RESEARCH PROTOCOL:

Association of alpha-1 blocker (α-1B) on coronavirus disease (COVID-19) susceptibility and severity

Version 1.1

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1. List of Abbreviations

5α-RI	5-alpha reductase inhibitor
α-1B	Alpha-1 blocker
ARDS	Acute respiratory distress syndrome
ATC	Anatomical Therapeutic Chemical Classification System
BPH	Benign prostatic hyperplasia
CDM	Common data model
COVID-19	Coronavirus disease 2019
CRS	Cytokine release syndrome
CSS	Cytokine storm syndrome
ECMO	Extracorporeal membrane oxygenation
IL-6	Interleukin 6
OMOP	Observational Medical Outcomes Partnership
OHDSI	Observational Health Data Science and Informatics
RxNorm	US-specific terminology in medicine that contains all medications available on the US market
SNOMED	Systematized Nomenclature of Medicine

2. Responsible Parties

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2.2 Sponsor

This study was undertaken by Observational Health Data Science and Informatics (OHDSI), an open collaboration. **MAS** receives grant funding from the US National Institutes of Health and contracts from Janssen Research and Development and IQVIA, all unrelated to the current

work. **DPA** receives funding from the National Institute for Health Research (UK) in the form of a Senior Research Fellowship award. **DPA's research group** has received funding in the form of research grants for pharmaco-epidemiological studies from different pharmaceutical companies, all unrelated to the current work.

3. Abstract

This study will evaluate the effect of alpha-1 blocker (α-1B) exposure on the risk of contracting COVID-19 infection and of subsequently requiring hospitalization and intensive services such as mechanical ventilation. The analysis will be undertaken across a federated multi-national network of electronic health records and administrative claims from primary care and secondary care that have been mapped to the Observational Medical Outcomes Partnership Common Data Model in collaboration with the Observational Health Data Sciences and Informatics (OHDSI) and European Health Data and Evidence Network (EHDEN) initiatives. These data reflect the clinical experience of patients from Spain, the United Kingdom, and the United States of America as data becomes available. We will use a prevalent user cohort design to estimate the relative risk of each outcome using an on-treatment and intention-to-treat analysis of monotherapy. Data driven approaches will be used to identify potential covariates for inclusion in matched or stratified propensity score models identified using regularized logistic regression. Large-scale propensity score matching and stratification strategies that allow balancing on a large number of baseline potential confounders will be used in addition to negative control outcomes to allow for evaluating residual bias in the study design as a whole as a diagnostic step.

4. Milestones and Amendments

Ver.	Date	Section of study protocol	Amendment or update	Reason
1.1	9/3/2020	Section 7, Analysis	Add intention-to-treat analysis	To include patients whose drug usage may not be well-captured in databases
1.1	9/3/2020	Section 7, Analysis / Covariates	Remove gender from propensity score model	The cohort is restricted male.
1.1	9/3/2020	Section 14.1	Broaden the outcome cohort for intensive services to include patients with COVID dx or lab result	Not all Covid patients are actually tested.

Key Dates and Milestones	Planned / Estimated Date
Registration in the EU PAS Register	July 7th
Start of analysis	July 7th
End of analysis	
Presentation of results	

5. Rationale and Background

Since January 2020, a growing number of infections caused by coronavirus SARS-Cov2, COVID-19 has resulted in unprecedented pressure on healthcare systems worldwide, and a great number of casualties on a global scale. With an approximate 4% mortality based on data from China where the outbreak originated, there is a paucity of data on an international level surrounding the factors associated with disease severity or morbidity/mortality.[1,2]

The mortality of COVID-19 appears to be driven by a dysregulated immune response to SARS-CoV-2, resulting in acute respiratory distress syndrome (ARDS), respiratory failure, and multi-organ failure.[3,4] Emerging evidence suggests that a subset of COVID-19 is characterized by the development of a cytokine storm syndrome (CSS) that resembles cytokine release syndrome (CRS).[3,5,6] Covid-19-CSS is immunologically characterized by the elevation of pro-inflammatory cytokines. Interleukin 6 (IL-6) levels diverge profoundly between non-survivors and survivors in the weeks after symptom onset, making them predictors of COVID-19 severity and in-hospital mortality.[7-9] Tocilizumab and sarilumab, monoclonal antibodies targeting the IL-6 receptor, are currently being investigated for the treatment of patients with COVID-19-CSS and ARDS. To date, these targeted therapies have shown promise in small case series,[10,11] but this strategy may likely be limited to patients who already developed severe COVID-19.[12]

It has been shown that CRS observed with bacterial infections, polymicrobial sepsis, chimeric antigen receptor T cell therapy, and other T cell-activating therapies is accompanied by a surge in catecholamines.[13] Catecholamines enhance inflammatory injury by augmenting the production of IL-6 and other cytokines through a self-amplifying feed-forward loop in immune cells that requires alpha-1 adrenergic receptor signaling.[13] Inhibition of catecholamine signaling

by prophylactic treatment with prazosin, a pan-alpha-1 adrenergic receptor antagonist targeting alpha-1A, alpha-1B, and alpha-1D adrenergic receptors as an inverse agonist, was effective at preventing cytokine storm and resulted in markedly reduced mortality in multiple animal models. The ability of pan-alpha-1 adrenergic receptor antagonism to block cytokine production by immune cells has similarly been observed in human peripheral blood mononuclear cells from patients with juvenile polyarticular arthritis where treatment with doxazosin abrogated catecholamine-induced secretion of IL-6.[14] These findings offer a rationale for studying alpha-1 blockers (α-1B) in the early stages of COVID-19 to prevent progression to severe disease, ARDS, and cytokine storm, thereby reducing necessity of and the length of time that critical care management is required.[15]

This protocol outlines a study in the Observational Health Data Science and Informatics (OHDSI) community[16] with federated access to international data assets mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).[17] This infrastructure provides a unique opportunity to address this question across a number of populations and contribute valuable insights that will inform the key clinical and policy decisions on treatment of COVID-19.

6. Study Objectives

To estimate the association between prevalent use of alpha-1 blockers (α-1B) and the risk of contracting COVID-19 infection and of subsequently requiring hospitalization and intensive services such as mechanical ventilation.

7. Research Methods

Data Sources

This study is a multi-national, observational prevalent user cohort study evaluating the association between α-1B exposure on the risk of contracting COVID-19 infection and of experiencing severe forms of COVID-19 disease.

The study will be conducted using data from real world data sources that have been mapped to the OMOP Common Data Model in collaboration with the Observational Health Data Sciences and Informatics (OHDSI) and European Health Data and Evidence Network (EHDEN) initiatives. The OMOP Common Data Model (https://github.com/OHDSI/CommonDataModel/wiki) includes a standard representation of health care experiences (such as information related to drug utilization and condition occurrence), as well as common vocabularies for coding clinical concepts and enables consistent application of analyses across multiple disparate data sources.[17]

The data sources include:

- Information Systems for Research in Primary Care (SIDIAP) database, covering approximately 80% of the population of Catalonia, Spain, with approximately six million patients. SIDIAP contains data since 2006 from general practice EHRs linked to hospital admissions with information on diagnoses, prescriptions, laboratory tests, and lifestyle and sociodemographics and the central database of RT-PCR COVID-19 tests; and
- US Department of Veterans Affairs (VA) database, covering approximately 12 million patients from 170 medical centers across the US and including administrative, clinical, laboratory, and pharmacy data repositories that are linked using unique patient identifiers.

As data become available, we will include additional databases that have been mapped to OMOP CDM.

Patient Cohort

The cohort will consist of adult male patients aged 18 years and over who receive at least one eligible prescription for an exposure drug between 1st November 2019 and 31st January 2020 (with index date set as the last prescription in this window) and are observable in each database for at least one year prior to the index date. To minimize confounding by indication, patients are required to have a history of benign prostatic hyperplasia at any point prior to or including the index date and to be prescribed medication (α-1B or 5-αRI) as treatment. Cohort

exit will be the earliest of: the occurrence of an outcome event; the end of exposure; death; loss or deregistration from the database; or date of last data collection.

Exposures

The exposures of interest are defined by classes of commonly prescribed medication for the treatment of BPH, with the primary (target) exposure of interest being α-1B class of medicines. Another classes of BPH medicine to define an active comparator will be 5-αRI. Details of these exposures may be found in Appendix 1. Specification of these medicines are based on any drug containing the RxNorm ingredients of interest for class.

BPH medication exposure will first be defined as: a patient issued or dispensed at least one eligible prescription between1st November 2019 and 31st January 2020 (with index date set as the last prescription in this window). We will require the absence of other BPH medication prescribed between –180 days and 0 days prior to the index date; for example for α-1B users, we require absence of 5-αRI and of tadalafil. Continuous drug exposures will be defined from the start of follow-up by grouping sequential prescriptions that have fewer than 30 days gap between prescriptions. End of exposure will be defined as the end of the last prescription's drug supply.

Controls or Comparators

An active comparator control population will be created consisting of patients prescribed 5-αRI to minimize confounding by indication. However, residual differences may still remain as suggested by difference in clinical practice around the choice of BPH treatment via medication, which will be addressed by applying statistical methods for confounding adjustment.

Outcomes

The primary outcomes of interest will be an incident of COVID-19 diagnosis or SARS-CoV-2 positive test 1) without hospitalization, 2) with hospitalization, and 3) requiring intensive in-patient services such as mechanical ventilation. The detailed definitions of these outcomes are given in Appendix 1. Up to 118 negative control outcome experiments will be performed examining the risk of residual confounding. The negative controls derive from a process similar to that outlined in Voss et al. and have been fully described previously.[18,19]

Covariates

Data driven approaches will be used to identify potential covariates for inclusion in matched or stratified propensity score models identified using regularized logistic regression. These will include: age group (5-year groups), index month, conditions (SNOMED concepts and descendants) any time prior to index, conditions in the 180 days prior to index, conditions in the 30 days prior to index, drugs (ATC classes and RxNorm ingredients) any time prior to index, drugs in the 180 days prior to index, drugs in the 30 days prior to index, procedures any time prior to index, procedures in the 180 days prior to index, procedures in the 30 days prior to index, devices any time prior to index, devices in the 180 days prior to index, devices in the 30 days prior to index, measurements any time prior to index, measurement in the 180 days prior to index, measurements in the 30 days prior to index, measurement values in the last 180 days, CHADS2Vasc, Diabetes Comorbidity Severity Index, and Charlson index.

Analysis

We will estimate the relative risk of each outcome using an on-treatment and intention-to-treat analysis for the target exposure (α-1B) against the comparator exposure (5-αRI) in patients with BPH.

We will describe patient characteristics (prevalence) for each cohort comparison and data source. To adjust for measured confounding, propensity score models for each class pair and data source will be created using a data-driven process using regularized logistic regression when target and comparator cohorts contain at least 500 patients within each data source. This process allows the data to decide which combinations of baseline patient characteristics, including demographics and previous conditions, drug exposures, procedures, and health-service-use behaviors are most predictive of treatment assignment. For cohorts with fewer than 500 patients, we will build propensity score models using age categorized in 5-year groups and index month examining for any heterogeneity.

Patients will be stratified by propensity score or variable-ratio matched to ensure sufficient balance is achieved if all after-adjustment baseline characteristics return absolute standardized mean differences of less than 0.1. We will make the choice for matching or stratification based on sufficient exposure cohort size. Cox proportional hazards models will be used to estimate

hazard ratios (HRs) between target and comparator treatment cohorts for the risk of each outcome in each data source. We will aggregate HRs across data sources to produce meta-analytic estimates using a random-effects meta-analysis.

For each effect estimate, we will evaluate associations using negative control outcome experiments. We will use the empirical null distributions to calibrate each HR estimate, its 95% CI, and the p value to reject the null hypothesis of no differential effect. A HR will be considered significantly different from the null value when its calibrated 95% CI does not include this value (and corresponds to a calibrated p of less than 0.05 without correcting for multiple testing).

The following additional calculations will be performed: power calculations estimating minimum detectable relative risk; preference score (a transformation of propensity score that adjusts for prevalence differences between populations) distributions to evaluate empirical equipoise and population generalizability; patient characteristics to evaluate cohort balance before and after propensity score adjustment; negative-control calibration plots to assess residual bias; and Kaplan-Meier plots to examine HR proportionality assumptions.

8. Sample Size and Study Power

See previous section.

9. Strengths and Limitations

Comparative cohort studies allow direct estimation of relative incident event rates between subjects with the exposures of interest and controls while accounting for observed confounding in these rates when populations are balanced. This protocol employs large-scale propensity score matching and stratification strategies that allow balancing on a large number of baseline potential confounders and have been shown to also balance on important unobserved confounders, like baseline blood pressure in studies of anti-hypertensive treatments. Further, the use of negative control outcomes allows for evaluating the study design as a whole in terms of residual bias as a diagnostic step to help ensure casual validity of estimates.

In the interest of generating actionable evidence that can address urgent public health need and support decision making, we have incorporated several study-design features that allow us to run this analysis as immediately as possible. We acknowledge, however, that there are also limitations to this analysis which need to be understood in order to properly interpret the results. To date, longitudinal healthcare data to study patients with COVID-19 is still accumulating, and there are only small amounts of data available in limited contexts and these data are held by independent data partners who cannot pool patient-level data across sites.

Ideally, a comparative cohort analysis estimating the effect of α-1B on the incidence of COVID-19 would be undertaken using a new user cohort design.[20] In a new user cohort design, all patients are aligned at the point of their drug initiation (which is referred to as the index date) and the variables included as confounders for adjustment in models include only those that preceded initiation of the drug. The new user design has advantages in reducing the risk of bias when time-varying hazards of the outcome exist. The new user design also reduces bias when depletion of susceptibles may occur, whereby people experiencing an event are more likely to do so shortly after drug initiation and those subjects with prevalent exposure are therefore at lower risk of experiencing the outcome of interest over time.

A new user design, however, would require a larger number of patients than a prevalent user design and a long history of longitudinal data (capturing both inpatient and outpatient care) that is not available for all study sites. During the COVID-19 pandemic, there may be a smaller pool of new users as fewer patients may initiate α-1B or 5-αRI for routine BPH management as social distancing and healthcare is prioritised on managing COVID-19. Additionally, COVID-19 is a new illness and did not exist in the population prior to the start of our observation period. Therefore, concerns over time-varying hazards and depletion of susceptibles are less likely to be relevant in this context. Similar arguments hold for evaluating the effect of α-1B use on outcomes of COVID-19 infection and severity of disease.

Due to these issues, we have elected for a prevalent user design.[21] We define the index date and align patients on a specific point in calendar time (a prescription between 1st November 2019 and 31st January 2020) at which point they become “at-risk” for COVID-19.

The prevalent user design was originally developed to address the challenge of having limited available data when comparing new-to-market drugs with established drugs.[21] In the original publication describing the prevalent user design, the authors highlight multiple sources of bias that are likely to arise in that context. Here, we use the prevalent user design to address the problem of not having sufficient data on a new illness (COVID-19), which affects all of our comparators equally. Thus, we assert that multiple forms of bias that arise in the new-to-market vs. traditional comparison (e.g. substantially longer duration of prior exposure among users of the established drug compared to users of the new-to-market drug, or unidirectional switching from the established drug to the new-to-market drug) are less likely to produce meaningful bias in our analysis.

Misclassification of study variables is unavoidable in observational analyses of secondary health data. It is possible that we misclassify our exposures by failing to observe medication use when a patient is actually taking it or, more commonly, seeing medication prescriptions in the data that the patient is not actually taking. However, we do not expect misclassification will be strongly differential with respect to the treatments being compared or with respect to outcome status. Thus, bias due to exposure misclassification will most likely be toward the null (i.e. increase the likelihood of a type II error).

Outcome misclassification is also an important concern since the COVID-19 outcome will be under-diagnosed due to limited availability of testing resources and the fact that many infected patients may remain asymptomatic or not require observed healthcare utilization. It is important to note that the extent of underdiagnosis will likely vary by site due to differences in national testing strategies. Furthermore, classification of the outcome could also vary with respect to calendar time, since underdiagnosis could become more or less frequent over the course of the pandemic. To address this inherent limitation, we have included a hospitalization-based COVID-19 outcome which will be well-classified in these data to provide additional context. We do not expect outcome misclassification to be differential with respect to these exposure groups. Thus, bias due to outcome misclassification will also most likely be toward the null.

Finally, the patient cohort in this study consist only of adult male with BPH, treatment of which is the predominant use case of α-1B. While the results from this study would be valuable in guiding ongoing clinical trials for potential Covid-19 treatments, they cannot be generalized to a broader population without follow-up investigations.

10. Protection of Human Subjects

The study uses only de-identified data. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians.

11. Management and Reporting of Adverse Events and Adverse Reactions

This study uses coded data that already exist in an electronic database. In this type of database, it is not possible to link (i.e., identify a potential causal association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual adverse events reports. The study results will be assessed for medically important results.

12. Plans for Disseminating and Communicating Study Results

This study protocol will be registered at the EU PAS Register and study results will be posted on the OHDSI website after completion of the study. At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal. The results will also be presented at the OHDSI in-person events.

13. References

1. *Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)* Geneva, Switzerland: World Health Organization (WHO);2020.

2. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020.

3. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med.* 2020.

4. Ruan, Q., Yang, K., Wang, W., Jiang, L. & Song, J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med (2020).

5. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020.

6. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunologic features in severe and moderate forms of Coronavirus Disease 2019. J. Clin. Invest. (2020)

7. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet (London, England).* 2020.

8. Chen, X. et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely associated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. medRxiv 2020.02.29.20029520 (2020) doi:10.1101/2020.02.29.20029520.

9. Liu, T. et al. The potential role of IL-6 in monitoring severe case of coronavirus disease 2019. http://medrxiv.org/lookup/doi/10.1101/2020.03.01.20029769 (2020).

10. Xu, X. et al. Effective treatment of severe COVID-19 patients with tocilizumab. PNAS (2020).

11. Luo, P. et al. Tocilizumab treatment in COVID-19: a single center experience. J. Med. Virol. (2020).

12. Sanofi: Press Releases, Monday, April 27, 2020. https://www.sanofi.com/en/media-room/press-releases/2020/2020-04-27-12-58-00

13. Staedtke, V. et al. Disruption of a self-amplifying catecholamine loop reduces cytokine release syndrome. Nature 564, 273–277 (2018).

14. Heijnen, C. J. et al. Functional alpha 1-adrenergic receptors on leukocytes of patients with polyarticular juvenile rheumatoid arthritis. J. Neuroimmunol. 71, 223–226 (1996).

15. Konig, M. F. et al. Preventing cytokine storm syndrome in COVID-19 using α-1 adrenergic receptor antagonists. J. Clin. Invest. (2020) doi:10.1172/JCI139642.

16. Hripcsak G, Duke JD, Shah NH, et al. Observational Health Data Sciences and Informatics (OHDSI): Opportunities for Observational Researchers. Studies in health technology and informatics. 2015;216:574-578.

17. Overhage JM, Ryan PB, Reich CG, Hartzema AG, Stang PE. Validation of a common data model for active safety surveillance research. Journal of the American Medical Informatics Association : JAMIA. 2012;19(1):54-60.

18. Suchard MA, Schuemie MJ, Krumholz HM, et al. Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. Lancet (London, England). 2019;394(10211):1816-1826.

19. Voss EA, Boyce RD, Ryan PB, van der Lei J, Rijnbeek PR, Schuemie MJ. Accuracy of an automated knowledge base for identifying drug adverse reactions. Journal of biomedical informatics. 2017;66:72-81.

20. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. American journal of epidemiology. 2003;158(9):915-20.

21. Suissa S, Moodie EE, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. Pharmacoepidemiology and drug safety. 2017;26(4):459-468.

14. Appendix 1: Target, Comparator, and Outcome Cohort Definitions

14.1 Exposure Cohort Definitions

This section documents the exposure cohort definitions. Below is the complete specification for prevalent α-1B users. Prevalent 5-αRI users are defined similarly, with the roles of α-1B and 5-αRI switched.

Prevalent users of α-1B with BPH

Initial Event Cohort

People having any of the following:

- a drug exposure of alpha-blockers[2]
    - occurrence start is between 2019-11-01 and 2020-01-31 (inclusive)

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **latest event per person.**

Inclusion Rules

Inclusion Criteria #1: Age >= 18 years old
Having all of the following criteria:

- with the following event criteria:
    - with age >= 18

Inclusion Criteria #2: has >=180d of prior observation
Having all of the following criteria:

- at least 1 occurrences of an observation period
- where event starts between all days Before and 180 days Before index start date and event ends between 0 days Before and all days After index start date

Inclusion Criteria #3: BPH diagnosis anytime before (and including) start-date
Having all of the following criteria:

- at least 1 occurrences of a condition occurrence of BPH[3]
- where event starts between all days Before and 0 days Before index start date

Inclusion Criteria #4: No exposure to 5-alpha inhibitors or tadalafil
Having all of the following criteria:

- at most 0 occurrences of a drug exposure of 5-alpha reductase inhibitors[1]
- where event starts between 180 days Before and 0 days Before index start date
- and at most 0 occurrences of a drug exposure of tadalafil[4]
- where event starts between 180 days Before and 0 days Before index start date

Inclusion Criteria #5: Male
Having all of the following criteria:

- with the following event criteria:
    - gender is any of: MALE
-

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

Custom Drug Era Exit Criteria

This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of alpha-blockers[2]

- allowing 30 days between exposures
- adding 0 days after exposure end

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

1. 5-alpha reductase inhibitors

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
989482	dutasteride	Drug	RxNorm	NO	YES	NO
996416	finasteride	Drug	RxNorm	NO	YES	NO

2. alpha-blockers

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
924566	tamsulosin	Drug	RxNorm	NO	YES	NO
930021	alfuzosin	Drug	RxNorm	NO	YES	NO
1341238	terazosin	Drug	RxNorm	NO	YES	NO
1350489	prazosin	Drug	RxNorm	NO	YES	NO
1363053	doxazosin	Drug	RxNorm	NO	YES	NO
19012925	silodosin	Drug	RxNorm	NO	YES	NO

3. BPH

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
198803	Benign prostatic hyperplasia	Condition	SNOMED	NO	YES	NO

4. tadalafil

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
1336926	tadalafil	Drug	RxNorm	NO	YES	NO

14.2 Outcome Cohort Definitions

This section documents the outcome cohort definitions. We consider

- COVID-19 diagnosis or SARS-CoV-2 positive test with no required prior observation
- Hospitalization with a COVID-19 diagnosis record or SARS-CoV-2 positive test with no required prior observation
- Hospitalization and requiring intensive services with a SARS-CoV-2 positive test with no required prior observation

Below are their complete specifications.

[COVID ID133 V1] Persons with a COVID-19 diagnosis or a SARS-CoV-2 positive test with no required prior observation

Initial Event Cohort

People having any of the following:

- a measurement of SARS-CoV-2 positive test measurement pre-coordinated[2]
    - occurrence start is after 2019-12-01
- a measurement of SARS-CoV-2 test measurement[3]
    - occurrence start is after 2019-12-01
    - value as concept is any of: Detected, Detected, Positive, Positive, Present, Present
- an observation of SARS-CoV-2 test measurement[3]
    - occurrence start is after 2019-12-01
    - value as concept is any of: Detected, Detected, Positive, Positive, Present, Present
- a condition occurrence of COVID-19 conditions[1]
    - occurrence start is after 2019-12-01

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

1. COVID-19 conditions

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
439676	Coronavirus infection	Condition	SNOMED	NO	YES	NO
4100065	Disease due to Coronaviridae	Condition	SNOMED	NO	YES	NO
37311060	Suspected disease	Observation	SNOMED	NO	YES	NO

	caused by 2019-nCoV					
37311061	Disease caused by 2019-nCoV	Condition	SNOMED	NO	YES	NO

2. SARS-CoV-2 positive test measurement pre-coordinated

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
37310282	2019 novel coronavirus detected	Measurement	SNOMED	NO	YES	NO

3. SARS-CoV-2 test measurement

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
756055	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Measurement	OMOP Extension	NO	YES	NO
37310281	2019 novel coronavirus not detected	Measurement	SNOMED	YES	YES	NO

[COVID ID135 V1] Persons hospitalized with a COVID-19 diagnosis record or a SARS-CoV-2 positive test with no required prior observation

Initial Event Cohort

People having any of the following:

- a visit occurrence of Inpatient Visit[2]
    - occurrence start is after 2019-12-01

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:
Having any of the following criteria:

- at least 1 occurrences of a measurement of SARS-CoV-2 positive test measurement pre-coordinated[3]
- where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrences of a measurement of SARS-CoV-2 test measurement[4]
    - value as concept is any of: Detected, Detected, Positive, Positive, Present, Present
- where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrences of an observation of SARS-CoV-2 test measurement[4]
    - value as concept is any of: Detected, Detected, Positive, Positive, Present, Present

- where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrences of a condition occurrence of COVID-19 conditions[1]
- where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

Limit cohort of initial events to: **earliest event per person.**
Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's end date plus 0 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

1. COVID-19 conditions

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
439676	Coronavirus infection	Condition	SNOMED	NO	YES	NO
4100065	Disease due to Coronaviridae	Condition	SNOMED	NO	YES	NO
37311060	Suspected disease caused by 2019-nCoV	Observation	SNOMED	NO	YES	NO
37311061	Disease caused by 2019-nCoV	Condition	SNOMED	NO	YES	NO

2. Inpatient Visit

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	Visit	Visit	NO	YES	NO
9201	Inpatient Visit	Visit	Visit	NO	YES	NO

3. SARS-CoV-2 positive test measurement pre-coordinated

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
37310282	2019 novel coronavirus detected	Measurement	SNOMED	NO	YES	NO

4. SARS-CoV-2 test measurement

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped

756055	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Measurement	OMOP Extension	NO	YES	NO
37310281	2019 novel coronavirus not detected	Measurement	SNOMED	YES	YES	NO

[COVID ID137 V1] Persons hospitalized and requiring intensive services with a COVID-19 diagnosis record or a SARS-CoV-2 positive test with no required prior observation

Initial Event Cohort

People having any of the following:

- a procedure of Mechanical ventilation[4]
    - occurrence start is after 2019-12-01
- a condition occurrence of Mechanical ventilation[4]
    - occurrence start is after 2019-12-01
- an observation of Mechanical ventilation[4]
    - occurrence start is after 2019-12-01
- a procedure of tracheostomy[7]
    - occurrence start is after 2019-12-01
- a procedure of Extracorporeal membrane oxygenation (ECMO) procedure[2]
    - occurrence start is after 2019-12-01

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:
Having all of the following criteria:

- at least 1 occurrences of a visit occurrence of Inpatient Visit[3]
    - Having any of the following criteria:
        - at least 1 occurrences of a measurement of SARS-CoV-2 positive test measurement pre-coordinated[5]
        - where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
        - or at least 1 occurrences of a measurement of SARS-CoV-2 test measurement[6]
            - value as concept is any of: Detected, Detected, Positive, Positive, Present, Present
        - where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
        - or at least 1 occurrences of an observation of SARS-CoV-2 test measurement[6]
            - value as concept is any of: Detected, Detected, Positive, Positive, Present, Present
        - where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
        - or at least 1 occurrences of a condition occurrence of COVID-19 conditions[1]

        - where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **earliest event per person.**
Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's end date plus 0 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

1. COVID-19 conditions

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
439676	Coronavirus infection	Condition	SNOMED	NO	YES	NO
4100065	Disease due to Coronaviridae	Condition	SNOMED	NO	YES	NO
37311060	Suspected disease caused by 2019-nCoV	Observation	SNOMED	NO	YES	NO
37311061	Disease caused by 2019-nCoV	Condition	SNOMED	NO	YES	NO

2. Extracorporeal membrane oxygenation (ECMO) procedure

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
1531630	Extracorporeal Oxygenation, Membrane, Peripheral Veno-venous	Procedure	ICD10PCS	NO	NO	NO
1531631	Extracorporeal Oxygenation, Membrane, Peripheral Veno-arterial	Procedure	ICD10PCS	NO	NO	NO
1531632	Extracorporeal Oxygenation, Membrane, Central	Procedure	ICD10PCS	NO	NO	NO
2002247	Extracorporeal membrane oxygenation [ECMO]	Procedure	ICD9Proc	NO	YES	NO

2787820	Extracorporeal Supersaturated Oxygenation, Intermittent	Procedure	ICD10PCS	NO	NO	NO
2787821	Extracorporeal Hyperbaric Oxygenation, Continuous	Procedure	ICD10PCS	NO	NO	NO
4052536	Extracorporeal membrane oxygenation	Procedure	SNOMED	NO	YES	NO
4338595	Cardiac support using extracorporeal membrane oxygenation circuitry	Procedure	SNOMED	NO	NO	NO
44515635	Extracorporeal membrane oxygenation	Procedure	OPCS4	NO	YES	NO
44811012	Fluoroscopy guided percutaneous insertion of cannula for extracorporeal membrane oxygenation	Procedure	SNOMED	NO	NO	NO

3. Inpatient Visit

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	Visit	Visit	NO	YES	NO
9201	Inpatient Visit	Visit	Visit	NO	YES	NO

4. Mechanical ventilation

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
765576	Orotracheal intubation using bougie device	Procedure	SNOMED	NO	YES	NO
2108641	Glossectomy; complete or total, with or without tracheostomy, without radical neck dissection	Procedure	CPT4	YES	YES	NO

2108642	Glossectomy; complete or total, with or without tracheostomy, with unilateral radical neck dissection	Procedure	CPT4	YES	YES	NO
2108681	Patient receiving care in the intensive care unit (ICU) and receiving mechanical ventilation, 24 hours or less (CRIT)	Observation	CPT4	NO	YES	NO
2788036	Respiratory Ventilation, Less than 24 Consecutive Hours	Procedure	ICD10PCS	NO	YES	NO
2788037	Respiratory Ventilation, 24-96 Consecutive Hours	Procedure	ICD10PCS	NO	YES	NO
2788038	Respiratory Ventilation, Greater than 96 Consecutive Hours	Procedure	ICD10PCS	NO	YES	NO
4006318	Respiratory assist, manual	Procedure	SNOMED	YES	YES	NO
4021786	Fear of disconnection from ventilator	Condition	SNOMED	YES	YES	NO
4031379	Artificial ventilation finding	Condition	SNOMED	YES	YES	NO
4072633	Weaning from mechanically assisted ventilation	Procedure	SNOMED	NO	YES	NO
4074663	Diaphragmatic augmentation	Procedure	SNOMED	YES	YES	NO
4080957	Endotracheal respiratory assistance	Procedure	SNOMED	NO	YES	NO
4107247	Inhalation anesthesia, machine system, semi-closed, no rebreathing of primary agent	Procedure	SNOMED	YES	YES	NO
4168966	Endotracheal tube present	Observation	SNOMED	NO	YES	NO
4219858	Problem with patient ventilator	Observation	SNOMED	NO	YES	NO

4230167	Artificial respiration	Procedure	SNOMED	NO	YES	NO
4232550	Home visit for mechanical ventilation care	Observation	SNOMED	NO	YES	NO
4232891	Mechanical ventilation response	Observation	SNOMED	YES	YES	NO
4235361	Hyperventilation therapy for traumatic brain injury	Procedure	SNOMED	NO	YES	NO
4237618	Ventilator care	Observation	SNOMED	NO	YES	NO
4251737	Ventilator care management	Procedure	SNOMED	NO	YES	NO
4254108	Resuscitation with artificial respiration	Procedure	SNOMED	YES	YES	NO
4254905	Ventilator care education	Procedure	SNOMED	YES	YES	NO
4259233	Ventilator care assessment	Procedure	SNOMED	YES	YES	NO
4332501	Management of noninvasive mechanical ventilation	Procedure	SNOMED	NO	YES	NO
4348300	Expired air ventilation	Procedure	SNOMED	YES	YES	NO
4353715	Ventilator finding	Observation	SNOMED	YES	YES	NO
37116689	Insertion of endotracheal ventilation catheter	Procedure	SNOMED	NO	YES	NO
37206832	Mechanical insufflation exsufflation	Procedure	SNOMED	NO	YES	NO
40481547	Dependence on ventilator	Condition	SNOMED	NO	YES	NO
40487536	Intubation of respiratory tract	Procedure	SNOMED	NO	YES	NO
42738852	Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; first day	Procedure	CPT4	NO	YES	NO

42738853	Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; subsequent days	Procedure	CPT4	NO	YES	NO
44509482	Other specified ventilation support	Procedure	OPCS4	NO	YES	NO
44791135	Ventilatory support	Procedure	SNOMED	NO	YES	NO
44808555	Provision of mechanical ventilator	Procedure	SNOMED	YES	YES	NO
45887795	Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing	Procedure	CPT4	NO	YES	NO

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
765576	Orotracheal intubation using bougie device	Procedure	SNOMED	NO	YES	NO
2108641	Glossectomy; complete or total, with or without tracheostomy, without radical neck dissection	Procedure	CPT4	YES	YES	NO
2108642	Glossectomy; complete or total, with or without tracheostomy, with unilateral radical neck dissection	Procedure	CPT4	YES	YES	NO
2108681	Patient receiving care in the intensive care unit (ICU) and receiving mechanical ventilation, 24 hours or less (CRIT)	Observation	CPT4	NO	YES	NO
2788036	Respiratory Ventilation, Less than 24 Consecutive Hours	Procedure	ICD10PCS	NO	YES	NO

2788037	Respiratory Ventilation, 24-96 Consecutive Hours	Procedure	ICD10PCS	NO	YES	NO
2788038	Respiratory Ventilation, Greater than 96 Consecutive Hours	Procedure	ICD10PCS	NO	YES	NO
4006318	Respiratory assist, manual	Procedure	SNOMED	YES	YES	NO
4021786	Fear of disconnection from ventilator	Condition	SNOMED	YES	YES	NO
4031379	Artificial ventilation finding	Condition	SNOMED	YES	YES	NO

5. SARS-CoV-2 positive test measurement pre-coordinated

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
37310282	2019 novel coronavirus detected	Measurement	SNOMED	NO	YES	NO

6. SARS-CoV-2 test measurement

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
756055	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Measurement	OMOP Extension	NO	YES	NO
37310281	2019 novel coronavirus not detected	Measurement	SNOMED	YES	YES	NO

7. tracheostomy

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
45887989	Transoral approach to skull base, brain stem or upper spinal cord for biopsy, decompression or excision of lesion	Procedure	CPT4	NO	YES	NO
4337047	Insertion of tracheostomy tube	Procedure	SNOMED	NO	YES	NO
4311023	Revision of stoma of trachea	Procedure	SNOMED	NO	YES	NO

4208093	Tracheostomy, emergency procedure by transtracheal approach	Procedure	SNOMED	NO	YES	NO
4199580	Mediastinal tracheostomy	Procedure	SNOMED	NO	YES	NO
4195473	Temporary tracheostomy	Procedure	SNOMED	NO	YES	NO
4168864	Lateral tracheostomy	Procedure	SNOMED	NO	YES	NO
4166281	Anterior tracheostomy	Procedure	SNOMED	NO	YES	NO
4115488	Emergency tracheostomy	Procedure	SNOMED	NO	YES	NO
4065590	Permanent tracheostomy	Procedure	SNOMED	NO	YES	NO
2870619	Medical and Surgical @ Respiratory System @ Revision @ Trachea @ Percutaneous @ Tracheostomy Device	Procedure	ICD10PCS	NO	YES	NO
2862930	Medical and Surgical @ Respiratory System @ Revision @ Trachea @ Open @ Tracheostomy Device	Procedure	ICD10PCS	NO	YES	NO
2836115	Medical and Surgical @ Respiratory System @ Bypass @ Trachea @ Percutaneous @ Tracheostomy Device	Procedure	ICD10PCS	NO	YES	NO
2831237	Medical and Surgical @ Respiratory System @ Bypass @ Trachea @ Open @ Tracheostomy Device	Procedure	ICD10PCS	NO	YES	NO
2829386	Medical and Surgical @ Respiratory System @ Revision @ Trachea @ Via Natural or Artificial Opening @ Tracheostomy Device	Procedure	ICD10PCS	NO	YES	NO

2829384	Medical and Surgical @ Respiratory System @ Revision @ Trachea @ Percutaneous Endoscopic @ Tracheostomy Device	Procedure	ICD10PCS	NO	YES	NO
2794811	Medical and Surgical @ Respiratory System @ Change @ Trachea @ External @ Tracheostomy Device	Procedure	ICD10PCS	NO	YES	NO
2743216	Removal of Tracheostomy Device from Trachea, Via Natural or Artificial Opening	Procedure	ICD10PCS	NO	YES	NO
2110486	Transoral approach to skull base, brain stem or upper spinal cord for biopsy, decompression or excision of lesion; requiring splitting of tongue and/or mandible (including tracheostomy)	Procedure	CPT4	YES	YES	NO
2106569	Tracheal puncture, percutaneous with transtracheal aspiration and/or injection	Procedure	CPT4	NO	YES	NO
2106568	Construction of tracheoesophageal fistula and subsequent insertion of an alaryngeal speech prosthesis (eg, voice button, Blom-Singer prosthesis)	Procedure	CPT4	NO	YES	NO
2106567	Tracheostomy, fenestration procedure with skin flaps	Procedure	CPT4	NO	YES	NO
2106565	Tracheostomy, emergency	Procedure	CPT4	NO	YES	NO

	procedure; cricothyroid membrane					
2106563	Tracheostomy, planned (separate procedure); younger than 2 years	Procedure	CPT4	NO	YES	NO
2106562	Tracheostomy, planned (separate procedure)	Procedure	CPT4	NO	YES	NO

15. Appendix 2: ENCePP Checklist for Study Protocols

We have filled out the ENCePP Checklist for Study Protocols (Revision 4) which was adopted by the ENCePP Steering Group on October 15, 2019. A link to the completed form is provided below:

Appendix 2: ENCePP Checklist for Study Protocol