoV
4100065	Disease due to Coronaviridae
439676	Coronavirus infection

1.2. Covid-19 positive test measurement

Concept ID	Concept name
37310282	2019 novel coronavirus detected

2. Covid-19 Symptoms

2.1. Fever episodes

Concept ID	Concept name
4329518	Body temperature taken with digital thermometer
4174894	Core body temperature
4212763	Forehead temperature
44809208	Maximum body temperature
4039793	O/E - level of fever
4077057	O/E - oral temperature
4039791	O/E - rectal temperature
4151775	O/E - tympanic temperature
4265708	Temperature of skin
444413	Febrile convulsion
437663	Fever
4141062	Fever greater than 100.4 Fahrenheit

4152360	O/E - fever

2.2. Cough

Concept ID	Concept name
254761	Cough
4089228	Sputum finding

2.3. Myalgia

Concept ID	Concept name
442752	Muscle pain

2.4. Malaise or fatigue

Concept ID	Concept name
4223659	Fatigue
4272240	Malaise
439926	Malaise and fatigue

2.5. Dyspnea

Concept ID	Concept name
4191650	Acute respiratory distress
312437	Dyspnea

2.6 Anosmia, hyposmia and dysgeusia episodes

Concept ID	Concept name
43530714	Sensory disorder of smell and/or taste
4185711	Loss of sense of smell
436235	Taste sense altered

3. Adverse events for steroids

3.1. Bacterial infections

Concept ID	Concept name
432545	Bacterial infectious disease
4200533	Bacterial infection by site

438064	Bacterial infection due to Pseudomonas
436339	Bacterial infection due to Klebsiella pneumoniae
4323342	Recurrent bacterial infection
4347525	Disseminated atypical mycobacterial infection
4141201	Beta lactam resistant bacterial infection
4008721	Atypical mycobacterial infection
46274040	History of bacterial infection
42872408	Atypical mycobacterial infection of lung
4029803	Bacterial infection of skin
4215457	Bacterial infection due to Serratia
4094504	Bacterial infection due to Proteus mirabilis
4009326	Mycobacterial infection
4027415	Bacterial infection due to Morganella morganii
438341	Bacterial infection due to Bacillus
46269700	Pleural effusion due to bacterial infection
45768744	Angular cheilitis due to bacterial infection
4193874	Bacterial infection of the digestive tract
37017103	Bursitis caused by bacterial infection
4174693	Atypical mycobacterial infection of hand
4027381	Bacterial infection of central nervous system
4231982	Mycobacterial infection of the central nervous system
46273201	Bacterial infection due to Streptococcus milleri group
37394468	Extended spectrum beta-lactamase resistant bacterial infection
37108786	Herpes zoster with secondary bacterial infection
45770039	SINBAD (site, ischemia, neuropathy, bacterial infection and depth) wound classification
4345453	Skin and soft tissue atypical mycobacterial infection

3.2. Fungal infections

Concept ID	Concept name
4207190	Fungal infection by site
4270197	Fungal infection of lung
4165570	Fungal infection of brain
4030507	Fungal infection of kidney
36717290	Invasive fungal infection

3.3. Pneumonia

Concept ID	Concept name
4050869	Atypical pneumonia
255848	Pneumonia

3.4. Hyperglycemia

Concept ID	Concept name
4214376	Hyperglycemia

3.5. Gastrointestinal bleeding

Concept ID	Concept name
4147683	Acute gastrojejunal ulcer without hemorrhage AND without perforation
40482685	Angiodysplasia of duodenum
28779	Bleeding esophageal varices
198798	Dieulafoy's vascular malformation
4198381	Ulcer of duodenum
4112183	Esophageal varices with bleeding, associated with another disorder
4265600	Gastric ulcer
192671	Gastrointestinal hemorrhage
4027663	Peptic ulcer

3.6. Composite cardiovascular disease events (ischemic stroke, hemorrhagic stroke, heart failure, acute myocardial infarction or sudden cardiac death)

Concept ID	Concept name
4329847	Myocardial infarction
316139	Heart failure
376713	Cerebral hemorrhage
439847	Intracranial hemorrhage
43530674	Spontaneous cerebellar hemorrhage
43530727	Spontaneous cerebral hemorrhage
42535425	Spontaneous hemorrhage of cerebral hemisphere
4148906	Spontaneous subarachnoid hemorrhage
432923	Subarachnoid hemorrhage
372924	Cerebral artery occlusion
375557	Cerebral embolism
443454	Cerebral infarction
441874	Cerebral thrombosis
4048809	Brainstem death
321042	Cardiac arrest
442289	Death in less than 24 hours from onset of symptoms
4317150	Sudden cardiac death
4132309	Sudden death

4. Disease outcomes

4.1. Hospital admission

Concept ID	Concept name
262	Emergency Room and Inpatient Visit
9201	Inpatient Visit

4.2. Hospital discharge

Concept ID	Concept name
4203130	Discharge from hospital

4.3. Intensive services

Concept ID	Concept name
4338595	Cardiac support using extracorporeal membrane oxygenation circuitry
4052536	Extracorporeal membrane oxygenation
44811012	Fluoroscopy guided percutaneous insertion of cannula for extracorporeal membrane oxygenation
4230167	Artificial respiration
40481547	Dependence on ventilator
4080957	Endotracheal respiratory assistance
4168966	Endotracheal tube present
4232550	Home visit for mechanical ventilation care
4235361	Hyperventilation therapy for traumatic brain injury
37116689	Insertion of endotracheal ventilation catheter
40487536	Intubation of respiratory tract
4332501	Management of noninvasive mechanical ventilation
37206832	Mechanical insufflation exsufflation
765576	Orotracheal intubation using bougie device
4219858	Problem with patient ventilator
4237618	Ventilator care
4251737	Ventilator care management
44791135	Ventilatory support
4072633	Weaning from mechanically assisted ventilation
4166281	Anterior tracheostomy
4115488	Emergency tracheostomy
4337047	Insertion of tracheostomy tube
4168864	Lateral tracheostomy
4199580	Mediastinal tracheostomy
4065590	Permanent tracheostomy

4311023	Revision of stoma of trachea
4195473	Temporary tracheostomy
4208093	Tracheostomy, emergency procedure by transtracheal approach
262	Emergency Room and Inpatient Visit
9201	Inpatient Visit

4.4. Invasive mechanical ventilation

Concept ID	Concept name
4230167	Artificial respiration
40481547	Dependence on ventilator
4080957	Endotracheal respiratory assistance
4168966	Endotracheal tube present
4232550	Home visit for mechanical ventilation care
4235361	Hyperventilation therapy for traumatic brain injury
37116689	Insertion of endotracheal ventilation catheter
40487536	Intubation of respiratory tract
4332501	Management of noninvasive mechanical ventilation
37206832	Mechanical insufflation exsufflation
765576	Orotracheal intubation using bougie device
4219858	Problem with patient ventilator
2788037	Respiratory Ventilation, 24-96 Consecutive Hours
2788038	Respiratory Ventilation, Greater than 96 Consecutive Hours
2788036	Respiratory Ventilation, Less than 24 Consecutive Hours
4237618	Ventilator care
4251737	Ventilator care management
44791135	Ventilatory support
4072633	Weaning from mechanically assisted ventilation

4.5. ECMO

Concept ID	Concept name
4338595	Cardiac support using extracorporeal membrane oxygenation circuitry
4052536	Extracorporeal membrane oxygenation
44811012	Fluoroscopy guided percutaneous insertion of cannula for extracorporeal membrane oxygenation

4.6. Venous thromboembolic (pulmonary embolism and deep vein thrombosis)

Concept ID	Concept name
40481089	Embolism from thrombosis of vein of lower extremity
440417	Pulmonary embolism
254662	Pulmonary infarction

318775	Venous embolism
444247	Venous thrombosis
36713113	Saddle embolus of pulmonary artery
35615055	Saddle embolus of pulmonary artery with acute cor pulmonale

4.7. Death

Concept ID	Concept name
4306655	Death

5. Comorbidities

5.1. Hypertension

Concept ID	Concept name
316866	Hypertensive disorder
4322024	Pulmonary hypertension
42709887	Hypertensive complication

5.2. Type 2 diabetes mellitus

Concept ID	Concept name
43021173	History of diabetes mellitus type 2
42539022	History of diabetes related lower limb amputation
46270562	History of small vessel disease due to diabetes mellitus
201820	Diabetes mellitus
442793	Complication due to diabetes mellitus
443238	Diabetic - poor control

5.3. Chronic obstructive pulmonary disease (COPD)

Concept ID	Concept name
255573	Chronic obstructive lung disease
258780	Emphysematous bronchitis

5.4. Asthma

Concept ID	Concept name
317009	Asthma
4235703	Asthma management
4279553	Eosinophilic asthma

5.5. Chronic kidney disease

Concept ID	Concept name
194385	Aneurysm of renal artery
46271022	Chronic kidney disease
192279	Disorder of kidney due to diabetes mellitus
4263367	Glomerulonephritis
261071	Glomerulosclerosis
201313	Hypertensive renal disease
4103224	Interstitial nephritis
193253	Nephritis
195314	Nephrotic syndrome
192359	Renal failure syndrome
45768812	Anemia in chronic kidney disease

5.6. Heart disease

Concept ID	Concept name
321588	Heart disease
443563	Arteriosclerosis of coronary artery bypass graft

5.7. Obesity

Concept ID	Concept name
4099154	Body weight
4060985	Body mass index 30+ - obesity
4256640	Body mass index 40+ - severely obese
45766204	Lymphedema associated with obesity
433736	Obesity
4176962	Obesity associated disorder
4081038	Pulmonary hypertension with extreme obesity

5.8. Smoker

Concept ID	Concept name
4298794	Smoker
4222303	Non-smoker

5.9. Autoimmune conditions

Concept ID	Concept name

374919	Multiple sclerosis
4137275	Vasculitis
443394	Addison's disease
194992	Celiac disease
201606	Crohn's disease
46269889	Complication due to Crohn's disease
46269999	History of Crohns disease
4232076	Graves' disease
135215	Hashimoto thyroiditis
76685	Myasthenia gravis
432893	Myasthenic syndrome due to another disorder
432295	Pernicious anemia
75614	Acrodermatitis continua
140168	Psoriasis
81931	Psoriasis with arthropathy
4297650	Cutaneous atrophy due to rheumatoid arthritis
4334806	Deformity of foot due to rheumatoid arthritis
46273442	Deformity of hand due to rheumatoid arthritis
4058299	H/O: rheumatoid arthritis
4107913	Myopathy due to rheumatoid arthritis
4102493	Polyneuropathy in rheumatoid arthritis
80809	Rheumatoid arthritis
4083556	Seronegative rheumatoid arthritis
4035611	Seropositive rheumatoid arthritis
438688	Sarcoidosis
4262578	Sarcoid arthropathy
45772123	Sarcoid iridocyclitis
4105005	Multiple cranial nerve palsies in sarcoidosis
46272236	Ischemic nephropathy
4331739	Linear scleroderma
441928	Localized scleroderma
255304	Lung disease with systemic sclerosis
4105026	Myopathy due to systemic sclerosis
46270482	Polyneuropathy due to systemic sclerosis
134442	Systemic sclerosis
4063582	Systemic sclerosis induced by drugs and chemicals
254443	Sjögren's syndrome
46273369	Endocarditis due to systemic lupus erythematosus
4145240	Renal tubulo-interstitial disorder in systemic lupus erythematosus
257628	Systemic lupus erythematosus
201254	Type 1 diabetes mellitus
435216	Disorder due to type 1 diabetes mellitus

40484648	Type 1 diabetes mellitus uncontrolled
46273477	Complication due to ulcerative colitis
81893	Ulcerative colitis
46273478	Rectal hemorrhage due to ulcerative colitis
46274082	Intestinal obstruction due to ulcerative colitis
46269952	Fistula of intestine due to ulcerative colitis
4116142	Arthropathy in ulcerative colitis

6. Respiratory support

6.1. Noninvasive respiratory support

Concept ID	Concept name
4239130	Oxygen therapy

6.2. Invasive respiratory support

Concept ID	Concept name
4338595	Cardiac support using extracorporeal membrane oxygenation circuitry
4052536	Extracorporeal membrane oxygenation
44811012	Fluoroscopy guided percutaneous insertion of cannula for extracorporeal membrane oxygenation
4230167	Artificial respiration
40481547	Dependence on ventilator
4080957	Endotracheal respiratory assistance
4168966	Endotracheal tube present
4232550	Home visit for mechanical ventilation care
4235361	Hyperventilation therapy for traumatic brain injury
37116689	Insertion of endotracheal ventilation catheter
40487536	Intubation of respiratory tract
4332501	Management of noninvasive mechanical ventilation
37206832	Mechanical insufflation exsufflation
765576	Orotracheal intubation using bougie device
4219858	Problem with patient ventilator
4237618	Ventilator care
4251737	Ventilator care management
44791135	Ventilatory support
4072633	Weaning from mechanically assisted ventilation
4166281	Anterior tracheostomy
4115488	Emergency tracheostomy
4337047	Insertion of tracheostomy tube
4168864	Lateral tracheostomy
4199580	Mediastinal tracheostomy
4065590	Permanent tracheostomy

2743216	Removal of Tracheostomy Device from Trachea, Via Natural or Artificial Opening
4311023	Revision of stoma of trachea
4195473	Temporary tracheostomy
4208093	Tracheostomy, emergency procedure by transtracheal approach

ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols (Revision 4)

Appendix 2   Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Systemic glucocorticoids use in the treatment of COVID-19 and risks of adverse outcomes in COVID-19 patients in the primary and secondary care setting

EU PAS Register® number: Not yet registered

Study reference number (if applicable):

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[4]	☐	☐	☒	4.0
1.1.2 End of data collection[5]	☐	☐	☒	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	5.0 and 6.0
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	

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[4] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[5] Date from which the analytical dataset is completely available.

Section 2: Research question	Yes	No	N/A	Section Number
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	7.0
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7.0
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	7.7.2.2
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	7.7.2.2
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	7.1/7.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	
4.2.2 Age and sex	☒	☐	☐	
4.2.3 Country of origin	☒	☐	☐	7.2
4.2.4 Disease/indication	☒	☐	☐	
4.2.5 Duration of follow-up	☒	☐	☐	

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	7.2.2

Comments:

4.1 Including the Data Sources section where details on conversion are given

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	7.3.2
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3	Is exposure categorised according to time windows?	☐	☐	☐	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	7.3.2
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	7.3.2

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	7.3.3/7.3.4
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.3.3/7.3.4

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	7.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	7.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	7.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	7.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	7.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	7.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	7.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☐	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	7.3.5/7.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	7.3.2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	
9.3.3 Covariates and other characteristics?	☒	☐	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	7.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	7.5
10.3 Are descriptive analyses included?	☒	☐	☐	7.7
10.4 Are stratified analyses included?	☒	☐	☐	7.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	7.7.2.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	7.6/8.0
11.2 Are methods of quality assurance described?	☒	☐	☐	7.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				7.9
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	

Section 12: Limitations	Yes	No	N/A	Section Number
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	8.0

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	3.0

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	10.0

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	10.0

Comments:

Name of the main author of the protocol: Alexandra Pacurariu

Date: 20th September 2020

Signature:

Appendix 3 Alternative treatments for COVID-19

Treatment	
Antiviral therapy (AV)	
P01BA02	Hydroxychloroquine
	Hydroxychloroquine + azithromycin combination
	Hydroxychloroquine + fluoroquinolones combination
	Hydroxychloroquine + amoxicillin combination
	Hydroxychloroquine + ceftriaxone combination
P01BA01	Chloroquine
P02CF01	Ivermectin
J02AC02	Itraconazole
J05AX27	Favipiravir
Not yet assigned	Remdesivir
J05AP01	Ribavirin
J05AH02	Oseltamivir
J05AR10	Lopinavir + ritonavir combination
J05AF09	Emtricitabine
G03XC01	Raloxifene
Antibiotic therapy (AB)	
J01CA04	Amoxicillin
J01MA01	Ofloxacin
J01MA02	Ciprofloxacin
J01MA03	Pefloxacin
J01MA04	Enoxacin
J01MA05	Temafloxacin

J01MA06	Norfloxacin
J01MA07	Lomefloxacin
J01MA08	Fleroxacin
J01MA09	Sparfloxacin
J01MA10	Rufloxacin
J01MA11	Grepafloxacin
J01MA12	Levofloxacin
J01MA13	Trovafloxacin
J01MA14	Moxifloxacin
J01MA15	Gemifloxacin
J01MA16	Gatifloxacin
J01MA17	Prulifloxacin
J01MA18	Pazufloxacin
J01MA19	Garenoxacin
J01MA21	Sitafloxacin
J01MA22	Tosufloxacin
J01MA23	Delafloxacin
J01DD04	Ceftriaxone
J01FA10	Azithromycin
Immune-based therapy (IB)	
L04AC07	Toclizumab
L04AC14	Sarilumab
L04AC11	Siltuximab
L04AA37	Baricitinib
L04AA29	Tofacitinib
L04AB04	Adalimumab

L04AB01	Etanercept
L04AB02	Infliximab
L04AC05	Ustekinumab
L04AC03	Anakinra
L01XE27	Ibrutinib
L01XE18	Ruxolitinib
L01XC07	Bevacizumab
L04AA27	Fingolimod
L04AA25	Eculizumab
L04AX02	Thalidomide
L04AD02	Tacrolimus
L03AB02	Interferon Beta Natural
L03AB07	Interferon Beta-1a
L03AB08	Interferon Beta-1b
L03AB13	Peginterferon Beta-1a
L03AB15	Ropeginterferon Alfa-2b
L03AB12	Albinterferon Alfa-2b
L03AB14	Cepeginterferon Alfa-2b
L03AB01	Interferon Alfa Natural
L03AB04	Interferon Alfa-2a
L03AB05	Interferon Alfa-2b
L03AB06	Interferon Alfa-N1
L03AB09	Interferon Alfacon-1
L03AB11	Peginterferon Alfa-2a
L03AB10	Peginterferon Alfa-2b
L03AA09	Sargramostim

A11CC05	Colecalciferol
A02BA01	Cimetidine
A02BA02	Ranitidine
A02BA03	Famotidine
A02BA04	Nizatidine
A02BA06	Roxatidine
Antithrombotic therapy (AT)	
B01AA01	Dicoumarol
B01AA07	Acenocoumarol
B01AA03	Warfarin
B01AB01	Heparin
B01AB05	Enoxaparin
B01AB04	Dalteparin
B01AB12	Bemiparin
B01AB06	Nadroparin
B01AB07	Parnaparin
B01AB08	Reviparin
B01AB09	Danaparoid
B01AB10	Tinzaparin
B01AB11	Sulodexide
B01AB51	Heparin Combinations
B01AC01	Ditazole
B01AC02	Cloricromen
B01AC03	Picotamide
B01AC04	Clopidogrel

B01AC05	Ticlopidine
B01AC06	Acetylsalicylic Acid
B01AC07	Dipyridamole
B01AC08	Carbasalate Calcium
B01AC09	Epoprostenol
B01AC10	Indobufen
B01AC11	Iloprost
B01AC13	Abciximab
B01AC15	Aloxiprin
B01AC16	Eptifibatide
B01AC17	Tirofiban
B01AC18	Triflusal
B01AC19	Beraprost
B01AC21	Treprostinil
B01AC22	Prasugrel
B01AC23	Cilostazol
B01AC24	Ticagrelor
B01AC25	Cangrelor
B01AC26	Vorapaxar
B01AC27	Selexipag
B01AD01	Streptokinase
B01AD02	Alteplase
B01AD03	Anistreplase
B01AD04	Urokinase
B01AD05	Fibrinolysin

B01AD06	Brinase
B01AD07	Reteplase
B01AD08	Saruplase
B01AD09	Ancrod
B01AD10	Drotrecogin Alfa (Activated)
B01AD11	Tenecteplase
B01AD12	Protein C
B01AD02	Alteplase
B01AD11	Tenecteplase
B01AD07	Reteplase
B01AE01	Desirudin
B01AE02	Lepirudin
B01AE03	Argatroban
B01AE04	Melagatran
B01AE05	Ximelagatran
B01AE06	Bivalirudin
B01AE07	Dabigatran Etexilate
B01AF01	Rivaroxaban
B01AF02	Apixaban
B01AF03	Edoxaban
B01AF04	Betrixaban
B01AX01	Defibrotide
B01AX04	Dermatan Sulfate
B01AX05	Fondaparinux
B01AX07	Caplacizumab

B02AA01	Aminocaproic Acid
B02AA02	Tranexamic Acid
B02AB04	Camostat
J06BA01	Immunoglobulins, Normal Human, For Extravascular Adm.
J06BA02	Immunoglobulins, Normal Human, For Intravascular Adm.
L03AX03	BCG Vaccine
Antihypertensives (AH)	
C03AA01	Bendroflumethiazide
C03AA02	Hydroflumethiazide
C03AA03	Hydrochlorothiazide
C03AA04	Chlorothiazide
C03AA05	Polythiazide
C03AA06	Trichlormethiazide
C03AA07	Cyclopenthiazide
C03AA08	Methyclothiazide
C03AA09	Cyclothiazide
C03AA13	Mebutizide
C08CX01	Mibefradil
C08DA01	Verapamil
C08DA02	Gallopamil
C08DA51	Verapamil, Combinations
C08DB01	Diltiazem
C08EA01	Fendiline
C08EA02	Bepridil
C09AA01	Captopril

C09AA02	Enalapril
C09AA03	Lisinopril
C09AA04	Perindopril
C09AA05	Ramipril
C09AA06	Quinapril
C09AA07	Benazepril
C09AA08	Cilazapril
C09AA09	Fosinopril
C09AA10	Trandolapril
C09AA11	Spirapril
C09AA12	Delapril
C09AA13	Moexipril
C09AA14	Temocapril
C09AA15	Zofenopril
C09AA16	Imidapril
C09CA01	Losartan
C09CA02	Eprosartan
C09CA03	Valsartan
C09CA04	Irbesartan
C09CA05	Tasosartan
C09CA06	Candesartan
C09CA07	Telmisartan
C09CA08	Olmesartan Medoxomil
C09CA09	Azilsartan Medoxomil
C09CA10	Fimasartan

Statins (S)	
C10AA01	Simvastatin
C10AA02	Lovastatin
C10AA03	Pravastatin
C10AA04	Fluvastatin
C10AA05	Atorvastatin
C10AA06	Cerivastatin
C10AA07	Rosuvastatin
C10AA08	Pitavastatin
Antidiabetic (AD)	
A10BA02	Metformin
A10BH01	Sitagliptin
A10BH02	Vildagliptin
A10BH03	Saxagliptin
A10BH04	Alogliptin
A10BH05	Linagliptin
A10BK01	Dapagliflozin
A10BK02	Canagliflozin
A10BK03	Empagliflozin
A10BK04	Ertugliflozin
A10BJ01	Exenatide
A10BJ02	Liraglutide
A10BJ03	Lixisenatide
A10BJ04	Albiglutide
A10BJ05	Dulaglutide

A10BJ06	Semaglutide