Methodologies for observational studies comparing inpatient COVID-19 treatments:
IL-6 receptor inhibitors and JAK inhibitors for hospitalized COVID-19 patients receiving corticosteroid therapy

[Research Objective 3]
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Contents

Abbreviations

Abbreviation	Description
AEP	Aetion Evidence Platform
BAR	Baricitinib
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMS	Centers for Medicare & Medicaid Services
COVID-19	coronavirus disease 2019
CPT	current procedural terminology
CS	corticosteroids
CSI	corticosteroids of interest
DAG	directed acyclic graph
ECMO	extracorporeal membrane oxygenation
ER	emergency room
EUA	Emergency Use Authorization
FDA	US Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System
HFO	high flow oxygen
HR	hazard ratio
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICU	intensive care unit
IL6Ri	interleukin-6 receptor inhibitors
IMA	intentional multiphase approach
IMV	invasive mechanical ventilation
IPW	inverse probability weighting
IQR	interquartile range
JAKi	Janus kinase inhibitors
MCM	medical countermeasures
mWHO	modified WHO severity score
NDC	national drug code
NIH	National Institutes of Health
NIV	noninvasive ventilation
O2	supplemental oxygen
PS	propensity score

PSW	propensity score weighting
RDV	remdesivir
RWD	real-world data
SAR	sarilumab
SARS-COV-2	severe acute respiratory syndrome coronavirus 2
SPA	single-phase prespecification approach
SoC	standard of care
SPACE	Structured Preapproval and Postapproval Comparative Study Design Framework to Generate Valid and Transparent Real-World Evidence for Regulatory Decisions
SPIFD	Structured Process to Identify Fit-For Purpose Data
STaRT-RWE	Structured template for planning and reporting on the implementation of real world evidence studies
TCZ	tocilizumab
TOF	tofacitinib
T	day of treatment initiation
US	United States
WHO	World Health Organization

Version History and Amendments

Version date	***Version number***	***Section of protocol***	***Amendment or update***	***Reason***
11 Jan 2023	v8 (v7 posted on clinicaltrials.gov 2 Dec 2022))	• Covariates table • Footnote • STaRT-RWE tables (Appendix D)	• Removed the facility level prescribing practices variable from covariates table • Removed the following footnote on each protocol page: “This document contains confidential and proprietary business information. Not disclosable pursuant to FOIA Exemption b(4). • Updated STaRT-RWE table to correspond with revisions to code list	• Variable highly correlated with other measured variables • Footer not relevant • STaRT-RWE table revised to reflect measures to be used for implementation All changes were made prior to study implementation.

1. BACKGROUND AND RATIONALE

1.1 Collaboration between Aetion and the US Food and Drug Administration (FDA)

Aetion is under contract with the US Food and Drug Administration (FDA) via a Broad Agency Announcement to use the Aetion Evidence Platform® (AEP) to develop a system of studies and a systematic process for the rapid assessment of COVID-19 inpatient medical countermeasures. This includes identifying and analyzing fit-for-purpose data sources to characterize inpatient COVID-19 patient populations, risk factors for COVID-19-related complications, and to explore methods for scientific evaluation of potential interventions for inpatient treatment of COVID-19.

1.2 Rationale for Inpatient Comparative COVID-19 Treatment Example

Understanding of coronavirus disease-2019 (COVID-19) pathogenesis and treatment evolved rapidly after the emergence of the SARS-CoV-2 virus in late 2019. Clinical and in-vitro studies have identified a dysregulated or overactive host immune response to SARS-CoV-2 infection as a key feature of severe COVID-19 disease [Chen 2020, Zhou 2020, Blanco-Melo 2020, Ruan 2020, Del Valle 2020]. Immunomodulators such as corticosteroids (CS), interleukin-6 receptor inhibitors (IL6Ri), and Janus kinase inhibitors (JAKi) have therefore been explored as potential strategies for controlling overactive immune responses in COVID-19 [Burrage 2020, Ngamprasertchai 2022, Kim 2020, Mehta 2020].

Given the limited number of recommended treatments early in the pandemic, much of the initial observational research evaluating immunomodulators for COVID-19 has relied on non-user comparisons [Gatto 2020, Hu 2020, Nelson 2020, Li 2020]. With the subsequent emergence of multiple immunomodulator options for management of inpatient COVID-19, it is now feasible to apply the active-comparator, new-user design, which is generally recommended to mitigate bias in observational (real-world data) studies (hereafter referred to as “observational” studies) [Lund 2015, Franklin 2017]. For the current collaboration, this active comparator approach will be applied to an illustrative observational study of two regimens indicated for similar COVID-19 inpatient populations (and, thus, ideal for the active comparator design): IL6Ri versus JAKi as add-on therapy to CS. Given limited comparative research for IL6Ri versus JAKi regimens, this comparison is also a relevant and clinically meaningful illustrative example to improve upon methods for conducting observational studies to evaluate the effectiveness of inpatient COVID treatments.

1.3 Background on Immunomodulators for COVID-19: Corticosteroids, IL-6 Receptor Inhibitors, and JAK Inhibitors

In June 2020, the systemic CS dexamethasone became the first immunomodulator in which a clinical benefit was demonstrated in patients hospitalized for COVID-19 receiving oxygen or mechanical ventilation [RECOVERY Collaborative Group 2020]. Since then, dexamethasone has become the most commonly used inpatient COVID-19 treatment in the United States

[Weckstein 2021]. In 2021, several large randomized controlled trials (RCTs) demonstrated that IL6Ri or JAKi, when added to dexamethasone, can yield further mortality benefits for certain subgroups of patients hospitalized for COVID-19 [REMAP-CAP Investigators 2021, RECOVERY Collaborative Group 2021, Marconi 2021]. As of February 28th, 2022 (the end of our study period), NIH guidelines [NIH Treatment Guidelines, 2022 (a)] recommended the addition of either IL6Ri or JAKi to dexamethasone for patients who are hospitalized and require supplemental oxygen (O2), non-invasive ventilation (NIV), or high-flow oxygen (HFO) and who have systemic inflammation and rapidly increasing oxygen needs (no recommended timing of administration). IL6Ri were additionally recommended for patients requiring invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO) within 24 hours after admission to the intensive care unit (ICU) [NIH Treatment Guidelines, 2022 (a)]; JAKi were not recommended for this patient population as of February 2022[1].

By the end of February 2022, two IL6Ri medications (tocilizumab, TCZ; sarilumab, SAR) were included in NIH treatment guidelines for use in addition to systemic CS for therapeutic management of adults hospitalized with COVID-19[2]. SAR is only recommended when TCZ is not available and is not currently authorized for emergency use or approved by FDA for COVID-19 related indications. Intravenous TCZ and subcutaneous SAR are monoclonal antibodies that inhibit binding of interleukin-6, a pro-inflammatory cytokine thought to play a critical role in COVID-19-induced systemic inflammation [Zhong, 2020]. NIH recommendations for use of TCZ in patients requiring supplemental O2 or NIV/HFO were largely based on results of the RECOVERY trial, which found a reduction in 28-day mortality for TCZ among those with elevated C-reactive protein requiring oxygen supplementation (RR 0.85; 95% CI 0.76–0.94) [RECOVERY Collaborative Group 2021]. Recommendations for IL6Ri among patients requiring IMV/ECMO recently admitted to the ICU were informed by REMAP-CAP trial findings that receipt of TCZ or SAR within 24 hours of ICU admission among critically-ill patients was associated with improvements in inpatient survival (HR 1.61; 95% CI 1.25-2.08) [REMAP-CAP Investigators 2021]. The totality of evidence from smaller RCTs [Stone 2020, Rosas 2021] and meta-analyses [Juul 2021, Kow 2021, Albuquerque 2022, REACT Working Group 2021, Rezaei 2021, Zhang 2022, Tleyjeh 2021] has varied for the effectiveness of IL6Ri in COVID-19, particularly with regard to the populations most likely to benefit. A meta-analysis of 21 RCTs conducted by the WHO [REACT Working Group 2021] found that TCZ was associated with a meaningful mortality reduction among those receiving supplemental O2 or NIV/HFO, with uncertain benefit for those receiving IMV/ECMO.

Two JAKi medications (baricitinib, BAR; tofacitinib, TOF) were included in NIH treatment guidelines by the end of the study period[3]. Like SAR, TOF is only recommended when BAR is not available and does not currently have EUA or approval for COVID-19 related indications.

[1] Of note, updated NIH guidance released in August 9th, 2022 [NIH Treatment Guidelines, 2022 (b)] added BAR as an option for patients receiving IMV/ECMO, and expanded the recommended TCZ and BAR populations by removing requirements for systemic inflammation and rapidly increasing oxygen needs (among NIV/HFO patients) and for admission to ICU within 24 hours (among IMV/ECMO patients). However, given the study period for our illustrative example ends on February 28th, 2022, we focus here on NIH guidance available in February 2022 [NIH Treatment Guidelines, 2022 (a)].

[2] IL6Ri were first included in NIH guidelines on April 23rd, 2021.

[3] JAKi were first included in NIH guidelines on July 9th, 2021.

BAR and TOF are oral JAKi that block release of pro-inflammatory cytokines implicated in COVID-19 immuno-pathophysiology [Bronte, 2020, Petrone 2021, Stebbing 2020, Marconi 2020]. In addition to known immunosuppressive effects, BAR also has potential antiviral activity through inhibition of proteins involved in viral propagation of SARS-CoV-2 [Richardson 2020, Stebbing 2020]. NIH recommendations for BAR use among patients on O2 or NIV/HFO were based on results from the ACTT-2 [Kalil 2020] and COV-BARRIER [Marconi 2021] trials, which found significant improvements in recovery time (RR 1.16; 95% CI 1.01-1.32) and 28-day mortality (HR 0.57; 95% CI 0.41–0.78), respectively, for those randomized to receive BAR for up to 14 days compared to trial-specific comparators. Positive results from the STOP-COVID trial [Guimarães 2021] led the NIH to suggest that TOF can be considered for patients receiving O2 and NIV/HFO when BAR is unavailable. A recent meta-analysis [Zhang 2022] of two BAR RCTs found that similar to TCZ, there is a mortality benefit in patients receiving O2 (pooled RR = 0.62, 95% CI 0.41–0.95) and NIV/HFO (pooled RR 0.59, 95% CI 0.42–0.85) that is attenuated among those requiring IMV/ECMO (pooled RR 0.77, 95% CI 0.51–1.15).

To our knowledge, only two studies (both single center observational RWD studies) comparing IL6Ri (TCZ) to JAKi (BAR) for COVID-19 have been published in peer-reviewed journals. Neither study found significant differences in outcomes for TCZ versus BAR treatment, however, both studies were limited by small sample size (n=20 vs. 11 [Rosas 2022] and n=63 vs. 33 [Kojima 2022]). A non peer-reviewed pre-print study [Karampitsakos 2022] for an RCT found BAR to be non-inferior to TCZ for the composite outcome of IMV or death and for time to discharge among a severe COVID-19 population. However, this study was not designed to determine relative benefits across severe and critical disease (IMV/ECMO) subgroups. The non-inferiority design does not permit conclusions regarding one drugs' relative superiority to the other. In the absence of direct head-to-head evidence, some researchers have attempted to compare results of separate IL6Ri and JAKi studies. Two separate indirect meta-analyses found seemingly contradictory results: BAR was better than TCZ for preventing 28-day mortality, but *worse* at preventing disease progression to IMV/ECMO [Shah 2022, Ngamprasertchai 2022]. Results of these indirect meta-analyses must be interpreted with caution due to the heterogeneity in inclusion criteria and differing background standards of care (SoCs)[4] within separate IL6Ri and JAKi RCTs.

2. RESEARCH QUESTION AND OBJECTIVES

In this study we seek to evaluate current methodologies for observational comparative studies of inpatient COVID-19 treatments [**Overall Study Objective**]. To support this overall study objective, we have defined additional supporting objectives related to the research process [**Process Objectives**] as applied to an illustrative example of an observational study to evaluate the comparative effectiveness of inpatient COVID-19 treatments [**Illustrative Example**].

[4] Many studies cited in NIH guidance for use of IL6Ri and JAKi in COVID patients did not include systemic CS therapy as a consistent background SoC [Rosas 2021, Stone 2020, Lescure 2021, Kalil 2020], limiting generalizability to the current COVID-19 treatment landscape. Inclusion of RDV as either an explicit combination therapy or optional background SoC also varied across clinical trials.

Process Objectives:
Characterize differences in study results when an intentional multiphase approach (IMA) to diagnostics and contingencies is applied to RWD analysis compared to an approach that pre-specifies all covariates and statistical approaches without consideration of whether key statistical assumptions hold (Single-phase Prespecification Approach, SPA). The SPA and two separate IMA approaches will be further described in section 3.1 Study Design and section 3.7 Analysis.

Illustrative Example:
Our illustrative example will use a large population-based US claims data source to emulate a hypothetical target trial to assess the comparative effectiveness of IL6Ri (TCZ or SAR) versus JAKi (BAR or TOF) added to systemic corticosteroids of interest (CSI)[5]. The underlying hypothetical target trial of interest consists of patients hospitalized and requiring respiratory support for COVID-19 and receiving a CSI who are assigned to receive either an IL6Ri or JAKi in addition to CSI within 4 days[6] after hospital/ICU admission. The patients are followed for up to 28 days for the outcomes of inpatient mortality and progression to IMV/ECMO. The Illustrative Example is separated into two sub-objectives based on the different COVID-19 severity populations of interest.

- **Illustrative Example - Objective I** aims to characterize the risk of inpatient mortality [**Primary Outcome**] and progression to IMV or ECMO [**Secondary Outcome**] up to 28 days after IL6Ri or JAKi initiation among patients hospitalized with COVID-19 who initiate a CSI and require supplemental O2/NIV/HFO (but not IMV/ECMO).
- **Illustrative Example - Objective II** aims to characterize the risk of inpatient mortality [**Primary Outcome**] up to 28 days after IL6Ri or JAKi initiation among patients admitted to the ICU at hospital admission[7] with COVID-19 who initiate a CSI and require IMV/ECMO.

Hazard ratios (HR) and corresponding 95% confidence intervals (CI) will be estimated and reported for all outcome risks in Illustrative Example objectives. Comparisons and populations within Illustrative Example objectives are summarized in **Table 1** below.

[5] CSIs include the following systemic glucocorticoids, administered in oral or injectable formulations: dexamethasone, methylprednisolone, prednisone, hydrocortisone, prednisolone, triamcinolone, cortisone, or betamethasone. Although dexamethasone is the preferred CS for COVID, NIH guidelines indicate that other CS types in equivalent doses can be used when dexamethasone is unavailable [NIH Treatment Guidelines].
[6] Threshold of 4 days was determined based on the distribution of duration between hospitalization and initiation of either IL6Ri or JAKi in the dataset (~90% of IL6Ri or JAKi initiators begin treatment within 4 days of hospital admission). See exploration 2 in section 3.1 for more detail.
[7] Patients in the Illustrative Example - Objective II cohort will be required to have an admission to the ICU on the same day as hospital admission. The same-day requirement was selected after an initial query confirmed that >70% of ICU admissions within this study population occur on the same day as hospital admission (see Exploration 4, in section 3.1). See section 3.3.2 for further rationale.

Table 1. Summary of comparisons of interest within the Illustrative Example

Objective	Comparison	Population	Effectiveness outcomes	Main measure of effect
Illustrative Example - Objective I	CSI + IL6Ri (TCZ or SAR) within 4 days after hospital admission ***versus*** CSI + JAKi (BAR or TOF) within 4 days after hospital admission	O2 or NIV/HFO	- Primary Outcome: Inpatient mortality - Secondary Outcome: Progression to IMV or ECMO	HR (95% CI)
Illustrative Example - Objective II	CSI + IL6Ri (TCZ or SAR) within 4 days after hospital/ICU admission ***versus*** CSI + JAKi (BAR or TOF) within 4 days after hospital/ICU admission	IMV or ECMO	- Primary Outcome: Inpatient mortality	HR (95% CI)

3. RESEARCH METHODS

3.1 Study Design

The Illustrative Example is an observational cohort study using the HealthVerity Chargemaster and Linked Medical and Pharmacy Claims secondary healthcare data source.

The research process for this study will be separated into three distinct sequential phases: (1) *Exploratory* (data explorations done in advance to facilitate key design decisions; linkage of treatment and outcome data was not done in this phase), (2) *Diagnostic* (requirements that must be satisfied prior to viewing treatment-specific outcomes for IMA analyses only, e.g., covariate balance), and (3) *Inferential* (final comparative analyses to address study objectives). See **Table 2** for more details.

The following explorations were completed prior to protocol finalization to inform overall study design, inclusion and exclusion criteria, and identification of potential confounding and effect modifying variables within the study dataset:

- **Exploration 1:** Description of characteristics of initiators of IL6Ri, JAKi, CSI, remdesivir (RDV), and other COVID-19 treatments.
- **Exploration 2:** Description of trends in drug initiation by class and individual drugs, including monotherapies and combination therapies, by calendar week, over the study period.
- **Exploration 3:** Description of inpatient treatment pathways (including time to treatment initiation/switch) among hospitalized COVID-19 patients stratified by calendar time, within severity subgroups based on oxygen requirements (at any time during hospitalization), and by COVID-19 severity at admission.
- **Exploration 4**: Description of the distribution of time to ICU admission among patients hospitalized and progressing to ICU.

For the *Diagnostic Phase (applicable to IMA only)*, we developed a checklist of diagnostic criteria (see section 3.7.2, Table 6) that must be satisfactorily met prior to beginning the implementation of the IMA *Inferential Phase*. The *Diagnostic Phase* is split into two distinct phases to separate diagnostic checks that do not require post-index information (*Diagnostic Phase I)* from checks that do require post-index data (*Diagnostic Phase II),* with guardrails to maintain blinding of exposure-outcome relationships. This distinction between pre-index and post-index diagnostics will separate traditional baseline diagnostic checks that maintain complete blinding of follow-up information from diagnostic checks that require analysis of follow-up data and therefore may to some degree require linkage of exposure and outcome information (e.g., assessment of the proportional hazards assumption). Accordingly, we will conduct two separate sets of IMA analyses to descriptively compare the impact of applying diagnostics and contingencies considering only baseline (pre-index, inclusive) data (*Diagnostic Phase I)* to IMA analyses that consider both baseline and post-index data (*Diagnostic Phases I and II*). The relationship between the treatment and outcome of interest will not be described or evaluated in the analytic dataset until consensus is reached that the relevant diagnostic criteria

are satisfied. Diagnostic criteria will also be evaluated for SPA, however analyses will proceed per *a priori* specifications regardless of whether or not each diagnostic check is satisfied.

Application of these research phases within separate SPA and IMA research **Process Objectives** are described in Table 2.

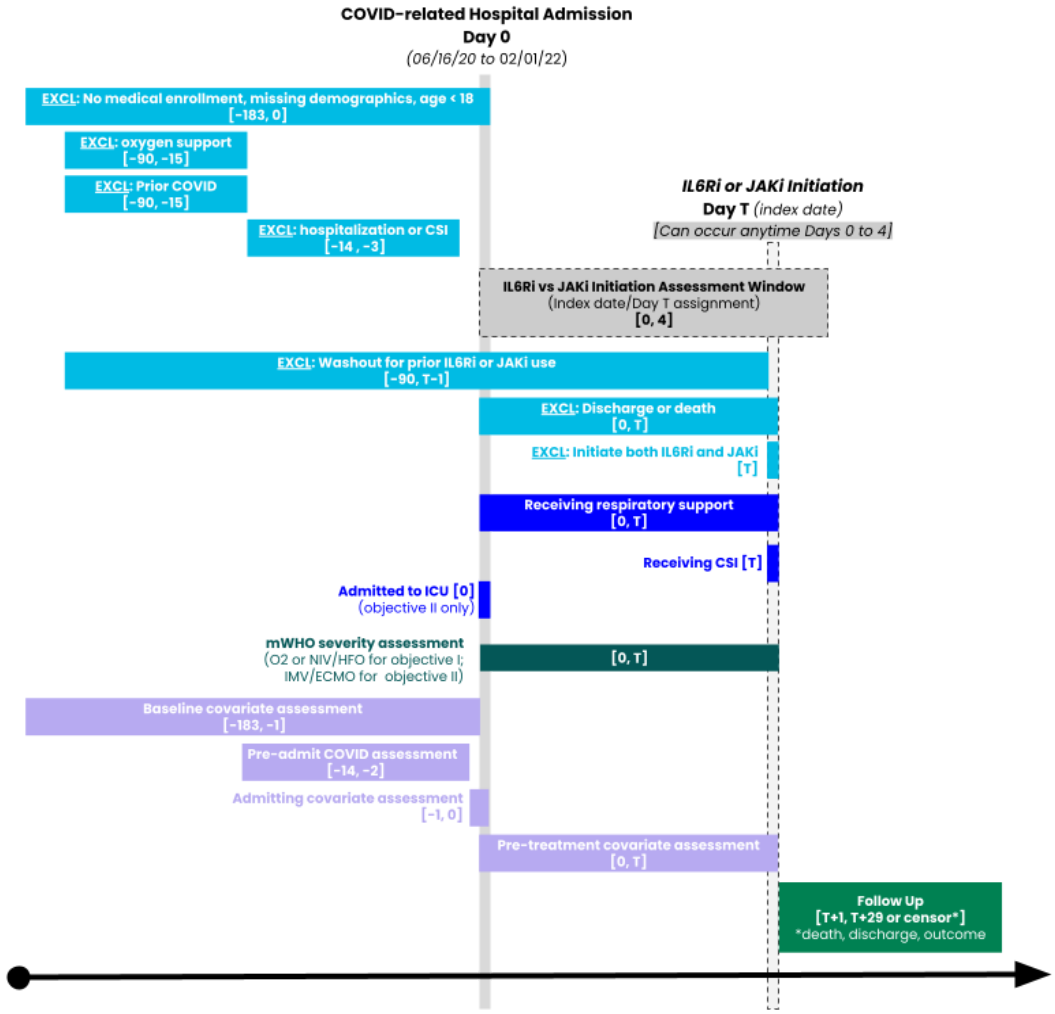
Table 2. Overview of SPA and IMA research process objectives

	Single-phase Prespecification Approach (SPA)	**Intentional Multi-phase Approach (IMA)**	
		IMA-1	***IMA-2***
Description of research process approach	**Pre-specifies covariates and statistical approaches without consideration of whether key statistical assumptions hold.**	**Apply diagnostic checks using baseline (pre-index) data (Dx phase I only) and pursue contingencies as indicated, prior to *Inferential Phase*.**	**Apply diagnostic checks using both baseline (pre-index) data (Dx phase I) and post-index data (Dx phase II), and pursue contingencies as indicated, prior to *Inferential Phase*.**
Exploratory Phase	Completed in advance to inform study/protocol development	Completed in advance to inform study/protocol development	Completed in advance to inform study/protocol development
Diagnostics Phase I	Diagnostics assessed for context only; no contingencies or changes to *a priori* specified analyses will be considered.	Diagnostics assessed and contingencies implemented as indicated. Proceed to *Inferential Phase* after satisfying all criteria.	Diagnostics assessed and contingencies implemented as indicated. Proceed to *Diagnostics Phase II* after satisfying all criteria.
Diagnostics Phase II		Diagnostics assessed for context only; no *Diagnostics Phase II* contingencies will be considered.	Diagnostics assessed and contingencies implemented as indicated. Proceed to *Inferential Phase* after satisfying all criteria.
Inferential Phase	Proceed to *Inferential Phase* using *a priori* specified methods, regardless of whether or not all diagnostic criteria are satisfied.	Proceed to *Inferential Phase* after satisfying all *Diagnostics Phase I* criteria and pursuing indicated contingencies.	Proceed to *Inferential Phase* after satisfying all *Diagnostics Phase I* and *Diagnostics Phase II* criteria and pursuing indicated contingencies.

3.2 Study Design Diagram for the Illustrative Example

The study diagram in Figure 1 depicts the assessment windows for entry criteria, covariates, and outcomes relative to hospital/ICU admission date and treatment initiation date.

Figure 1: Study design diagram



3.3 Setting

3.3.1 Data sources

Details on the metadata of the database are shown in Table 3.

Table 3. Metadata on database

Data source	HealthVerity Chargemaster + Claims Data
Study period (including look-back period)	June 16 2020 to February 28 2022*
Database Date Range	March 1 2019 to February 28 2022 [Available June 2022]*
Total Patients in Database	~1.2 million
Eligible cohort entry period	June 16 2020 to February 1, 2022
Data version (date received)	June 2022*

Data sampling / extraction criteria	Patients with at least one day of medical benefit enrollment during the study period AND Patients with a hospitalization recorded in the chargemaster data
Type of data	Closed medical and pharmacy claims (Private Source 17, Private Source 20) and inpatient chargemaster (private Source 88)
Data linkage	HealthVerity chargemaster and medical and pharmacy claims data (linked at patient level prior to receipt of data)
Conversion to common data model	N/A

HealthVerity data has several strengths for answering this Illustrative Example, including near-real time delivery of data, information on both patient history (e.g., baseline medical and pharmacy claims) and granular inpatient hospitalization data not typically available in claims data sources (e.g., day-level inpatient drug utilization, mortality outcomes), and a large patient population. HealthVerity data include patients from all US regions, with healthcare insurance coverage from all major payer types (Medicare, Medicaid and commercial).

This data source also has limitations. As of yet, there are no validation studies of this data source for our endpoints of mortality or progression to IMV/ECMO. However, use of discharge status to determine mortality endpoints among hospitalized COVID-19 patients has been used in both a similar chargemaster data source [Rosenthal 2020] and for national surveillance reporting [CDC-NCHS 2021].

In a previous study [Gatto 2021], we compared use of discharge status of death from the hospital chargemaster files to the separate raw data files from the vendor providing month of death (date of death was redacted for privacy concerns) and found that all patients with a recorded death month also met our endpoint definition. Further, when we compared weekly deaths over time in our overall cohort of patients hospitalized with COVID-19, we identified similar trends to those of two external national benchmarks, the Centers for Disease Control [CDC-NCHS 2021] and data sourced from State and local health agencies [NYT 2021], mitigating potential concern of mortality misclassification. validity

Despite lack of validation studies for the endpoint of progression to IMV or ECMO, we anticipate this outcome to be well captured in the data source, given that mechanical ventilation is an objective and serious outcome that is typically recorded for billing purposes via standardized procedure codes and/or chargemaster charge codes. IMV/ECMO endpoints have also been used in other studies of COVID-19 within similar inpatient data sources [Giabicani 2022, Rosenthal 2020, Nguyen 2021].

3.3.2 Population

The overall cohort for our Illustrative Example will consist of insured adults hospitalized with COVID-19 between June 16, 2020 to February 01, 2022 who require supplemental oxygen or ventilation support and initiate either IL6Ri (TCZ or SAR) or JAKi (BAR or TOF) in addition to systemic CSIs within 4 days after hospital admission. All patients will be required to have at least one procedure for oxygen supplementation and at least one recorded CSI administration

from admission to treatment initiation, since during the study period IL6Ri and JAKi were only indicated for patients receiving CSIs and some level of oxygen or ventilation support.

From this population, the subcohort used to meet **Illustrative Example - Objective I** will consist of adults hospitalized with COVID-19 who require supplemental O2/NIV/HFO (but not IMV/ECMO) from admission to the day of IL6Ri or JAKi initiation. The subcohort used to meet **Illustrative Example - Objective II** will include adults who are admitted to the ICU at hospital admission and require IMV/ECMO prior to the day of IL6Ri or JAKi initiation. Given the lack of day-level diagnosis codes (i.e., occurring after hospital admission) in the database, requiring the ICU admission date be the same as the hospital admission date (Day 0) for **Illustrative Example - Objective II** cohorts decreases the potential for misclassification of variables assessed during periods anchored to the hospital admission date (e.g., baseline clinical covariates). In other words, if ICU admission was not anchored to the hospital admission date, any clinical events (defined by diagnostic codes) that occurred between hospital admission date and the date of ICU admission would not be captured in the data, leading to differential capture of such variables for patients admitted to the ICU later in their hospital stay.

Algorithms for identification of respiratory support requirements for O2/NIV/HFO (**Illustrative Example- Objective I**) and IMV/ECMO (**Illustrative Example - Objective II**) subcohorts will be based on a previously published WHO (mWHO) disease severity algorithm [Garry 2022], with minor modifications to fit our study specifications [see Appendix F, available upon request]. This algorithm classifies disease severity using procedure and free text charge codes for various oxygen and ventilation-related procedures, as well as admitting diagnosis codes indicating clinical need for different levels of respiratory support (e.g., hypoxia for O2, ARDS for IMV). Operationalization of these measures is detailed in Appendix D3, Appendix D4, Appendix D5, and section 3.3.3 below; inclusion and exclusion criteria are described in more detail in section 3.3.5 and section 3.3.6.

3.3.3 Cohort Entry, Treatment Index and Inclusion and Exclusion Criteria Assessment Windows

See study design diagram in **Figure 1** for a detailed overview of study time anchors and assessment windows for the Illustrative Example. Appendix A further describes key study components with respect to the hypothetical target trial that we seek to emulate.

Patients will enter the cohort upon the admission date of their first qualifying hospital admission observed in the hospital chargemaster data (cohort entry date, CED; or Day 0). The first eligible cohort entry date is June 16, 2020. This date was chosen to align with availability of dexamethasone results from the RECOVERY trial, after which systemic CS became increasingly used among adults hospitalized with severe or critical COVID-19. The last possible cohort entry date will be 28 days prior to the last date of available data (i.e., February 1, 2022 at the latest), to ensure complete follow-up data for all patients.

Patients are eligible for IL6Ri or JAKi treatment initiation (Day T, treatment index) any time from admission date (Day 0) to 4 days after admission (Day 4). CSI use, oxygen support

requirements (O2/NIV/HFO for **Illustrative Example - Objective I**, IMV/ECMO for **Illustrative Example - Objective II**) will be assessed from hospital admission (Day 0) until treatment index (Day T). Timing of treatment initiation will be assessed relative to hospital/ICU admission (Day 0). Inclusion criteria, exclusion criteria, and covariates of interest will be assessed during the time periods specified in **Figure 1**. Assessment windows are defined relative to time anchors for hospital/ICU admission (Day 0) and IL6Ri/JAKi treatment initiation (Day T). Operationalization details are shown in Appendix D1.

3.3.4 Follow-up

Follow-up for outcomes will begin 1 day after treatment index (Day T+1) to distinguish between events occurring before or at treatment initiation from outcomes beginning after treatment initiation. This is necessary given that in this dataset we cannot identify the specific time of treatment and outcome events, only the specific day, therefore outcome events recorded on Day T may have begun before or after treatment initiation. For primary analyses, follow-up for outcomes will begin on Day T+1 and continue until the earliest occurrence of death, outcome (if different from death), discharge from the hospital, or 28 days of follow-up reached (Day T+29). This utilizes an initial treatment design, whereby all patients initiating either IL6Ri or JAKi within 4 days after admission (Days 0 to 4) are assumed to complete their treatment course per guidelines, regardless of early discontinuation (for JAKi users only) or potential crossover between groups. Changes in inpatient treatments after initial treatment (Days T+1 to T+29) are assumed to be part of routine care and therefore post-index treatment changes are not considered in SPA.

This initial treatment approach may be modified to an as-treated follow-up design in IMA-2 contingency analyses depending on diagnostic checks assessing the extent of crossover and discontinuation of JAKi during follow-up [see **Table 7**]. See operationalization details in Appendix D2.

Potential bias resulting from censoring on competing risks will also be addressed in IMA-2 via contingent analyses if indicated [See **Table 7**]. A competing risk is an event that precludes the chance of occurrence of the primary event of interest and can occur when a person is at risk of more than one type of event [Dutz 2019]. IMA-2 contingency analyses will include assessment of potential bias from the competing risk of hospital discharge (for primary outcome in both **Illustrative Example - Objectives I and II**) and for the competing risk of death (for secondary outcome of IMV/ECMO in **Illustrative Example - Objective I**).

3.3.5 Inclusion Criteria

Patients who meet the following criteria will be included in the overall study cohort for the Illustrative Example:

- Hospitalized from June 16, 2020 to February 01, 2022 with an ICD-10 diagnosis code of U07.1 in any admitting diagnosis position (Day 0)
- Initiate either IL6Ri or JAKi within 4 days after hospital admission (Days 0 to 4)
- Receiving systemic CSI on day of IL6Ri/JAKi initiation (Day T)

- Receipt of at least one respiratory support procedure (oxygen supplementation at a minimum) from admission to IL6Ri/JAKi initiation (Days 0 to T)
    - For **Illustrative Example - Objective I** only: maximum mWHO disease severity of O2/NIV/HFO from admission to IL6Ri/JAKi initiation (Days 0 to T)
    - For **Illustrative Example - Objective II** only: Admission to ICU at hospital admission (Day 0) and mWHO disease severity of IMV/ECMO from hospital/ICU admission to IL6Ri/JAKi initiation (Days 0 to T)
- Continuous medical claims enrollment (60-day gaps permitted) during the 183 day baseline period prior to and including hospital or ICU admission (Days -183 to 0) to minimize the potential for misclassification of baseline covariates

Hospitalization due to COVID-19 will be defined as an inpatient chargemaster record with an ICD-10 diagnosis code of U07.1 in any admitting diagnosis position, as per CDC Coding Guidance for COVID-19 effective on April 1, 2020 [CDC Coding Guidelines 2020]. Although this definition does not explicitly require COVID-19 as the primary admitting cause, requirements for CSI use, oxygen supplementation, and IL6Ri or JAKi initiation within the first 4 days after hospital admission should exclude most patients with incidental SARS-CoV-2 infections. See operationalization details in Appendix D3.

3.3.6 Exclusion Criteria

Patients not meeting the above inclusion criteria or who meet any of the following criteria will be excluded from the study cohort:

- Exclude patients without continuous medical claims enrollment (60-day gaps permitted) during the 183-day baseline period prior to and including hospital/ICU admission (Days -183 to 0) to minimize the potential for misclassification of baseline covariates.
- Exclude patients if COVID-19 hospitalization (Day 0) begins >14 days after initial COVID-19 diagnosis. Patients will be excluded if any COVID-19 diagnosis is recorded from 90 days to 15 days before admission (Days -90 to -15) to exclude patients with possible long-term COVID or post-acute sequelae while still permitting prior infections recorded more than 90 days pre-admission.
- No age, sex, or geographic region recorded on hospital admission (Day 0)
- Age less than 18 years at hospital admission (Day 0)
- Evidence of a prior COVID-related inpatient hospitalization in the previous 14 days (Days -14 to -3), with a two-day buffer to permit brief inpatient utilization directly proceeding transfer to a chargemaster hospital (i.e., inpatient utilization permitted on Days -2 to -1)
- Systemic CSI use (dispensing or remaining supply) in the previous 14 days (Days -14 to -3), with a two-day buffer to permit CSI use beginning in the emergency department or other healthcare setting immediately prior to chargemaster hospital admission (CSI use permitted Days -2 to -1)
- Any recorded use of IL6Ri or JAKi (dispensing or remaining supply) in the 90-day washout period before IL6Ri or JAKi initiation (Days -90 to T-1), to satisfy new use definition
- Baseline receipt of oxygen or ventilation support for non-COVID conditions (e.g., supplemental oxygen for COPD), defined as two or more respiratory support procedures

recorded on different days from Days -90 to -15 via procedure codes from medical claims, chargemaster, and where available, oxygen supplies recorded in pharmacy settings.
- Death or discharge occurs before or on the day of treatment initiation (Days 0 to T)
- Recorded use of both IL6Ri and JAKi on Day T

The 14-day window for COVID-related exclusion criteria was chosen based on published research describing time from illness onset to hospital admission in COVID-19 cohorts from Europe [Faes 2020] and the United States [Bhatraju 2020]. Given unavailability of laboratory results and potential for diagnosis of COVID in healthcare settings where insurance claims are not submitted, this window assumes that illness onset may occur as early as 14 days before hospital admission for all patients, regardless of the presence or absence of pre-admission COVID-19 confirmation in the dataset. Similarly, systemic CSI use, new oxygen supplementation requirements, and prior inpatient hospitalizations beginning during this 14-day pre-admission period are assumed to be plausibly COVID-related events. We exclude patients with these events beginning within 14 days up until 3 days prior to chargemaster admission (Days -14 to -3) to remove patients with longer duration of severe disease (to reduce heterogeneity of the study population), with a two-day buffer to permit utilization occurring in the emergency department or other healthcare setting immediately prior to chargemaster admission.

Other than known hypersensitivity to these medications, there are no absolute contraindications for IL6Ri/JAKi use in COVID-19 [FDA 2020, FDA 2021, Lilly USA 2022]. However, there are populations for which IL6Ri and/or JAKi use is cautioned, including patients with concurrent active non-COVID infections, liver disease, demyelinating disorders, patients who are severely immunosuppressed (including those who have been recently treated with other biologic immunomodulators), patients with history of tobacco use or other cardiovascular risk factors, patients with known malignancies, and patients with renal impairment, including end stage renal disease or acute kidney injury or those on dialysis. SPA analyses will *a priori* adjust for these conditions without excluding patients with potential contraindications. To account for uncertainty with regard to adherence to such precautions in real-world clinical practice, IMA analyses will permit inclusion of patients with these conditions if balance for these factors can be achieved for IL6Ri and JAKi groups during the study's diagnostic stage.

See operationalization details of exclusion criteria in Appendix D4.

3.4 Variables

STaRT-RWE templates [Wang, 2021] were used to document the operational definitions of the variables in this study (see Appendix D). Key study variables are described in sections 3.4.1-3.4.4 below.

3.4.1 Cohort Definition

Cohort definition details, including the operationalization of cohort entry and inclusion and exclusion defining variables can be found in Appendix D1, Appendix D3, and Appendix D4.

3.4.2 Exposure Definition

The primary exposures of interest are new initiation of either IL6Ri or JAKi medications within 4 days after hospital admission (Days 0 to 4). IL6Ri and JAKi exposures will be identified in inpatient chargemaster records with standardized procedure codes (from current procedural terminology/healthcare common procedure coding system, CPT/HCPCS [CMS 2021]; and ICD-10 procedure code system, ICD-10 PCS) and hospital charge codes containing text strings indicating administration of IL6Ri or JAKi medications (e.g., 'tocilizumab', 'Actemra', 'baricitinib', 'Olumiant'). Only procedure and hospital charge codes for routes of administration recommended by NIH for COVID-19 will be included in exposure definitions (e.g., intravenous for TCZ, oral for BAR).

Inpatient IL6Ri and JAKi use is considered "new" if patients had no record of IL6Ri nor JAKi dispensing during the 90-day treatment washout period (Days -90 to T-1). Treatment washouts for prior IL6Ri or JAKi use will include all possible routes of administration captured in all available data types with treatment-specific information, including inpatient chargemaster (Days -90 to T-1), as well as outpatient hospital chargemaster, medical claims, and pharmacy claims (Days -90 to T-1). See operationalization details in Appendix D1.

All IL6Ri and JAKi initiators will be required to have systemic CSI use on the day of treatment initiation (Day T), per NIH recommendations that IL6Ri/JAKi should only be given in combination with course of dexamethasone or other CSI [NIH treatment guidelines]. CSI use can begin prior to or concurrent with IL6Ri/JAKi initiation (Day T). Both IL6Ri and JAKi exposed patients may be treated with other therapeutic agents. Complete exposure and comparator definition details can be found in Appendix D1; code lists can be found in Appendix F.

As detailed in diagnostic check #1 of **Table 7**, IMA analyses may instead conduct comparisons of individual drugs (e.g., TCZ versus BAR) rather than evaluation of class-level effects (as done in SPA) if in both drug classes an individual IL6Ri or JAKi drug constitutes greater than 90% of use within its respective class.

3.4.3 Outcome Definition

The outcomes of interest will be inpatient mortality (primary outcome) and progression to IMV/ECMO (secondary outcome for **Illustrative Example - Objective I**) during the follow-up period beginning 1 day after IL6Ri or JAKi treatment initiation and continuing for up to 28 days. Death and date of death will be sourced from the chargemaster discharge status field. IMV/ECMO will be defined using standardized procedure codes and hospital charge codes. Outcome definition details can be found in Appendix D5; code lists can be found in Appendix F.

3.4.4 Covariates

Propensity score-based weighting methods will be used to control for confounding in the analysis. **Table 4** provides a list of the covariates considered for inclusion in the propensity

score (PS) model and their corresponding assessment windows (see further operationalization details in Appendix D6). These variables were selected *a priori* due to a determination that they are prognostically important (i.e., related to outcomes) or are potential confounders of the relationship between treatment and outcomes. Covariates were informed by prior published studies of inpatient COVID-19 [Nigo 2021, Gupta 2021, Crothers 2021], including other studies using the HealthVerity chargemaster data source [Stewart 2021, Gordon 2020], clinical expert input, and CDC's list of conditions placing individuals at high risk of severe COVID-19 [CDC 2022]. SPA analyses will include all *a priori* specified covariates in **Table 4** in final PS models, regardless of whether or not assumptions of positivity and other diagnostic criteria are met. For analyses following the IMA approach, PS model assumptions for **Illustrative Example - Objective I** and **Illustrative Example - Objective II** populations will be checked via a diagnostic checklist (see section 3.7.2) prior to model finalization. IMA analyses will consider all covariates in Table 4, but some covariates may not be included in final models as described in section 3.7.1. Individual covariates and assessment windows may be combined if warranted based on variable distributions, and final PS model inputs may vary across different subcohorts within this study. Missingness among covariates of interest within our study cohort will be enumerated and reported in study findings for both SPA and IMA approaches.

Table 4: Description of patient characteristics and covariate assessment windows

Baseline Covariates *(Days -183 to -1)*	Baseline (pre-admission) comorbidities, co-medications, and health resource utilization.	- **Lifestyle factors:** history of smoking/tobacco use* - **Comorbidities and comedications**: asthma, any cancer (active hematological cancer, active solid tumor), chronic lung disease, cardiovascular disease (any), diabetes, immunosuppressive conditions or medications (including blood/organ transplant, rheumatoid arthritis and other autoimmune conditions), kidney disease (end stage renal disease, acute kidney injury, dialysis), overweight or obese (via diagnosis codes), liver dysfunction (hepatic impairment, active liver disease), other conditions with potential IL6Ri or JAKi cautions (bowel obstruction, necrosis, ulcerative disease, Iatrogenic GI injury, demyelinating disorders, serious infections, cystic fibrosis, pregnancy, sickle cell / thalassemia), frailty score, neurological/cognitive impairment, mental health/psychosis, hypertension, statin use, systemic and non-systemic corticosteroid use, anticoagulant and/or antiplatelet use as well as the combined comorbidity score *[Gagne 2011]* - **Health resource utilization**: number of days hospitalized, number of outpatient visits, number of pharmacy claims, number of distinct medications dispensed, any encounter indicating skilled nursing facility (SNF) or long-term care (LTC), 7+ days in SNF or LTC, COVID-19 vaccination status (ever vs. never), record of prior COVID-19 (*from start of data to Day -15*)
Pre- admission COVID-related covariates *(Days -14 to -2)*	Pre-admission COVID-19 severity	- **COVID-19 severity before admission:** time since first COVID-19 diagnosis to admission, pre-admission *(Days -14 to -1)* use of potential COVID-19 medications (systemic or inhaled corticosteroids, monoclonal antibodies, antivirals, RDV, COVID-19 convalescent plasma), COVID-19-related utilization prior to admission (urgent care, emergency department), respiratory support required

(Days -1 to 0)	Admitting healthcare resource utilization	**Admitting healthcare resource utilization characteristics:** admission source (admitted from emergency department, immediate transfer from other inpatient facility, etc), ambulance, admitted directly to ICU at hospital admission, admitting type, mWHO disease severity at inpatient admission
Demographics, clinical and admission covariates *(Day 0)*	Demographics, hospital facility characteristics, and COVID-19 severity on the admission date.	- **Demographics:** age, sex, insurance type, US region, month and year of hospital admission - **Hospital characteristics**: hospital setting type (urban vs rural), hospital teaching status, hospital number of beds, facility COVID-19 admitting volume, facility level of immunomodulator prescribing - **Admitting diagnoses:** dyspnea or hypoxia, pneumonia, ARDS or acute respiratory failure, shock, non-respiratory organ failure, delirium, sepsis, acute cardiovascular events, thromboembolic events, do not resuscitate order, COVID vs non-COVID diagnoses in primary position, presence of possible contraindication (concurrent non-COVID infection, end stage renal disease or acute kidney injury, liver dysfunction)
Inpatient Covariates *(Days 0 to T)*	COVID-19 status and treatments	- **Concomitant medications:** Anticoagulant and/or antiplatelet agents, antibiotic (any and individual classes), vasopressors or inotropes, neuromuscular blockades, number of unique medication classes administered**, inhaled CS, RDV, non-RDV antivirals (including lopinavir/ritonavir, other HIV protease inhibitors, ivermectin, etc), other immunomodulators (non-JAK kinase inhibitors, non-IL6 interleukin inhibitors, anti-TNF biologics, B or T-cell inhibitors, etc) - **Pre-treatment COVID-19 healthcare resource utilization characteristics:** Intensive care utilization (regular ICU, intermediate ICU, critical care procedures), major surgical procedures, specialty care services (radiology, cardiovascular, respiratory therapy, surgical services), renal replacement therapy or dialysis, IMV/ECMO, number of O2/ventilation procedures administered, COVID-19-related lab orders (e.g., PCT, ferritin, D-dimers, troponin, PaO2, CRPs, AST/ALTs, blood viscosity, and others), number of unique procedure codes**, number of unique department codes, maximum intensity respiratory support procedure recorded, most frequently recorded mWHO status, number of days from admission to treatment initiation, number of days from CSI initiation to treatment initiation, number of days from max respiratory support status to treatment initiation, number of days with O2/NIV/HFO/IMV/ECMO support prior to treatment initiation, mWHO disease severity at treatment initiation

**Smoking/tobacco use may be under-reported [see section 4. Potential Limitations for more detail]*
***IL6Ri and JAKi will be excluded from variable definitions to avoid adjustment for exposure-related characteristics*

The baseline covariate period will be extended to 12 months (Days -365 to -1) as part of a sensitivity analysis (see **Table 8**).

3.5 Study Size

Minimal sample size estimates were calculated for context only, given that the analyses are an illustrative example used to compare different methodological approaches. Analyses will proceed regardless of sample size considerations for this reason.

The sample size that would be required to estimate differences between outcome rates in CSI+IL6Ri versus CSI+JAKi populations is dependent on the expected outcomes rates in our study population. Rates of 28-day mortality and progression to IMV/ECMO in hospitalized adults with COVID-19 vary across published RCT and RWD studies due to differences in underlying study populations, study periods, background and concomitant therapies, disease severity, and other factors.

Among RCTs of IL6Ri, during the study period, mortality rates for IL6Ri-treated patients ranged from <10% in studies of moderately-ill cohorts (e.g., EMPACTA [Salama 2020], BACC Bay [Stone 2020, Lescure 2021]) to over 25% in studies including severe-critical patients (RECOVERY [RECOVERY Collaborative Group 2021] and REMAP-CAP [REMAP-CAP Investigators 2021]). 28-day mortality rates from JAKi RCTs also varied, with mortality under 10% in the ACTT-2 [Kalil 2020] and COV-BARRIER trials [Marconi 2021] and over 35% in the critically-ill addendum population to COV-BARRIER [Ely 2022]. For studies of both IL6Ri and JAKi medications, mortality rates increased with higher levels of disease severity, ranging from <2% mortality for JAKi-treated patients with moderate disease (O2 only) in the ACTT-2 trial [Kalil 2020] to 49% mortality for critically-ill (IMV) IL6Ri-treated patients in the RECOVERY trial [RECOVERY Collaborative Group 2021].

Rates of progression to IMV or ECMO among those not on IMV/ECMO at baseline also varied across published studies. Only 7% of IL6Ri-treated patients in the BACC Bay trial [Stone 2020], progressed to IMV, compared to 35% among critically-ill patients in REMAP-CAP [REMAP-CAP Investigators 2021]. For BAR, the only RCT evaluating progression to IMV or ECMO reported an outcome rate of 10% for BAR-treated patients [Kalil 2020].

Given uncertainties around outcome rates in our specific study population, we calculated the sample size that would be required to detect differences in outcome rates for IL6Ri or JAKi-treated populations across a range of hypothetical scenarios. To determine the sample size required to estimate differences between outcome rates in CSI+IL6Ri versus CSI+JAKi populations, we used the EpiR package (R version 4.1.2) with the following assumptions:

- 80% power
- 5% test size (alpha)
- 2-sided confidence interval

Table 5 summarizes the sample size requirements assuming a 1:1 ratio of IL6Ri to JAKi-treated patients and outcome rate estimates ranging from 0.1 to 0.6. A 1:1 ratio is provided for ease of display, however, differing ratios may decrease total sample size requirements. Finer granularity of risk estimates is arbitrarily shown for the JAKi+CSI group only in **Table 5** to demonstrate sample size scenarios where outcome risks are fairly similar (+/-10%) between groups.

Table 5: Sample size requirements for number of JAKi+CSI-treated patients assuming 1:1 matching of IL6Ri+CSI to JAKi+CSI patients

		Outcome Risk in IL6Ri + CSI group					
		0.1	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**
Outcome Risk in JAKi + CSI group	**0.1**	NA	123	38	19	11	7
	0.15	419	581	76	30	16	10
	0.225	84	2718	342	67	27	14
	0.25	61	705	790	92	33	16
	0.275	47	323	3225	134	41	19
	0.325	31	122	3317	377	68	26
	0.35	26	86	837	849	92	31
	0.375	22	65	374	3389	131	37
	0.425	17	40	135	3351	354	59
	0.45	14	32	94	830	784	79
	0.475	13	27	68	364	3081	111
	0.5	11	23	52	202	NA	169
	0.6	7	12	22	46	169	NA

3.6 Data Management

Measure and cohort creation and analysis will be done on the Aetion Evidence Platform (AEP). At Aetion, raw data review is conducted to understand the contents of the database and scientific integrity checks are performed to ensure the contents of the data are consistent with the expected data as laid out in the applicable data usage agreement.

Following receipt and review of the raw data, each data cut is connected to the AEP. A data connector specification is drafted by a data scientist, which provides a map for transformation of raw data to the Aetion longitudinal patient timeline. Validation of the database connection, via double programming, is completed to ensure that the implementation of database connection logic leads to transformed data output that connects to and behaves within AEP exactly as intended. Following validation, the specification files are used to create an Aetion data dictionary for the dataset. Prior to connection of the data to the AEP, a manual test to ensure certain platform features and dataset values are visible and testable on the front-end is implemented.

See Appendix E for additional details on the process of raw data review and connection to the AEP.

Software used for data analyses is detailed in **Table 6** below.

Table 6. Software used for cohort creation and data analyses

Software	Version	Analyses	Validation Studies
Aetion Evidence Platform®	2022	Measure and cohort creation, time to outcome analyses. All SPA analyses and IMA-1 analyses will be conducted with this software.	[Wang, 2016]
R	4.1.2	Some analyses (e.g., IMA-2 analysis components) may be conducted with this software. Use (including version and libraries used) will be documented as required	Various; contingent on IMA analyses required

3.7 Analysis

We describe below two analytic approaches: SPA and IMA. SPA will be implemented based on *a priori* specified covariates and statistical approaches without consideration of whether key statistical assumptions hold. Conversely, IMA will conduct diagnostic checks and implement contingencies as indicated to evaluate whether such an approach can be used to strengthen current methodologies for observational comparative studies of COVID-19 treatments.

3.7.1 Application of Single-phase Prespecification Approach (SPA)

Time to death (for primary outcome in **Illustrative Example - Objectives I and II**) and progression to IMV or ECMO (for secondary outcome in **Illustrative Example - Objective I**) among patients treated with IL6Ri+CSIs will be compared with time to death or progression to IMV or ECMO among those treated with JAKi+CSIs. Censoring will occur at the earliest of death, receipt of IMV or ECMO (for secondary outcome of progression to IMV or ECMO only), hospital discharge or end of the 28-day follow-up period. See Appendix D2 and **Figure 2** for additional details on censoring and follow-up designs.

To compare differences in time to outcome events, we will generate Kaplan-Meier plots and estimate hazard ratios and 95% confidence intervals using a Cox proportional hazards analysis. Inverse probability weighting (IPW) methods will be used to control confounding.

A propensity score model will be estimated with IL6Ri receipt as the outcome of the logistic regression model. Variables to be included in the SPA IPW model will comprise all variables in **Table 4**. Patient demographic and clinical characteristics at baseline will be compared for IL6Ri-treated and JAKi-treated patients pre- and post-IPW. Balance will be assessed by calculating absolute standardized differences (ASD); covariates with ASD greater than or equal to 0.1 will be considered imbalanced. The *a priori* specified approach of SPA will proceed with inferential analyses regardless of covariate imbalance.

The weights for each patient will be calculated as the inverse of the probability of receiving the treatment the patient actually received conditional on observed covariates. Each individual's contribution to the survival curves and to the Cox regression model will be weighted by the inverse probability of receiving the treatment the patient actually received conditional on observed covariates. Use of robust standard errors will account for the weighted design and potential clustering, including clustering by facility.

SPA analyses will be applied separately for comparisons outlined in **Illustrative Example - Objective I** and **Illustrative Example - Objective II**.

3.7.2 Application of Intentional Multi-phase Approach (IMA)

IMA analyses will conduct a series of diagnostic checks to assure analytic assumptions are met (**Table 7**) prior to implementation of the *Inferential Phase*. Each diagnostic check includes a description of the requirements that must be satisfied prior to beginning the implementation of the *Inferential Phase*, as well as objective thresholds used to determine if a contingency should be triggered.

Diagnostic Phase I includes diagnostic checks conducted using baseline treatment index data, without use of post-index information; *Diagnostic Phase II* includes certain checks of post-index data, including outcome information, with guardrails to maintain blinding of exposure-outcome relationships. Upon completion of the *Diagnostic Phase*, the analytic dataset is locked and propensity score models are finalized. All treatment effects will be examined during the *Inferential Phase,* which cannot begin for IMA until each diagnostic step has been satisfactorily checked to determine what contingencies are appropriate.

As described in **Table 2**, we will conduct two separate IMA analyses to characterize the impact of applying diagnostics and contingencies considering only baseline treatment index data (*Diagnostic Phase I only* for IMA-1*)* to analyses that consider both baseline and post-index data *(Diagnostic Phases I and II* for IMA-2*)*.

Both IMA-1 and IMA-2 will follow SPA with exceptions and possible contingencies as described here. Follow-up for outcomes and censoring criteria will similarly follow SPA, with possible inclusion of additional censoring criteria in the IMA-2 analysis as described in Appendix D2 and **Figure 2**.

Figure 2. Censoring reasons for Illustrative Objectives, by Process Objective

	RO3 Process Objective: SPA		RO3 Process Objective: IMA-1		RO3 Process Objective: IMA-2	
Censoring reasons:	**Objective I (O2/HIV/NFO)**	**Objective II (ICU+ IMV/ECMO)**	**Objective I (O2/HIV/NFO)**	**Objective II (ICU+ IMV/ECMO)**	**Objective I (O2/HIV/NFO)**	**Objective II (ICU+ IMV/ECMO)**
Day 29 of follow up	✓	✓	✓	✓	✓	✓
Discharge	✓	✓	✓	✓	✓	✓
Inpatient death	✓	✓	✓	✓	✓	✓
Progression to IMV/ECMO *(for secondary outcome of IMV/ECMO only)*	✓	N/A	✓	NA	✓	NA
Potential additional censoring reasons pending diagnostics and contingencies in Table 7:						
End of exposure (JAKi discontinuation)	***N/A*** *(No contingencies considered for SPA)*		***N/A*** *(No Diagnostic Phase II post-index contingencies considered for IMA-1)*		✓	✓
Date of crossover (add to/switch from one exposure to the other)					✓	✓

Balance in patient demographics and clinical characteristics will be assessed by calculating absolute standardized differences (ASD); covariates with ASD greater than or equal to 0.1 will be considered imbalanced and addressed according to diagnostic contingencies described in **Table 7**.

IPW will be used to adjust for confounding as described in section 3.7.1. Covariates listed in **Table 4** will be considered as potential independent variables, and included pending diagnostics and contingencies described in **Table 7**. Weight stabilization or trimming / truncation will also be considered pending diagnostic checks described in **Table 7**. Variables not balanced after weighting will either be included in the outcome model or considered for restriction (see **Table 7**).

For IMA-2, in which both *Diagnostic Phases I and II* are completed prior to the *Inferential Phase*, we will conduct additional diagnostic checks for competing risks, treatment crossover and discontinuation, and inspection of survival curves to assess that the proportional hazards assumption holds over the follow-up period. Contingent analyses for IMA-2 are described in the *Diagnostic Phase II* section of **Table 7**.

Table 7: Diagnostic checklist (with contingency plans*) to complete prior to progression to the inferential phase of IMA

Diagnostic Phase I				
#	**Diagnostic**	**Description**	**Threshold**	**Contingency triggered***
1	Evaluate distribution of individual drugs within each class to determine whether class-level comparisons are warranted	Evaluate proportion of patients in each class-level treatment arm (IL6Ri, JAKi) who initiate individual drugs within each class (TCZ and SAR for IL6Ri; BAR and TOF for JAKi).	90% of patients within both classes initiate individual drugs	Proceed with comparison of individual drugs (e.g., TCZ versus BAR) rather than evaluation of class-level effects. In this scenario, patients initiating individual drugs constituting <10% of class-level use will be excluded from study cohorts. All protocol elements will otherwise remain unchanged. If only within one class 90% of patients initiate a single drug, class level analyses will be pursued.
2	Assess baseline confounder balance before IPW weighting	We will evaluate balance in the distributions of all potential confounders between IL6Ri+CSI versus JAKi+CSI groups in the unweighted sample. Covariate balance will be defined as absolute standardized differences (ASDs) < 0.10 [Austin 2009].	Covariate imbalance, considered ASD ≥0.1	Variables with balance prior to IPW may be excluded from PS model if needed to satisfy checks #4-7 below.

3	Assess baseline confounder balance following IPW	We will confirm that the distributions of all potential confounders are balanced between IL6Ri+CSI versus JAKi+CSI groups in the weighted sample. Covariate balance will be defined as absolute standardized differences (ASDs) < 0.10 [Austin 2009]. Although variables with balance prior to IPW may be removed from the PS model per diagnostic check #2, balance of these variables will still be confirmed after IPW.	Covariate imbalance, considered ASD ≥0.1	For variables with residual imbalance after weighting one of two courses of action may be taken: 1) Variables not balanced may be included in the subsequent outcome model. 2) Study cohorts may be restricted, stratified, or direct-matched on certain variables as deemed appropriate if balance cannot be achieved via IPW.
4	Assess the positivity assumption	Positivity violations will be assessed using tabular approaches [Westreich 2010] and / or by evaluating the distribution of weights [Peterson 2012] using graphical aids (e.g., histograms of weights) and data driven tools.	Exposure probabilities larger than 6 standard deviations away from the average probability value will be evaluated as extreme. However, a more stringent criteria (i.e., probabilities that are within less than 6 standard deviations away from the average probability value) may be considered, depending on the variability of the computed probabilities.	In the event that the positivity assumption is violated, sample restriction or combination or recategorization of covariates and assessment windows will be considered if warranted.
5	Assess model coefficients for extreme values	Evaluate PS model coefficients to identify extreme coefficients which may indicate collinearity or positivity violations.	Any coefficient with extreme values that strongly predicts presence or absence of the exposure of interest (i.e., potential instrumental variables) or another covariate (i.e., multicollinearity).	In the case of extreme coefficients, variables may be dropped, combined, or recategorized within PS models and coefficients re-evaluated for extreme values.
6	Confirm models are not overfit	We will confirm that all models contain a sufficient number of exposed patients per covariate level (non-continuous variables only).	At least 12 exposed patients or more per covariate level	Variables with balance prior to IPW may be removed from the PS model, and if necessary, covariates without at least 12 exposed patients per covariate level may be removed from the model. Individual covariates and assessment windows may also be combined to address overfitting if warranted based on variable distributions.
7	Explore	The distribution of estimated	Weights larger than 6 standard	Weight stabilization or trimming / truncation

	weight distributions to evaluate whether outlier observations influence data	weights will be evaluated [Peterson 2012] via graphical approaches (e.g., histograms or boxplots); these approaches will be used to evaluate the presence of extreme weights and to define cut-off values for stabilization or truncation/trimming, if necessary.	deviations away from the average weight value will be evaluated as extreme. However, a more stringent criteria (i.e., weights that are within less than 6 standard deviations away from the average weights value) may be considered, depending on the variability of the computed weights.	will be considered.
Diagnostic Phase II				
#	**Diagnostic**	**Description**	**Threshold**	**Contingency triggered***
8	Evaluate probability of censoring due to a competing risk**	Calculate proportions of individuals in each treatment group experiencing a competing risk over time	20% (or more) of patients in either IL6Ri or JAKi arms experience a competing risk during follow-up.	Analyses accounting for discharge as a competing risk will be considered. Thresholds and possible contingencies will be considered separately for each outcome (death for both Illustrative Example objectives; progression to IMV/ECMO for illustrative Example - Objective I).
9	Evaluate treatment crossover after treatment index (Day T)	Evaluate proportion of patients in each treatment arm who initiate the other medication after day T (IL6Ri-treated patients on Day T initiating JAKi after Day T, and vice versa).	20% (or more) of the patients in either IL6Ri or JAKi arms initiate the other medication during follow-up from days T+1 to T+29.	Implications with regard to modifying the research question or for result interpretation will be evaluated. If threshold is met, IMA-2 will implement an as-treated follow-up design with censoring on treatment crossover between groups (initiation of JAKi medications among those initially treated with IL6Ri, and vice-versa). If crossover is differential by treatment group, this analysis may incorporate models to adjust for informative censoring.
10	Evaluate early treatment discontinuation among JAKi-treated	Evaluate proportion of patients in JAKi+CSI arm who discontinue JAKi treatment prior to discharge and before completion of recommended course of 14 days.	20% (or more) of the patients in the JAKi+CSI arm discontinue their JAKi treatment before discharge and before 14 days of treatment.	Implications with regard to modifying the research question or for result interpretation will be evaluated. If threshold is met, IMA-2 will implement an as-treated follow-up design with censoring

	patients			for early discontinuation of JAKi (before 14 days of treatment or discharge). Given that a single infusion of IL6Ri (at initiation) is considered a complete treatment dose, whereas a full course of JAKi requires once-daily oral treatment administered for up to 14 days or until discharge, only JAKi treated patients can be subject to censoring for discontinuation. Thus, this censoring design may also consider informative censoring adjustments to address potential selection bias.
11	Inspect survival curves to assess the proportional hazards assumption over the follow-up period	Prior to calculation of overall hazard ratios, we will visually inspect survival curves to assess that the proportional hazards assumption holds over the follow-up period.	Proportional hazards assumption is not satisfied, as demonstrated in visual aids (e.g. Schoenfeld residual plots or log-log plots).	If the proportional hazards assumption is not satisfied then shorter follow-up times, during which this assumption is likely to hold, will be analyzed. Alternatively other methods, such as restricted mean survival times, will be considered as an alternative to calculating hazard ratios via Cox models. Restricted mean survival times are a measure of average survival from time 0 to a specified time point, and may be estimated as the area under the survival curve up to that point. This analysis would compare the computed difference between the areas under the survival curve for each treatment arm. This method does not rely on an assumption of proportional hazards of the treatment effect.

*Contingent analyses are changes to the primary (SPA) analyses unless otherwise specified. IMA-1 and IMA-2 will consider contingencies in *Diagnostic Phase I*; IMA-2 will additionally consider contingencies in *Diagnostic Phase II*.

Models incorporating competing risks require measurement of time-varying covariates; these covariates after day T will include measures of disease severity (operationalized via procedure codes, charge codes, and department codes) and medications outlined in **Table 4.

3.7.3 Sensitivity Analyses

A priori-defined sensitivity analyses are described in **Table 8** below.

Table 8: Sensitivity Analyses*

#	Sensitivity Analysis	Parameter being varied?	Expected learning	Weaknesses and strengths of the analysis compared to the primary	Analysis type
1	Extend baseline period from 183 days to 365 days	Baseline period	This analysis will help elucidate the extent to which extension of the baseline period influences study results, including treatment effects but also prevalence of comorbidities and medications recorded during baseline.	Limitations: Requiring 365 days of continuous enrollment may decrease sample size. Strengths: Health-care seeking behavior during the pandemic (particularly early in the pandemic) is not representative of routine behavior. This analysis may improve capture of pre-COVID conditions and potential confounders by providing a wider span of time for baseline assessment to account for potentially sparse medical visits during the pandemic.	Design variation
2	Restrict cohorts to patients initiating IL6Ri or JAKi medications within 1 day after hospital/ICU admission (Days 0 to 1)	Inclusion criteria	This exploratory analysis will help elucidate the extent to which truncation of the IL6Ri/JAKi exposure assessment window influences relative effectiveness of IL6Ri versus JAKi medications.	Limitations: These analyses may be underpowered and may have limited generalizability relative to primary analyses. Strengths: By restricting to patients treated at or shortly after hospital admission, this analysis may improve specificity of disease severity classifications given that diagnoses recorded at admission (Day 0) are likely more reflective of disease severity at treatment initiation (Day T) than in primary analyses.	Design variation

*Table template adapted from STaRT-RWE.

4. POTENTIAL LIMITATIONS

4.1 Addressed in Design and Analyses

The following limitations have been addressed via study design or analyses, but will still be taken into consideration when interpreting and disseminating the findings from the implementation of this protocol:

- **Unstructured inpatient medication and procedure data:** In addition to standardized procedure codes (HCPCS/CPT or ICD-10-PCS), inpatient medication and oxygen supplementation information can be recorded in non-standardized free-text charge code descriptions. Therefore, text search strings will be used to query the charge code data when procedure codes are not available. Text strings used to query the data are not based on validated algorithms and may result in misclassification. Comprehensive text string searches will be used to minimize the potential for misclassification and additional manual review will be incorporated for key measures.
- **Limited capture of indication and heterogeneity in COVID-19 severity**: Although best practices will be applied to control for confounding, the potential for residual confounding still exists in observational cohort analyses. The indication for use of both

IL6Ri or JAKi in patients on O2 and NIV is “rapidly increasing oxygen needs and systemic inflammation”, which are not possible to measure using HealthVerity data. Further, since JAKi are not recommended for patients receiving IMV/ECMO, those patients receiving JAKi for these indications may be different (e.g., have more severe illness) than patients receiving IL6Ri for these indications. We are unable to fully measure the indication for O2 and NIV patients receiving these drug classes, nor assess whether one class of drugs is preferentially prescribed for more severe patients within any population defined by respiratory support requirements, potentially resulting in residual confounding by indication. Residual confounding is also a possibility if certain unmeasured characteristics associated with disease severity are also associated with preference for a given route of administration (e.g., if intravenous infusions are preferred to oral tablets for heavily-sedated patients).

While we cannot fully eliminate the potential for residual confounding, we will adjust for many measurable characteristics relating to disease severity, and assess covariate balance after application of IPW. Further, given that both drug classes are indicated for the same O2/NIV/HFO populations, we anticipate that any residual confounding will be minimal. Although not empirically verifiable within our dataset, if warranted, we will consider sensitivity analyses that evaluate the potential impact of unmeasured confounding [Schneeweiss 2006].

In this study (as in previous studies), we will compare the risk of endpoints in those treated or not treated with either drug class within 4 days after admission under routine care. Treatments on days 5-28 after admission are thus part of routine care and should not be controlled. Likewise, changes in severity may occur during follow-up and should not be controlled. Changes in treatment, care, and severity during follow-up may be causal mediators and thus contribute to the effect of IL6Ri or JAKi on the endpoints of interest. Any association of these post-index covariates with the treatments of interest could arise from the treatments (i.e. would be mediators), or from other baseline covariates that predicted treatment (i.e. would be mediators of a baseline covariate and controlled via control of the baseline covariate). Thus, the only post-index control considered in this study will be for differences in censoring.

- **Baseline (pre-admission) clinical characteristics (comorbidities, COVID-19 health care utilization) are limited to information available in claims:** Claims data are primarily collected for reimbursement purposes rather than research or clinical record-keeping, which can lead to misclassification and under-reporting of certain conditions or variables. In particular, behaviors and events such as smoking/tobacco use, COVID-19 diagnostic test results and outpatient or home oxygen use are likely to be under-recorded. Our data does not include nursing notes, which have been shown in a previous study conducted by the FDA Sentinel System to increase capture of O2 use [Cocoros 2021]. Where possible, claims algorithms have been defined broadly to account for potential under-reporting of such variables. For example, smoking/tobacco use is defined with diagnoses indicating use or abuse of tobacco, procedure codes for cessation consultations, and pharmacy claim records for cessation-related medications; similarly, although we do not have access to pre-admission laboratory results we define

pre-admission COVID-19 with diagnosis codes for confirmed COVID-19. We assume misclassification in baseline clinical characteristics to be non-differential between treatment groups.

- **Possibility of uncontrolled confounding by facility-level differences:** Facility-level factors (e.g., drug availability, facility- or provider-level treatment practices) may be associated with both use of IL6Ri/JAKi and patient outcomes, and cannot be directly accounted for within this analysis. However, our analyses will adjust for hospital characteristics such as number of beds, teaching status, level of immunomodulator prescribing, and demonstrated preference for either IL6Ri or JAKi as a proxy to help account for facility-level differences.
- **Possibility of exposure mis-classification and uncontrolled confounding due to differences in mode of administration and treatment courses for IL6Ri and JAKi:** We will attempt to restrict exposures evaluated in this study to IL6Ri or JAKi events delivered via their recommended routes of administration for COVID-19 (e.g., intravenous for TCZ, oral for BAR). However, there is a potential for misclassification due to the availability of other modes of administration for certain products (e.g., subcutaneous injection for TCZ and SAR), potential for under-capture of route of administration in this database, and uncertainty with regard to how subcutaneous formulations of IL6Ri reconstituted for intravenous use are recorded in chargemaster data. Finally, IL6Ri and JAKi treatments differ in terms of their recommended treatment courses. A single infusion of IL6Ri (at initiation) is considered a complete treatment dose, whereas a full course of JAKi requires daily oral treatment administered for up to 14 days or until discharge. We account for these differences by considering a separate as-treated contingency analysis for and possible adjustment for informative censoring in diagnostic phase II of the IMA-2 analysis.

4.2 To Be Considered in Interpretation Only

The following limitations will be taken into consideration when interpreting and disseminating the findings from the implementation of this protocol:

- **Lack of indicators of socio-economic status (SES):** The HealthVerity data leveraged for this study does not include SES measures. We will include insurance type in the PS model for covariate adjustment as it may be associated with SES (e.g., patients with a PPO generally have higher SES than those with HMO), but no other proxies are available to adjust for SES.
- **Lack of race/ethnicity information:** The HealthVerity data leveraged for this study does not include race or ethnicity demographic data. Therefore, we are unable to evaluate whether the effect of either IL6Ri or JAKi on 28-day mortality varies by race or ethnicity, explore potential racial and ethnic disparities related to COVID-19 severity and treatment, or control for confounding by race or ethnicity.
- **Lack of post-discharge outcome information**: Follow-up for death and IMV/ECMO outcomes must be censored at discharge from hospital, given lack of reliable

post-discharge outcome information. Therefore, there may be some patients who experience outcomes after discharge from their initial hospitalization, either during subsequent re-admissions or after transfer to a different healthcare facility. We will not capture these outcomes nor consider post-discharge follow-up time in our analyses.

- **Lack of generalizability to certain populations**: Study design decisions that improve internal validity of Illustrative Example Objectives may in some cases limit generalizability to populations of interest. For example, patients with baseline O2 use (to the extent it was captured in claims data) were excluded from study cohorts in order to ensure that any O2 use during their hospitalization was for COVID-19 and not a pre-existing comorbidity. However, this may result in exclusion of patients most at-risk for severe COVID-19 (e.g. patients with COPD) from study populations. Similarly, requirements for IL6Ri and JAKi initiation to occur no later than 4 days after admission, the exclusion for pre-admission CS use, and the exclusion for prior COVID-19 hospitalizations improve internal validity while potentially reducing generalizability to populations of interest. While HealthVerity data include patients from all major insurance types (Medicaid, Medicare and commercial insurance), results may not be generalizable to non-insured patients.

5. STRENGTHS

The generation of methodologically robust evidence from observational studies can be challenging; this is particularly true when evaluating potential treatments for COVID-19 when there is still more to learn about its natural history, and when the standard of care is still evolving. By implementing a head-to-head comparison of treatments with the same indication, along with a new user design, our study minimizes the potential of bias including confounding by indication and immortal time bias, and ensures the correct temporality between covariate and exposure assessment [Lund 2015; Franklin 2017]. In order to evaluate optimal methodologies for observational comparative studies of COVID-19 treatments, we evaluate and compare two different approaches: 1) an approach based on pre-specified covariates and statistical approaches without consideration of whether key statistical assumptions hold, and 2) an approach whereby two-phases (pre- and post-index) of diagnostic checks are performed and corresponding contingencies implemented to ensure that analytic assumptions are fully satisfied prior to finalizing the inferential analysis plan and estimating and interpreting treatment effects. Diagnostic checks evaluate potential sources of bias (e.g. competing risk bias) omitted in many other studies evaluating drug effectiveness in hospitalized patients with COVID-19 [Martinuka 2021].

For the Illustrative Example we followed structured processes [Gatto 2019] to articulate the research question, conceptualize the underlying hypothetical pragmatic target trial [Hernan, Robins 2016; Hernan, Sauer 2016], design the real-world emulation study, and to identify a fit-for-purpose data source [Gatto 2022, FDA 2018]. Based on this systematic assessment we selected a RWD source with near-real-time information, a reasonable population size, and sufficient capture of key study parameters and longitudinal patient experience to evaluate our

research question. Next, we explored the data to confirm data feasibility and inform key study design decisions. Sensitivity analyses have been developed a priori with documented justifications to evaluate the robustness of findings.

6. HUMAN SUBJECTS

The use of this de-identified data source was approved for exemption by the New England Independent Review Board.

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8. APPENDICES

Appendix A. SPACE Template and / or other documentation supporting development of a hypothetical target clinical trial.

Available upon request.

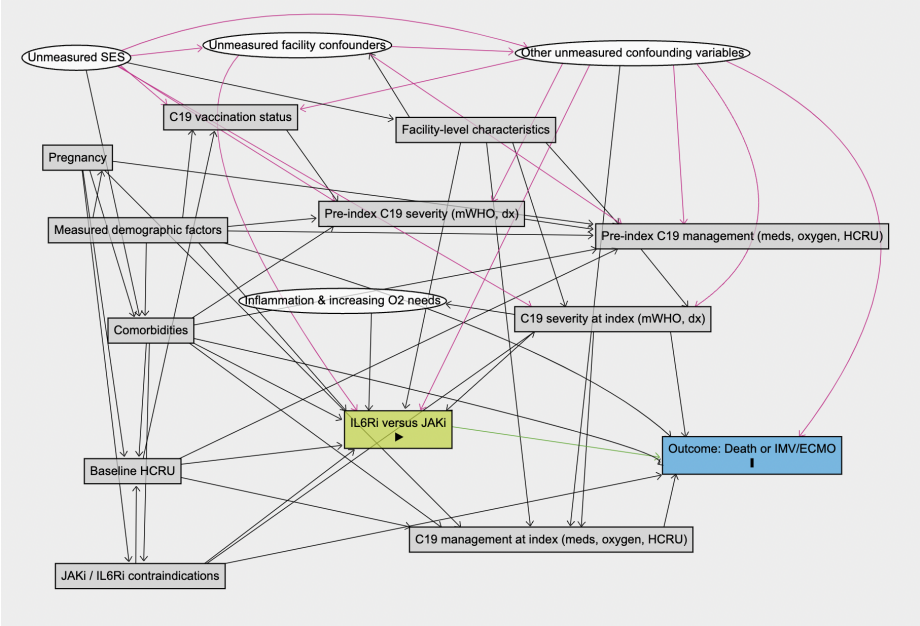
Appendix B: Description of Phased Study Approach

Not applicable; included in protocol

Appendix C: Detailed context and rationale for covariates, including DAG

Directed acyclic graph (DAG) was generated using Daggity: http://www.dagitty.net/

For purposes of display, variables in the DAG have been condensed where similar in terms of relationships with exposure, outcome, and antecedents. The following high-level DAG applies to both death and IMV/ECMO outcomes.



Appendix D: Full START-RWE Tables

For SPA analyses unless otherwise specified. Complete code lists and definitions for all study variables are available in ***Appendix F. Code Lists.***

Appendix D1: START-RWE Table. Index Date (Time T) defining criterion

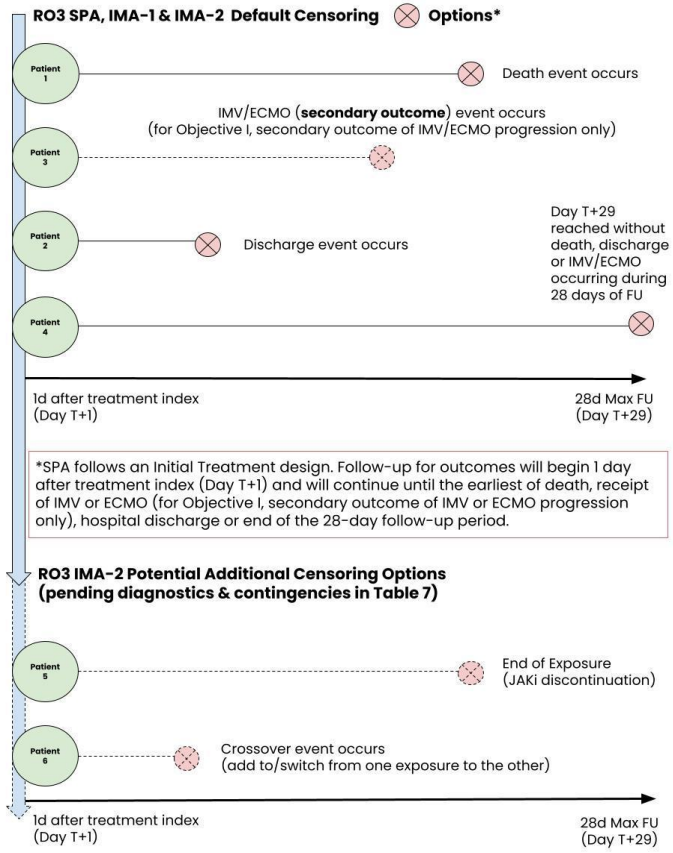
Study population name(s)	Day 0 Description	Type of entry	Washout window	Care Setting[1]	Code Type	Incident with respect to…	Pre-specified	Varied for sensitivity	Source of algorithm
Exposure Groups	IL6Ri initiation within 4 days after Day 0	Incident	[Days -90 to T-1]	IP CDM	ICD-10-PCS, HCPCS/CPT, charge code (see code list appendix)	IL6Ri dispensing or remaining supply during washout	Yes	Yes	De Novo Code Search
	JAKi initiation within 4 days after Day 0	Incident	[Days -90 to T-1]	IP CDM	ICD-10-PCS, HCPCS/CPT, charge code (see code list appendix)	JAKi dispensing or remaining supply during washout	Yes	Yes	De Novo Code Search

All temporal windows anchored on study population entry date (Day 0) unless otherwise specified.
( ) represent open intervals that do not include the endpoints
[ ] represent closed intervals that do include the endpoints
[1] IP CDM = inpatient (chargemaster only), OP CDM = outpatient (chargemaster only), Med Claims = medical claims, Rx Claims = pharmacy claims

Appendix D2: START-RWE Table: Follow up

			Pre-specified	Varied for sensitivity
Begins	Day T+1		Yes	Yes
Ends	**Select all that apply**	**Specify**		
Date of outcome:	Yes (all analyses)	- Inpatient mortality (Illustrative Example Objectives I & II) - Progression to IMV/ECMO (Illustrative Example Objective I only, for secondary outcome of IMV/ECMO only)	Yes	Yes
Day 29 following T+1	Yes (all analyses)	T+29	Yes	No
Date of discharge	Yes (all analyses)	Date of discharge from inpatient hospital	Yes	No
End of exposure *(JAKi discontinuation)*	Possible contingency for IMA-2	Early discontinuation of JAKi (Only individuals who initiate JAKi at treatment index are eligible for this criterion (i.e., IL6Ri initiators at treatment index cannot be censored for this reason). For this study, JAKi treatment is considered complete when a person has been treated for 14 days OR if a person with ongoing JAKi treatment is discharged from the hospital (before 14 days), after applying a 2 day event extension and 2 day grace period. Please see code list for further detail on operationalization of this censoring criterion.)	Yes	Yes
Date of crossover *(add to/switch from one exposure to the other)*	Possible contingency for IMA-2	Treatment crossover between IL6Ri or JAKi drug groups (any add-on or switch)	Yes	Yes

Supplemental Figure for Appendix D2. Censoring Reasons During Follow-up



Appendix D3: START-RWE Table. Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populat-ions:	Pre - specified	Varied for sensitivity	Source for algorithm
Hospitalized Patients	Date Range: June 16 2020 to February 01 2022	Before selection of index date	Day 0 - Hospital Admission	IP CDM	-	-	All[3]	Yes	No	-
Patients with admitting diagnosis of COVID-19	-	Before selection of index date	Day 0	IP CDM	ICD-10-CM	Any admitting	All[3]	Yes	No	CDC Coding Guidelines, 2020
Initiate either IL6Ri or JAKi	-	Defines index event	[Days 0, 4]	IP CDM	ICD-10-PCS, HCPCS/CPT, charge code (see code list appendix)	-	All[3]	Yes	Yes	De Novo Code Search
Receipt of at least one respiratory support procedure	Includes codes for oxygen supplementation or ventilation (Does not include intubation codes alone)	After selection of index date	[Days 0, T]	IP CDM, OP CDM	ICD-10-PCS, HCPCS/CPT, charge code (see code list appendix)	-	All[3]	Yes	No	Garry, 2022; De Novo Code Search

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populat-ions:	Pre - specified	Varied for sensitivity	Source for algorithm
Maximum mWHO disease severity	Objective I: max = O2 or NIV/HFO Objective II: max = IMV/ECMO	After selection of index date	[Days 0, T]	IP CDM, OP CDM	Various (see code list Appendix. This inclusion variable uses mWHO version with both procedure and admitting diagnosis codes)	-	-	Yes	No	Garry, 2022; De Novo Code Search
Receipt of systemic CSI	-	After selection of index date	Day T	IP CDM, OP CDM	Various (see code list Appendix)	-	All[3]	Yes	No	De Novo Code Search
ICU admission	Objective II population only; any ICU/CCU	Before selection of index date	Day 0 = same day as ICU admission	IP CDM, OP CDM	Dept codes HCPCS/ CPT, charge codes	-	Objective II population only	Yes	No	-

All temporal windows anchored on study population entry date (Day 0) unless otherwise specified.

( ) represent open intervals that do not include the endpoints

[ ] represent closed intervals that do include the endpoints

[1] IP CDM = inpatient (chargemaster only), OP CDM = outpatient (chargemaster only), Med Claims = medical claims, Rx Claims = pharmacy claims.

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

[3] All study populations, including Illustrative Example Objective I population (O2/NIV/HFO) and Illustrative Example Objective II population (IMV/ECMO +ICU).

Appendix D4: START-RWE Table. Exclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations:	Pre-specified	Varied for sensitivity	Source for algorithm
Missing continuous medical claims enrollment	60 day gaps permitted	Before selection of index date	[Days -183, 0]	Med Claims	-	-	All[3]	Yes	No	-
COVID-19 related hospitalization occurs >14 days after initial diagnosis (or if any diagnosis is recorded 90 days prior to admission)	Excludes patients with possible long-term COVID or post-acute sequelae while still permitting prior infections recorded more than 90 days pre-admission	Before selection of index date	[Days -90, -15]	IP CDM, OP CDM, Med Claims	ICD-10-CM	Any	All[3]	Yes	No	-
Missing age, sex and geographic region	-	Before selection of index date	Day 0	-	-	-	All[3]	Yes	No	-
Age less than 18 years	-	Before selection of index date	Day 0	-	-	-	All[3]	No	No	
Evidence of prior COVID-related hospitalization	2 day buffer permits brief inpatient utilization directly proceeding transfer to charge-master hospital	Before selection of index date	[Days -14, -3]	IP CDM, Med Claims	ICD-10-CM in inpatient settings	-	All[3]	Yes	No	-
Evidence of prior systemic CSI use	2 day buffer permits CSI use in other healthcare settings directly before charge-master hospital admission	Before selection of index date	[Days -14, -3]	IP CDM, OP CDM, Med Claims, Rx Claims	Various (see code list Appendix)	-	All[3]	Yes	No	De Novo Code Search

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations:	Pre-specified	Varied for sensitivity	Source for algorithm
Evidence of prior IL6Ri use	Dispensing or remaining supply	Before selection of index date	[Days -90, -1] for claims only; [Days -90 to T-1] for IP/OP CDM only	IP CDM, OP CDM, Med Claims, Rx Claims	Various (see code list Appendix)	-	All[3]	Yes	No	De Novo Code Search
Evidence of prior JAKi use	Dispensing or remaining supply	Before selection of index date	[Days -90, -1] for claims only; [Days -90 to T-1] for IP/OP CDM only	IP CDM, OP CDM, Med Claims, Rx Claims	Various (see code list Appendix)	-	All[3]	Yes	No	De Novo Code Search
Baseline respiratory support for non-COVID conditions	2 or more respiratory support procedures recorded on different days	Before selection of index date	[Days -90, -15]	IP CDM, OP CDM, Med Claims	Various (See code list appendix)	-	All[3]	Yes	No	Garry, 2022
Death or discharge occurs	Before or on the day of treatment initiation	Before selection of index date	[Days 0, T]	IP CDM	-	-	All[3]	Yes	No	-
Recorded use of both IL6Ri AND JAKi on index date	-	On index date	Day T	IP CDM	Various (see code list Appendix)	-	All[3]	Yes	No	De Novo Code Search

All temporal windows anchored on study population entry date (Day 0) unless otherwise specified.
( ) represent open intervals that do not include the endpoints
[ ] represent closed intervals that do include the endpoints

[1] IP CDM = inpatient (chargemaster only), OP CDM = outpatient (chargemaster only), Med Claims = medical claims, Rx Claims = pharmacy claims.

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

[3] All study populations, including Illustrative Example Objective I population (O2/NIV/HFO) and Illustrative Example Objective II population (IMV/ECMO+ICU).

Appendix D5: START-RWE Table: Outcome

Outcome name	Outcome measurement characteristics	Primary outcome?	Type of outcome	Assessment window	Care Settings[1]	Code Category	Applied to study populations:	Pre - specified	Varied for sensitivity	Source of algorithm
Inpatient mortality	Hazard ratios and 95% CIs will be estimated using a marginal structural model Cox proportional hazards analysis	Yes	Time-to-event	[Days T+1, end of FU[3]]	IP CDM, OP CDM	Defined using discharge status field (see code list Appendix)	All[3]	Yes	No	-
Progression to IMV or ECMO	Hazard ratios and 95% CIs will be estimated using a marginal structural model Cox proportional hazards analysis	No	Time-to-event	[Days T+1, end of FU[3]]	IP CDM, OP CDM	ICD-10-PCS, HCPCS/ CPT, charge codes (see code list Appendix)	Illustrative Example Objective I population (O2/NIV/HFO) only	Yes	No	Garry, 2022; De Novo Code Search

All temporal windows anchored on study population entry date (Day 0) unless otherwise specified.( ) represent open intervals that do not include the endpoints
[ ] represent closed intervals that do include the endpoints

[1] IP CDM = inpatient (chargemaster only), OP CDM = outpatient (chargemaster only), Med Claims = medical claims, Rx Claims = pharmacy claims, ED = emergency department, any, other, n/a = not applicable.

[2] All study populations, including Illustrative Example Objective I population (O2/NIV/HFO) and Illustrative Example Objective II population (IMV/ECMO +ICU).

[3] For primary analyses, follow-up for outcomes will begin on Day T+1 and continue until the earliest occurrence of death, outcome (if different from death), discharge from the hospital, or 28 days of follow-up reached (Day T+29).

Appendix D6: START-RWE Table. Covariates

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diag-nosis Pos-ition[2]	Applied to study popul-ations:	Pre - specified	Varied for sensitivity	Source for algorithm
History of smoking/tobacco use (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims, Rx Claims	ICD-10-CM, HCPCS/ CPT, NDC generic name	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search
Asthma (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims	ICD-10-CM	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search
Any cancer (active hematological cancer, active solid tumor) (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims	ICD-10-CM	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search
Chronic lung disease (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims	ICD-10-CM	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search
Any cardiovascular disease (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims	ICD-10-CM	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search
Type 1 or 2 Diabetes (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims	ICD-10-CM	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search
Immuno-suppressive conditions or medications (including blood/organ transplant, rheumatoid	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims, Rx Claims	ICD-10-CM, ICD-10-PCS, HCPCS/CPT, charge	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diag-nosis Pos-ition[2]	Applied to study popul-ations:	Pre - specified	Varied for sensitivity	Source for algorithm
arthritis and other autoimmune conditions) (baseline)				codes, NDC generic name, NDC code, WHO ATC code					
Kidney disease (end stage renal disease, acute kidney injury, dialysis) (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims	ICD-10-CM, HCPCS/CPT, ICD-10-PCS, charge codes, revenue codes, dept codes	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search
Overweight/ obese (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims	ICD-10-CM	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search
Liver dysfunction (hepatic impairment, active liver disease) (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims	ICD-10-CM	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search
Other conditions with potential IL6Ri or JAKi cautions (bowel obstruction, necrosis, ulcerative disease, latrogenic GI injury, demyelinating disorders, serious infections, cystic fibrosis, pregnancy, sickle cell / thalassemia) (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims	ICD-10-CM	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations:	Pre - specified	Varied for sensitivity	Source for algorithm
Pregnancy (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims	ICD-10-CM, HCPCS/CPT	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search
Frailty score (baseline)	Numeric	Baseline† (assessed at Day -1 with 183 day lookback)	IP CDM, OP CDM, Med Claims	ICD-10-CM, HCPCS/CPT	-	All[3]	Yes	Yes (SA-1 extended baseline period)	Kim, 2017
Neurological/ cognitive impairment (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims	ICD-10-CM	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search
Mental health/ psychosis (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims	ICD-10-CM	-	All[3]	Yes	Yes (SA-1 extended baseline period)	Component of Gagne, 2011
Hypertension (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims	ICD-10-CM	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search
Combined Comorbidity score	Continuous	Baseline† (assessed at Day -1 with 183 day lookback)	IP CDM, OP CDM, Med Claims	ICD-10-CM	-	All[3]	Yes	Yes (SA-1 extended baseline period)	Gagne, 2011
Statin use (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims, Rx Claims	HCPCS/CPT NDC generic name, charge codes	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diag-nosis Pos-ition[2]	Applied to study popul-ations:	Pre - specified	Varied for sensitivity	Source for algorithm
Systemic and inhaled corticosteroid use (baseline)	Binary (Yes or No) (Record of new or existing corticosteroid use during baseline period)	Baseline†	IP CDM, OP CDM, Med Claims, Rx Claims	Various (see code list appendix)	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search
Anticoagulant and/or antiplatelet use (baseline)	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims, Rx Claims	HCPCS/CPT NDC generic name, charge codes	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search
Days hospitalized (baseline)	Numeric	Baseline†	IP CDM, Med Claims	-	-	All[3]	Yes	Yes (SA-1 extended baseline period)	-
Number of outpatient visits (baseline)	Numeric	Baseline†	OP CDM, Med Claims	-	-	All[3]	Yes	Yes (SA-1 extended baseline period)	-
Number of pharmacy claims (baseline)	Numeric	Baseline†	Rx Claims	-	-	All[3]	Yes	Yes (SA-1 extended baseline period)	-
Number of distinct medications dispensed (baseline)	Numeric	Baseline†	Rx Claims	NDC generic name	-	All[3]	Yes	Yes (SA-1 extended baseline period)	-
Any baseline encounter indicating skilled nursing facility (SNF) or long-term care (LTC)	Numeric	Baseline†	IP CDM, OP CDM, Med Claims	Various (see code list Appendix)	-	All[3]	Yes	Yes (SA-1 extended baseline period)	Twiddy 2016; De Novo Code Search

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diag-nosis Pos-ition[2]	Applied to study popul-ations:	Pre - specified	Varied for sensitivity	Source for algorithm
7+ days in SNF or LTC during baseline	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims	Various (see code list Appendix)	-	All[3]	Yes	Yes (SA-1 extended baseline period)	-
COVID-19 vaccination status	Binary (Yes or No)	Baseline†	IP CDM, OP CDM, Med Claims	Various (see code list Appendix)	-	All[3]	Yes	Yes (SA-1 extended baseline period)	De Novo Code Search
Record of prior COVID-19	Binary (Yes or No)	[Start of data, -15]	IP CDM, OP CDM, Med Claims	ICD-10 CM	-	All[3]	Yes	No	CDC Coding Guidelines, 2020; De Novo Code Search
Days since first COVID-19 diagnosis to admission	Numeric	[Days -14, -1]	IP CDM, OP CDM, Med Claims	-	-	All[3]	Yes	No	-
Pre-admission use of potential COVID-19 medications (systemic or inhaled corticosteroids, monoclonal antibodies, antivirals, RDV, etc)	Binary (Yes or No)	[Days -14, -1]	IP CDM, OP CDM, Med Claims, Rx Claims	ICD-10 PCS, HCPCS/CPT, NDC generic name, charge codes	-	All[3]	Yes	No	De Novo Code Search
COVID-19-related utilization prior to admission (urgent care, emergency department)	Binary (Yes or No)	[Days -14, -2]	IP CDM, OP CDM, Med Claims	Place of service, revenue, dept codes, HCPCS/CPT	-	All[3]	Yes	No	De Novo Code Search

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diag-nosis Pos-ition[2]	Applied to study popul-ations:	Pre - specified	Varied for sensitivity	Source for algorithm
Receipt of respiratory support prior to inpatient admission	Binary (Yes or No)	[Days -14, -1]	IP CDM, OP CDM, Med Claims	ICD-10 PCS, HCPCS/CPT charge codes	-	All[3]	Yes	No	De Novo Code Search
Age	Continuous Numeric	Day 0	-	-	-	All[3]	Yes	No	-
Sex	Categorical (male or female)	Day 0	-	-	-	All[3]	Yes	No	-
Insurance type	Categorical (Commercial only, Medicare w/ or w/o Commercial, Medicaid w/ or w/o Medicare/Commercial)	Day 0	-	-	-	All[3]	Yes	No	-
US region	Categorical (Midwest, Northeast, South, or West)	Day 0	-	-	-	All[3]	Yes	No	-
Month and year of hospital admission	Ordinal	Day 0	-	-	-	All[3]	Yes	No	-
Quarter-Year of admission	Ordinal	Day 0	-	-	-	All[3]	Yes	No	-
Hospital setting type = Urban	Binary (Yes for urban hospital, no for rural hospital)	Day 0	IP CDM	-	-	All[3]	Yes	No	-
Hospital teaching status = teaching	Binary (Yes for major or minor teaching hospital; no for non-	Day 0	IP CDM	-	-	All[3]	Yes	No	-

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations:	Pre - specified	Varied for sensitivity	Source for algorithm
	teaching)								
Hospital number of beds	Categorical (<200 beds, 200-299 beds, 300-399 beds, 400+ beds)	Day 0	IP CDM	-	-	All[3]	Yes	No	-
Hospital facility COVID-19 admitting volume[4]	Categorical (low: admitted to facility with <10 COVID-19 admissions per year-quarter; medium: admitted to facility with 10-29 COVID-19 admissions per year-quarter; high: admitted to facility with ≥ 30 COVID-19 admissions per year-quarter) Individuals were assigned to one of these mutually exclusive categories based on observed COVID-19 admitting volume at their admitting facility during their year-quarter of admission.	Day 0	IP CDM	-	-	All[3]	Yes	No	COVID-19 admission volume was calculated by facility and year-quarter among the overall hospitalized cohort prior to identification of IL6Ri/JAKi initiators.

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diag-nosis Pos-ition[2]	Applied to study popul-ations:	Pre - specified	Varied for sensitivity	Source for algorithm
Hospital facility level of immunomodulator (IL6Ri/JAKi) prescribing[4]	Categorical (low: ≤25th percentile; medium: 26th-74th percentiles; high: ≥75th percentile). Percentiles represent the facility-level percentage of COVID-19 admissions with recorded immunomodulator (IM) treatment during a given year-quarter, relative to all other facilities in that same year-quarter. Individuals were assigned to one of these mutually exclusive categories based on their facility's level of IM prescribing percentile within that year-quarter of admission.	Day 0	IP CDM	-	-	All[3]	Yes	No	Level (percentage) of IM treatment was calculated by facility and year-quarter among the overall hospitalized COVID-19 cohort prior to identification of IL6Ri/JAKi initiators.
Admitting diagnoses: Dyspnea/ hypoxia	Binary (Yes or No)	Day 0	IP CDM, OP CDM	ICD-10-CM	Any Admitting	All[3]	Yes	No	De Novo Code Search
Admitting diagnoses: Pneumonia	Binary (Yes or No)	Day 0	IP CDM, OP CDM	ICD-10-CM	Any Admitting	All[3]	Yes	No	De Novo Code Search

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diag-nosis Pos-ition[2]	Applied to study popul-ations:	Pre - specified	Varied for sensitivity	Source for algorithm
Admitting diagnoses: ARDS or acute respiratory failure	Binary (Yes or No)	Day 0	IP CDM, OP CDM	ICD-10-CM	Any Admitting	All[3]	Yes	No	De Novo Code Search
Admitting diagnoses: ARDS (for objective II only)	Binary (Yes or No)	Day 0	IP CDM, OP CDM	ICD-10-CM	Any Admitting	Objective II only	Yes	No	De Novo Code Search
Admitting diagnoses: Shock	Binary (Yes or No)	Day 0	IP CDM, OP CDM	ICD-10-CM	Any Admitting	All[3]	Yes	No	De Novo Code Search
Admitting diagnoses: Non-respiratory organ failure	Binary (Yes or No)	Day 0	IP CDM, OP CDM	ICD-10-CM	Any Admitting	All[3]	Yes	No	De Novo Code Search
Admitting diagnoses: Delirium	Binary (Yes or No)	Day 0	IP CDM, OP CDM	ICD-10-CM	Any Admitting	All[3]	Yes	No	De Novo Code Search
Admitting diagnoses: Sepsis	Binary (Yes or No)	Day 0	IP CDM, OP CDM	ICD-10-CM	Any Admitting	All[3]	Yes	No	De Novo Code Search
Admitting diagnoses: Do not resuscitate order	Binary (Yes or No)	Day 0	IP CDM, OP CDM	ICD-10-CM	Any Admitting	All[3]	Yes	No	De Novo Code Search
Admitting diagnoses: Acute cardiovascular event	Binary (Yes or No)	Day 0	IP CDM, OP CDM	ICD-10-CM	Any Admitting	All[3]	Yes	No	De Novo Code Search

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diag-nosis Pos-ition[2]	Applied to study popul-ations:	Pre - specified	Varied for sensitivity	Source for algorithm
Admitting diagnoses: Thromboembolic events	Binary (Yes or No)	Day 0	IP CDM, OP CDM	ICD-10-CM	Any Admitting	All[3]	Yes	No	De Novo Code Search
Admitting diagnoses: U07.1 diagnosis in primary position	Binary (Yes for U07.1 in primary position; No for non-U07.1 in primary position)	Day 0	IP CDM, OP CDM	ICD-10-CM	Primary, Priority 1, or Primary Admitting	All[3]	Yes	No	De Novo Code Search
Admitting diagnoses: COVID complication-related diagnoses in primary position	Binary (Yes for COVID-related diagnosis in p; No for non-COVID diagnosis in primary position)	Day 0	IP CDM, OP CDM	ICD-10-CM	Primary, Priority 1, or Primary Admitting	All[3]	Yes	No	De Novo Code Search
Admitting diagnoses: Presence of possible contraindication (concurrent non-COVID infection, end stage renal disease or acute kidney injury, liver dysfunction)	Binary (Yes or No)	Day 0	IP CDM, OP CDM	ICD-10-CM	Any Admitting	All[3]	Yes	No	De Novo Code Search
Admitting diagnoses: non-COVID opportunistic or serious infections	Binary (Yes or No)	Day 0	IP CDM, OP CDM	ICD-10-CM	Any Admitting	All[3]	Yes	No	De Novo Code Search

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diag-nosis Pos-ition[2]	Applied to study popul-ations:	Pre - specified	Varied for sensitivity	Source for algorithm
Admitted from Emergency Department	Binary (Yes or No)	[Days -1, 0]	IP CDM, OP CDM, Med Claims	Place of service, revenue, dept codes, HCPCS/CPT	-	All[3]	Yes	No	-
Ambulance	Binary (Yes or No)	[Days -1, 0]	IP CDM, OP CDM, Med Claims	Place of service, revenue, dept codes	-	All[3]	Yes	No	-
Admitted directly to ICU/CCU at admission	Binary (Yes or No)	Day 0	IP CDM, OP CDM	Revenue Dept codes, IP indicator	-	Objective l only[3]	Yes	No	-
Admitting type	Binary (Yes for emergency/traumal, no for elective/urgent)	[Days -1, 0]	IP CDM, OP CDM	Admit type	-	All[3]	Yes	No	-
Admitting status is transfer from other facility	Binary (Yes or No)	[Days -1, 0]	IP CDM, OP CDM	Admission Source	-	All[3]	Yes	No	De Novo Code Search
Pre-admission SNF, Nursing Home, or LTC utilization occurs	Binary (Yes or No)	[Days -2, -1]	IP CDM, OP CDM, Med Claims	Revenue/Dept codes, IP indicator, ICD-10 PCS, HCPCS/CPT, Place of Service, Bill Type	-	All[3]	Yes	No	De Novo Code Search
Pre-admission inpatient utilization occurs	Binary (Yes or No)	[Days -2, -2]	IP CDM, Med Claims	Suspected IP Indicator (claims), any IP CDM event	-	All[3]	Yes	No	De Novo Code Search

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations:	Pre - specified	Varied for sensitivity	Source for algorithm
Admitting mWHO severity (max level of respiratory support received, diagnosis and procedure-based mWHO)	Categorical (NONE, O2, NIV/HFO, IMV/ECMO)	[Days -1, 0]	IP CDM, OP CDM	Various (see code list Appendix. This inclusion variable uses procedure and diagnosis-based mWHO)	-	All[3]	Yes	No	De Novo Code Search
Anticoagulant/ antiplatelet agents	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	HCPCS/CPT, generic name, charge codes	-	All[3]	Yes	No	De Novo Code Search
Antibiotics	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	Generic name, charge codes	-	All[3]	Yes	No	De Novo Code Search
Vasopressors or inotropes	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	HCPCS/CPT, charge codes	-	All[3]	Yes	No	De Novo Code Search
Neuromuscular blockades	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	HCPCS/CPT, generic name, brand name, charge codes	-	All[3]	Yes	No	De Novo Code Search
Number of unique medication classes administered[5]	Numeric (see code lists for details)	[Days T-4, T]	IP CDM, OP CDM	Various (see code list Appendix)	-	All[3]	Yes	No	-
Number of unique injectable medication procedure codes recorded	Numeric	[Days 0, T]	IP CDM, OP CDM	HCPCS/CPT	-	All[3]	Yes	No	-

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diag-nosis Pos-ition[2]	Applied to study popul-ations:	Pre - specified	Varied for sensitivity	Source for algorithm
Number of unique oral, injectable, or inhaled medication procedure codes recorded	Numeric	[Days 0, T]	IP CDM, OP CDM	HCPCS/CPT	-	All[3]	Yes	No	-
Inhaled CS	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	HCPCS/CPT, generic name, charge codes	-	All[3]	Yes	No	De Novo Code Search
Remdesivir	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	ICD-10-PCS, HCPCS/CPT, generic name, brand name, charge code	-	All[3]	Yes	Yes	De Novo Code Search
Non-RDV antivirals (including lopinavir/ritonavir, other HIV protease inhibitors, ivermectin, etc)	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	Various (see code list appendix)	-	All[3]	Yes	No	De Novo Code Search
Other biologic immunomodulators (Non-JAK kinase inhibitors, non-IL6 interleukin inhibitors, anti-TNF biologics, B or T- cell inhibitors, etc)	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	Various (see code list appendix)	-	All[3]	Yes	No	De Novo Code Search
Any ICU/CCU	Binary (Yes or No)	[Days 0, T] for Objective	IP CDM, OP CDM	Dept Codes (Rev), HCPCS/	-	All[3]	Yes	No	De Novo Code Search

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diag-nosis Pos-ition[2]	Applied to study popul-ations:	Pre - specified	Varied for sensitivity	Source for algorithm
		I; [Day T] for Objective II		CPT, charge codes					
Specific ICU/CCU (not intermediate)	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	Dept Codes HCPCS/ CPT, charge codes	-	All[3]	Yes	No	De Novo Code Search
Intermediate or step-down ICU	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	Revenue/Dept Codes HCPCS/ CPT, charge codes	-	All[3]	Yes	No	De Novo Code Search
Critical care procedures	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	HCPCS/ CPT	-	All[3]	Yes	No	De Novo Code Search
Major surgery	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	HCPCS/CPT, ICD-10-PCS (see code lists)	-	All[3]	Yes	No	Component of Kim, 2017 and Clinical Classifications Software Refined (CCSR) 2021
Specialty care services (radiology, cardiovascular, respiratory therapy, surgery, dialysis)	Numeric, count of unique specialty care services recorded	[Days T-4, T]	IP CDM, OP CDM	Dept codes, HCPCS/CPT, ICD-10-PCS, charge codes	-	All[3]	Yes	No	De Novo Code Search
specialty care component: respiratory therapy/services	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	Dept codes, HCPCS/CPT, ICD-10-PCS	-	All[3]	Yes	No	De Novo Code Search

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations:	Pre - specified	Varied for sensitivity	Source for algorithm
specialty care component: cardiovascular therapy/services	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	Dept codes, HCPCS/CPT, ICD-10-PCS	-	All[3]	Yes	No	De Novo Code Search
specialty care component: radiology/imaging services	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	Dept codes, HCPCS/CPT, ICD-10-PCS	-	All[3]	Yes	No	De Novo Code Search
specialty care component: surgical utilization	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	Dept codes, HCPCS/CPT	-	All[3]	Yes	No	De Novo Code Search
Renal replacement therapy or dialysis	Binary (Yes or No)	[Days 0, T]	IP CDM, OP CDM	HCPCS/CPT, ICD-10-PCS, charge codes, dept codes	-	All[3]	Yes	No	De Novo Code Search
Number of O2/ventilation procedures administered	Numeric	[Days 0, T]	IP CDM, OP CDM	ICD-10-PCS HCPCS/CPT charge codes	-	All[3]	Yes	No	Garry, 2022
(Count of unique) COVID-19 related lab orders (e.g. PCT, ferritin, D-Dimers, troponin, PaO2, CRPs, AST/ALTs, blood	Numeric, count of unique COVID-19-related lab orders	[Days T-4, T]	IP CDM, OP CDM	HCPCS/CPT, charge codes	-	All[3]	Yes	No	De Novo Code Search

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diag-nosis Pos-ition[2]	Applied to study popul-ations:	Pre - specified	Varied for sensitivity	Source for algorithm
viscosity, lactate dehydrogenase, etc.)									
Number of unique procedure codes[5]	Numeric	[Days 0, T]	IP CDM, OP CDM	HCPCS/CPT, ICD-10-PCS	-	All[3]	Yes	No	-
Number of unique department codes	Numeric	[Days 0, T]	IP CDM, OP CDM	Dept codes	-	All[3]	Yes	No	-
Max respiratory support procedure recorded (procedure-based mWHO)	Categorical (NONE, O2, NIV/HFO, IMV/ECMO)	[Days 0, T]	IP CDM, OP CDM	Various (See code list appendix. This covariate uses the procedure only mWHO algorithm)	-	All[3]	Yes	No	-
Most frequently recorded mWHO status (procedure-based mWHO)	Categorical (NONE, O2, NIV/HFO, IMV/ECMO)	[Days 0, T]	IP CDM, OP CDM	Various (See code list appendix. This covariate uses the procedure only mWHO algorithm)	-	All[3]	Yes	No	-
Number of days from admission to treatment initiation	Numeric or categorical (0, 1, 2, 3, 4, 5)	[Days 0, T]	IP CDM	-	-	All[3]	Yes	No	-
Number of days with CSI use prior to treatment initiation	Numeric	[Days -2, T] (assessed using a 6-day extension)	IP CDM, OP CDM	-	-	All[3]	Yes	No	-
Number of days from max respiratory support	Numeric	[Days 0, T]	IP CDM, OP CDM	Various (See code list appendix. This	-	All[3]	Yes	No	-

Covariate / Characteristic	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations:	Pre - specified	Varied for sensitivity	Source for algorithm
status to treatment initiation (procedure-based mWHO)				covariate uses the procedure only mWHO algorithm)					
Number of days with O2/NIV/HFO/IMV/ECMO support prior to treatment initiation	Numeric	[Days 0, T]	IP CDM, OP CDM	Various (see code list appendix)	-	All[3]	Yes	No	-
mWHO disease severity at treatment initiation (procedure-based mWHO)	Categorical (NONE, O2, NIV/HFO, IMV/ECMO	Day T	IP CDM, OP CDM	Various (See code list appendix. This covariate uses the procedure only mWHO algorithm)	-	All[3]	Yes	No	-

All temporal windows anchored on study population entry date (Day 0) unless otherwise specified.

† Baseline period is defined as [Days -183, -1]

( ) represent open intervals that do not include the endpoints

[ ] represent closed intervals that do include the endpoints

[1] IP CDM = inpatient (chargemaster only), OP CDM = outpatient (chargemaster only), Med Claims = medical claims, Rx Claims = pharmacy claims.

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

[3] All study populations, including Illustrative Example Objective I population (O2/NIV/HFO) and Illustrative Example Objective II population (IMV/ECMO+ICU).

[4] For some patient covariates pertaining to the facility at which they are admitted, it is necessary to first conduct a facility-level analysis of the overall hospitalized COVID-19 cohort. This analysis will be executed on a separate analytic cohort consisting of all hospitalized COVID-19 patients with CSI use and oxygen/ventilation supplementation from Day 0 to Day 4, prior to identification of IL6Ri and JAKi initiators. Within this population, COVID-19 admission volume and level (proportion) of IM (IL6Ri or JAKi) use will be calculated separately by facility and by calendar year-quarter, to account for temporal changes in COVID-19 incidence and IM treatment. Finally, within Objective I and II study cohorts, each individual will be assigned a categorical value for “Hospital facility COVID-19 admitting volume “ and “Hospital facility level of immunomodulator (IL6Ri/JAKi) prescribing” based on their admitting facility and year-quarter of admission.

[5] IL6Ri and JAKi will be excluded from variable definitions to avoid adjustment for exposure-related characteristics

Appendix D7: START-RWE Table: Analyses

Hypothesis:	Hypothesis is that IL6Ri+CSI exposure, as compared to JAKi+CSI exposure, is associated with different risks of death and IMV/ECMO (for Illustrative Example - Objective I only), with either the lower bound of the 95% hazard ratio above 1.0 or the upper bound of the 95% hazard ratio below 1.0.
Study population(s):	IL6Ri/JAKi initiators within 4 days of hospital admission
Outcome:	Inpatient 28-day mortality (primary outcome for both Illustrative Example Objectives), progression to IMV/ECMO (secondary outcome for Illustrative Example Objective I)
Software:	Aetion Evidence Platform, version 2022 for SPA and IMA-1 analyses. R version 4 for select IMA-2 analyses (contingent on diagnostic checks)
Model(s):	*Outcome model:* Cox proportional hazards; *Propensity score model*: logistic regression See potential covariates for model inclusion in Table 4
Confounding adjustment method	
Bivariate	☐
Multivariable	☐
Propensity score matching *(specify matching algorithm, ratio and caliper)*	☐
Propensity score weighting *(specify weight formula, trimming, truncation decisions)*	☒ Inverse probability weighting. The weights for each patient will be calculated as the inverse of the probability of receiving the treatment the patient actually received conditional on observed covariates. Each individual's contribution to the survival curves and to the Cox regression model will be weighted by the inverse probability of receiving the treatment the patient actually received conditional on observed covariates. A robust variance estimator will account for the weighted design. Any variables not balanced after weighting will be included in the outcome model. Trimming and / or truncation will be considered pending assessment of weight distribution in diagnostic check #9. If appropriate, stabilized weights will be used and a select number of patients (e.g. 10) with the most extreme high and low weights will be trimmed.

Propensity score stratification *(specify strata definition)*	☐
Other *(specify details)*	☐
Missing data methods *(check all that apply, provide relevant details)*	
Missing indicators	☒ Patients with missing age, gender, or geographic region were excluded from study cohorts.
Complete case	☒ Patients with missing or unknown gender, age and region are excluded
Last value carried forward	☐
Multiple imputation *(specify variables)*	☐
Other (please specify)…	☒ Assumed that if there were no codes indicative of a binary (yes/no) condition or characteristic within the assessment window, that it was not present for the patient.
Subgroup Analysis	NA

Appendix E: Data Management Process Details

Raw data review

At Aetion, raw data review is conducted to understand contents of the data table(s), establish relationships, and help inform the database connection specification. Scientific integrity checks are performed to understand if the contents of the data shipment is consistent with the expected data as laid out in the applicable data usage agreement. Some of the key characteristics explored in this process include:

- Table structure (number of rows, columns, column names etc.)
- Summary counts per table (i.e., non-missing counts, unique counts)
- Variable distribution (e.g., min, mean, median, max for numeric variables; top frequencies for categorical variables)
- Date range (min, max and distribution over a time period)
- Missingness percentage of attributes

Database connection process

Following receipt and review of the raw data, a data connector specification is drafted by a data scientist. The specification provides a map to Engineering for transformation of raw data to the Aetion longitudinal patient timeline. It includes information such as:

- Overall schema including tables (event types), rows (events), and columns (attributes); derivation of attributes to improve data flexibility on Platform and rationale for any attributes or events that are dropped
- Event dates that define how data will be reflected on the longitudinal patient timeline, and any minimal processing rules (e.g., drop an event that does not include a start or end date)
- Skeleton structure that represents the logical view of the entire database, defining how the data is organized and how the relations among them are associated
- Information for UI and labeling
- Codes and definitions; typically used to substitute users' having to look-up multiple resources to understand/process data

Validation of the database connection (DBC) is completed to ensure that the implementation of DBC logic leads to transformed data output that connects to and behaves within AEP exactly as intended. Raw data are never loaded as-is directly into the Aetion Evidence Platform; rather, data are transformed (via the DBC) into an Aetion-compatible format. DBC validation is required to confirm that this transformation was performed correctly. This helps to ensure validity/accuracy of the connected data and its importance cannot be ignored. Validation is performed via double programming, where two different people work independently from the same DBC specification and then compare their output. The DBC is considered validated if the outputs are identical. If the outputs are not identical, then the source of the discrepancy must be investigated and resolved.

Following validation, the specification files are used to create an Aetion data dictionary for the dataset. In addition, throughout the data connector spec / creation process, any issues or decisions that have to be made that are not otherwise specified in the Specification files (e.g., how missing dates are handled), are noted in the data dictionary.

Prior to deployment on the AEP, a pre-flight checklist (PFC) is implemented. The PFC is a manual test of certain platform features and dataset values as visible and testable on the

front-end. A PFC is run following any deployment activity (such as a version update and/or data/shard update). What's checked for includes:

- Baseline values for database information (dataset name, patient counts, earliest and latest event dates)
- Database configuration (specified dataset values)
- Measure, Cohort, and Analysis Generations to confirm this functionality using the dataset
- Output from generated analysis output
- Coding Systems, if applicable

Appendix F: Code Lists

Available upon request

Appendix G: Exploratory Analysis Results

Not applicable; included in protocol

Appendix H: Potential Addendum 1: Final List of Covariates Included in Model(s) and Contingencies Pursued

Will be included in the final study report.

Appendix I: References for Appendix

Contains references within Appendices A-H that are not cited in main protocol text.

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