Real-world Evidence and Network Meta-analysis for the Effectiveness of Remdesivir and Tocilizumab for Hospitalised Patients with COVID-19

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***Abstract*—The COVID-19 pandemic and the strain it placed on healthcare systems highlighted a key role for real-world data in quickly generating health evidence. A growing demand for large-scale health analytics has also resulted in the existence of large health data networks and opportunities for the incorporation of both randomised and non-randomised evidence in the health regulation decision-making process. This study collected non-randomised evidence on COVID-19 treatment effects on short-term mortality among patients hospitalised with COVID-19 from the European Health Data and Evidence Network (EHDEN) and synthesised these data with randomised evidence.**

Randomised evidence was collected through literature search among two published NMAs, COVID-NMA, and clinicaltrials.gov for trials which studied the target treatments in hospitalised COVID-19 patients aged 18 years or older. Results of 21 randomised trials including 15,246 patients were combined through Bayesian network meta-analysis. Non-randomised evidence was collected as a retrospective, multinational comparative cohort study with a new user, active comparator design through EHDEN. Included patients were aged 18 years or over at cohort entry, had at least 365 days of continuous observation time prior to cohort entry, had 0 prior exposures to index treatment in the 365 days prior to index, had at least 1 COVID-19 diagnosis or positive test results in the 30 days prior to or on index, and were hospitalised on index. Although target treatments included aspirin, baricitinib, heparin, remdesivir, and tocilizumab, only evidence for remdesivir and tocilizumab was available. 475 patients from one data partner were included.

This study generated inconclusive evidence for the comparative effectiveness of remdesivir and tocilizumab in reducing short-term mortality among hospitalised patients with COVID-19. Randomised evidence showed no difference between remdesivir and tocilizumab, while non-randomised evidence showed remdesivir to significantly reduce short-term mortality compared to tocilizumab.

The non-randomised results indicate a need for more streamlined observational data collection pathways, but show that it is feasible to collect non-randomised evidence through EHDEN and that this non-randomised evidence can be compared with randomised evidence. Future studies investigating non-randomised evidence collection may build upon the infrastructure developed for this study at participating hospitals.

***Index Terms*—Real-world evidence, OHDSI, COVID-19, Network Meta-analysis**

1. Introduction

Since the emergence of SARS-CoV-2 and its associated disease COVID-19 in 2020, there have been over 750 million confirmed cases and 6.5 million COVID-related deaths [1]. The resulting pandemic put unprecedented strain on healthcare systems and exposed a need for quick and reliable evidence-gathering mechanisms.

Real-world evidence was one of the key sources for healthcare providers to make treatment decisions early in the pandemic [2]. While there were some notable early randomised control trials (RCTs), including RECOVERY [3] and Solidarity [4, 5], and network meta-analyses (NMAs) which provided an up-to-date summary of findings [6, 7, 8], such studies are generally time consuming and difficult to initiate during a healthcare crisis. Observational data can be collected quicker to provide timely insights for decision making.

Growing interest in the value of observational data to generate real-world evidence has led to the creation of health data networks [9]. One such observational health data network is the European Health Data and Evidence Network (EHDEN), which is comprised of 187 data partners across 29 European countries. EHDEN, within the Innovative Medicines Initiative (IMI), is a public-private partnership responding to the need to improve our speed to answers in real-world research. By harmonising real world data to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), it enables federated analysis with large scale analytics tools. EHDEN collaborates closely with the Observational Health Data Sciences and Informatics (OHDSI) program, a global collaborative to produce health data evidence through large scale analytics [10]. EHDEN, and its associated analytical tools, can facilitate the generation of real-world evidence to directly inform health technology assessment (HTA) and regulation in the context of COVID-19.

In response to the rapid spread of COVID-19, some treatments entered clinical practice without undergoing HTA, and there remains a need for HTA agencies to assess the comparative effectiveness of these treatments. One of EHDEN's objectives within its Work Package 2, Outcome Driven Health-

care, aims to test whether the OMOP CDM and the EHDEN network can be used for HTA activities. This study thus investigates the opportunity to collect real-world evidence through the EHDEN network to produce treatment effect estimates for COVID-19 treatments which can be synthesised with RCT data.

Currently, there are eight treatments authorised for use in the EU to treat COVID-19 [11]. These treatments include tixagevimab/cilgavimab, anakinra, ritonavir, regdanvimab, tocilizumab, casirivimab/imdevimab, remdesivir, and sotrovimab. Two treatments (tixagevimab/cilgavimab and tixagevimab/cilgavimab) are indicated for the prevention of COVID-19, five treatments (tixagevimab/cilgavimab, ritonavir, regdanvimab, casirivimab/imdevimab, and remdesivir) are indicated for use in COVID-19 patients who do not have severe disease or require supplemental oxygen, and three treatments (anakinra, tocilizumab, and remdesivir) are indicated for use in COVID-19 patients with more severe disease requiring supplemental oxygen or mechanical ventilation. A summary of all treatments approved by the EMA including their full indications is available in *Appendix 6.1*.

Additionally, the World Health Organization (WHO) provides a strong recommendation for the following treatments among patients with severe or critical COVID-19: systemic corticosteroids, tocilizumab (IL-6 inhibitor), sarilumab (IL-6 inhibitor), and baricitinib (JAK inhibitor), as well as a conditional recommendation for remdesivir (RNA polymerase inhibitor) [12]. It also recognizes the concomitant use of the IL-6 inhibitors tocilizumab and sarilumab with systemic corticosteroids or baricitinib.

Among the treatments WHO strongly recommends for severe COVID-19, only tocilizumab and remdesivir are approved as COVID-19 treatments in the EU, while corticosteroids, sarilumab, and baricitinib are all approved for use in the EU as treatments for other conditions. Still, all strongly recommended treatments have been used for COVID-19 within the EU without EMA authorisation [13], [14], [15].

The WHO guideline and EMA authorisation are both based entirely on RCT data. RCTs are valuable to provide reliable evidence for efficacy of new medicines, but there remains a possibility to examine observational evidence [16]. To our knowledge, there are currently no published RCTs directly comparing tocilizumab and remdesivir and only one RCT directly comparing baricitinib and tocilizumab [17]. Observational evidence can be used to fill this gap in direct comparison, as medicines which may not be directly compared in an RCT setting could be used alongside each other in a real-world situation [18]. Additionally, evidence of treatment effect in the real world is an important addition to evidence obtained from RCTs to reflect the application of treatments in daily care and in a more general population [19].

As such, the incorporation of both randomised evidence and non-randomised evidence is of growing interest in the decision-making process for HTA and regulators. However, there is a relative lack of guidance and use cases to demonstrate the feasibility of such methodology [20]. This study acts as a use case for the collection of non-randomised evidence through the EHDEN network and synthesis of such observational evidence with RCT data.

2. Methods

This study investigates the effectiveness of remdesivir and tocilizumab in hospitalised patients with a COVID-19 diagnosis. Aggregate data were retrieved from randomised trials and pooled using meta-analysis methods. Additionally, aggregate data from hospital registries participating in EHDEN were analysed and results were synthesised with the randomised evidence.

2.1 Randomised Evidence

Eligible trials were extracted from the following sources: published NMAs by Selvarajan *et al.* and Siemieniuk *et al.* that used RCT data to estimate drug treatment effects for COVID-19 [6], [8], the COVID-NMA Initiative [21], and trials registered on clinicaltrials.gov.

The COVID-NMA Initiative is an international initiative, led by Cochrane France and the Centre of Research in Epidemiology and Statistics at the University of Paris, which produces a living mapping of trials, results, and bias assessments including pharmacological treatments until December 2022. Searches were conducted using the search terms *"remdesivir"* and *"tocilizumab"*.

Clinicaltrials.gov is a global database of publicly and privately funded clinical trials and was searched including results until May 2023. A search was conducted with the search term *Condition: "COVID-19"*, and other search terms *"remdesivir" or "tocilizumab"*, and filters *Recruitment: "Completed"* and *Study Type: "Interventional"* applied.

Trials were included in this study if the patient population included hospitalised COVID-19 patients, active treatment was remdesivir or tocilizumab, comparator treatment was placebo or standard care, short-term mortality data was available, and the trial was published.

For included trials, a risk of bias score was extracted from the COVID-NMA Initiative if available, and otherwise from the published NMA by Siemieniuk *et al*. COVID-NMA assessed trials according to the Cochrane RoB-2 tool, while Siemieniuk *et al.* assessed trials according to a modified version of the Cochrane RoB-2 tool plus GRADE. When neither source assessed a risk of bias, a risk of bias assessment was conducted for this study according to the Cochrane RoB-2 tool.

Mortality data (number of deaths and number of subjects in each arm) were extracted from included trials and used in a Bayesian NMA between remdesivir, tocilizumab, and standard care/placebo. In trials for which different lengths of treatment courses were separated (e.g. 5 days of treatment with remdesivir vs 10 days of treatment with remdesivir), treatment arms of the same treatment with different course length were combined to align with other trials.

In line with the work of Siemieniuk *et al.*, the Bayesian NMA was conducted using a random-effects model with 3 Markov chains with 100,000 iterations after an initial burn-in of 10,000 and a thinning of 10 to produce an odds ratio for short-term mortality. This was performed using the gemtc and rjags packages in R 4.2.1. A prior distribution was not specified and no selections were made for variance structure or multi-arm trial handling. The package gemtc sets the prior distribution, variance structure, and multi-arm trial handling automatically. Trace plots, Gelman plots, and Gelman potential scale reduction factor were used to assess model fit.

Sensitivity analyses were conducted to assess the effects of not including certain trials, such as those with no mortality or shorter lengths of follow-up. Another sensitivity analysis included only results with concomitant use of corticosteroids and tocilizumab. Additionally, analyses were conducted to include only the trials within each published NMA and to recreate the separation of remdesivir treatment lengths within Selvarajan *et al*.

Reporting of this NMA was assessed according to the PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis [22].

2.2 Non-randomised Evidence

We implemented a retrospective, multinational comparative cohort study using the new user, active comparator design. Aggregate data were obtained through EHDEN (the European Health Data and Evidence Network), a shared data network in which partners each map their data to the OMOP CDM standard to facilitate data access. The software ATLAS, an open-source tool produced by OHDSI, was used to produce a study code package compatible with the data format of any participating centres. A full version of the study package is available online: https://atlas-demo.ohdsi.org/#/estimation/cca/587.

The study protocol was shared with all data partners within EHDEN, and interested data holders were approached to perform the feasibility step of running Cohort Diagnostics. This feasibility process involved running a shortened version of the study package which populated relevant study cohorts using data from the database and created aggregate statistics on populated cohorts. This allowed the identification of sites with data that met the cohort requirements coded within the study package. These sites were eligible to participate in the study and were then provided with the full study package to run. If necessary, sites were provided with a modified version of the study package which included code only for comparisons among cohorts for which the site database contained data.

2.2.1 Patient Inclusion Criteria

This study focused on hospitalised patients diagnosed with COVID-19. Patients were included if they were aged 18 or over at cohort entry, had at least 365 days of continuous observation time prior to cohort entry, had 0 prior exposures to index treatment in the 365 days prior to index, had at least 1 COVID-19 diagnosis or positive test results in the 30 days prior to or on index, and were hospitalised on index, defined by an inpatient visit with an admission date in the 30 days prior to or on index and no corresponding discharge date prior to or on index. Index date was defined by the first prescription/dispensation of a treatment, without prior exposure in the past 365 days.

Specific ATLAS definitions for each treatment are described in *Appendix 6.2*.

Patients were eligible for the subgroup analysis if they received at least 1 intensive service (mechanical ventilation OR tracheostomy OR ECMO) in the 30 days prior to or on index (ICU subgroup), had a drug exposure of corticosteroids in the 30 days prior to or on index (corticosteroids subgroup), or received oxygen therapy in the 30 days prior to or on index (oxygen subgroup).

2.2.2 Exposures

The key exposures of this study are treatment for COVID-19 using baricitinib, remdesivir, tocilizumab, aspirin, or heparin.

Specific ATLAS definitions for each treatment are described in *Appendix 6.3*.

2.2.3 Outcomes

Effectiveness outcomes included 30-day all-cause mortality and length of hospital stay (measured by time until discharge from hospital). Safety outcomes included sepsis, respiratory tract infection, venous thromboembolic (pulmonary embolism and deep vein thrombosis) events, and total cardiovascular disease events. These safety outcomes were selected as common safety outcomes in clinical trials focused on the target exposures.

Specific ATLAS definitions for each outcome are contained in *Appendix 6.4*.

2.2.4 Negative Controls

91 potential negative control outcomes were defined based on earlier research by multinational network comparative cohort COVID-19 study SCYLLA [23].

All negative controls and specific ATLAS definitions for each negative control are contained in *Appendix 6.5*.

2.2.5 Covariates

Two sets of confounders were predefined according to clinician input and evidence from the literature. The first set includes age and sex, while the second set is more extensive and includes the Charlson Comorbidity Index score and sex. The Charlson Comorbidity Index assigns patients a score according to age and a predefined set of comorbidities: myocardial infarction, CHF, peripheral vascular disease, CVA or TVA, dementia, COPD, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe CKD, solid tumor, leukemia, lymphoma, AIDS.

All values for covariates were expected to be available in EHDEN data, including comorbidity values. The absence of a value for a comorbidity measurement was assumed to correspond with non-presence of that comorbidity, so no missing values were expected or imputed.

2.2.6 Follow-up

In the observational evidence, two periods of follow-up were considered for all outcomes. In the fixed 30-day time-at-risk analysis, the analysis follow-up started 1 day after therapy initiation and continued up until the first of: 30 days after therapy initiation, death, or end of observation period. In the on-treatment analysis, the analysis follow-up started 1 day after therapy initiation and continues until the first of: discontinuation of treatment, death, or end of observation period.

2.2.7 Data Analysis

Treatment effect was estimated using 2 approaches: logistic regression and cox proportional hazards regression. For both models, propensity score matching was used to adjust for confounders.

Propensity score matching was conducted with a caliper of 0.2 on a standardized logit scale. Each comparator was matched to a person in the treatment arm with no maximum applied for the number of each comparator to be matched to each person in the treatment arm. Cohorts were not trimmed based on the propensity score distribution and regularization was not used when fitting the propensity model.

Propensity scores were estimated based on the baseline covariates recorded on the day of hospitalisation. These values were not expected to vary over the course of the study as all covariates measure long-term conditions.

2.2.8 Critical Appraisal

The ROBINS-I Risk of Bias tool was used to assess risk of bias in the collected non-randomised evidence [24]. Calculation of an E-value was used to assess the potential impact of unmeasured confounding and performed using the EValue package in R 4.2.1 [25].

2.3 Synthesis of Evidence

Synthesis of evidence was conducted in alignment with an ISPE-approved framework for the synthesis of non-randomised studies and RCTs [16]. The non-randomised evidence was first appraised through the Cochrane ROBINS-I Risk of Bias assessment tool to ensure it was of high enough quality and fit for the purpose of combination with RCT evidence. The framework was then applied to assess which method should be used to combine the randomised and non-randomised evidence.

3. Results

3.1 Randomised Evidence

177 trials were identified and 21 trials (including 15,246 patients) were included in the network meta-analysis (Fig. 1). Characteristics of included trials are summarised in Table I.

Risk of bias assessments extracted from the COVID-NMA Initiative for each trial are shown in Fig. 2. Three studies ([26], [27], [28]) were not assessed by COVID-NMA and so risk of bias assessments were extracted from Siemieniuk *et al*. For these three studies, the terms "some concerns–probably high" and "some concerns–probably low" were converted to "some concerns" to conform to the Cochrane RoB-2 standard. One study [29] was not critically appraised by COVID-NMA Initiative or Siemieniuk *et al.* and so a new critical appraisal was conducted for this study according to the Cochrane RoB-2 standards. Only one study [30] was found to be at high risk of bias for one category (bias due to deviations from standard intervention), and all other studies were assessed as "low" or "some concerns" across all domains.

A heterogeneity plot of included trials is shown in Fig. 3. There was no considerable heterogeneity: I^2 = 0% for the remdesivir trials and I^2 = 17% for the tocilizumab trials.

Fig. 1: *PRISMA flowchart delineating the study selection for network meta-analysis*

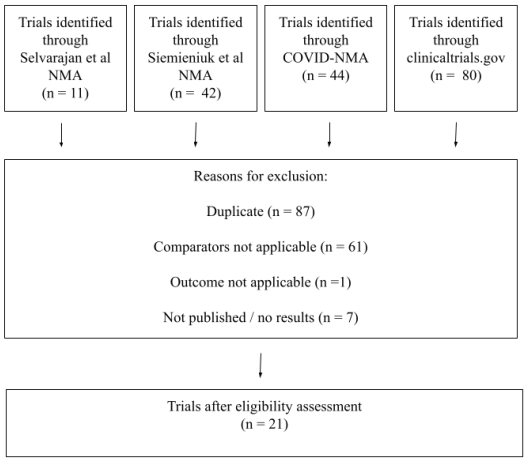


Fig. 4 shows the network plot and Fig. 5 shows the calculated odds ratio for short-term mortality among remdesivir and tocilizumab users vs standard care and for remdesivir users vs tocilizumab users. There is not evidence of a treatment effect difference between remdesivir and tocilizumab from the RCT data.

Sensitivity analyses considering the following subgroups of trials were conducted: 19/21 trials with calculable OR in all arms (at least 1 death in all arms), 19/21 trials with follow-up period of 28-30 days, 20/21 trials included in Siemieniuk *et al.* BMJ review, 10/21 trials included in Selvarajan *et al.* review, 10/21 trials plus separation of remdesivir treatment time as included in Selvarajan *et al.* review, 16/21 trials with corticosteroid data for comparison of remdesivir vs tocilizumab with corticosteroids. The corticosteroid sensitivity analysis included 16 studies total: all 8 remdesivir studies plus the 8/12 tocilizumab studies which included information on mortality among patients receiving corticosteroids.

Results of sensitivity analyses are presented in Table II. Sensitivity analyses showed no evidence of a treatment effect difference between remdesivir and tocilizumab.

TABLE I: *RCTs included in this study (M (days) = All-cause mortality follow-up time (days), Risk of Bias: Randomization, Deviations from intervention, Missing outcome data, Measurement of outcome, Selection of reported results)*

First Author	Treatments	Patient Population	Enrollment Period	M (days)	Published NMA Inclusion
Ader [31]	Remdesivir for 10 days vs Standard Care	Hospitalized patients with COVID-19 and evidence of pneumonia or need for supplemental oxygen	Mar 2020 to Jan 2021	28	Siemieniuk *et al.*
Beigel (ACTT-1) [32]	Remdesivir up to 9 days vs Placebo	Hospitalized patients with COVID-19	Feb to April 2020	28	Siemieniuk *et al.* and Selvarajan *et al.*
Criner [26]	Remdesivir for 5 days vs 10 days vs Standard Care	Hospitalized patients with COVID-19 and peripheral oxygen saturation 93% on ambient air or respiratory rate 30/min	Aug 2020 to June 2021	28	Siemieniuk *et al.*
Islam [29]	Remdesivir vs Standard Care	Hospitalized patitents with moderate COVID-19 (pulmonary infiltrates and room-air saturation 94%)	Mar to May 2020	10	N/A
Mahajan [33]	Remdesivir for 5 days vs Standard Care	Hospitalized patients with COVID-19 and respiratory distress (30 breaths/min) or finger oxygen saturation 93% at rest or arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) 300 mmHg.	Sep 2020 to Mar 2021	14	Siemieniuk *et al.*
Pan (WHO Solidarity) [34]	Remdesivir for 9 days vs Standard Care	Hospitalized patients with COVID-19	June to Dec 2020	24	Siemieniuk *et al.* and Selvarajan *et al.*
Spinner [35]	Remdesivir 5 days vs 10 days vs Standard Care	Hospitalized patients with COVID-19	March to Oct 2020	28	Siemieniuk *et al.* and Selvarajan *et al.*
Wang [36]	Remdesivir for 10 days vs Placebo	Hospitalized patients with moderate COVID-19 (pulmonary infiltrates and ambient oxygen 94%)	March to April 2020	28	Siemieniuk *et al.* and Selvarajan *et al.*
Broman [37]	Tocilizumab vs Standard Care	Hospitalized patients with severe COVID-19 (ambient oxygen 94% and evidence of pneumonia)	Feb to March 2020	28	Siemieniuk *et al.*
Declerq [38]	Tocilizumab vs Standard Care	Hospitalized patients with COVID-19 and P:F ratio 350 mm Hg on room air or 280 mm Hg on supplemental oxygen and bilateral pulmonary infiltrates	April to Dec 2020	28	Siemieniuk *et al.*
Gordon (REMAP-CAP) [39]	Tocilizumab vs Standard Care	Hospitalized patients with COVID-19 in ICU	March to Nov 2020	28	Siemieniuk *et al.*
Hermine [40]	Tocilizumab vs Standard Care	Hospitalized patients with COVID-19 and moderate or severe pneumonia	March to April 2020	28	Siemieniuk *et al.* and Selvarajan *et al.*
Horby (RECOVERY) [41]	Tocilizumab vs Standard Care	Hospitalized patients with severe COVID-19 (oxygen saturation 92% on air or requiring oxygen therapy and evidence of systemic inflammation)	April 2020 to Jan 2021	28	Siemieniuk *et al.*
Rosas (COVACTA) [42]	Tocilizumab vs Placebo	Hospitalized patients with severe COVID-19 (ambient oxygen 93%)	April to May 2020	28	Siemieniuk *et al.* and Selvarajan *et al.*
Rutgers [43]	Tocilizumab vs Standard Care	Hospitalized COVID-19 patients in need of supplemental oxygen	April 2020 to Jan 2021	30	Siemieniuk *et al.*
Salama (EMPACTA) [30]	Tocilizumab vs Placebo	Hospitalized patients with COVID-19 (ambient oxygen 94% but not receiving mechanical ventilation)	May to Aug 2020	28	Siemieniuk *et al.* and Selvarajan *et al.*
Salvarani [27]	Tocilizumab vs Standard Care	Hospitalized patients with COVID-19 pneumonia	March to June 2020	30	Siemieniuk *et al.* and Selvarajan *et al.*
Soin (COVINTOC) [44]	Tocilizumab vs Standard Care	Hospitalized patients with moderate to severe COVID-19	May to Aug 2020	28	Siemieniuk *et al.*
Stone [28]	Tocilizumab vs Placebo	Hospitalized patients with severe COVID-19 (at least two of the following: fever, pulmonary infiltrates, need for supplemental oxygen to maintain oxygen 92%)	April to June 2020	28	Siemieniuk *et al.* and Selvarajan *et al.*
Talaschian [45]	Tocilizumab vs Standard Care	Hospitalized patients with severe COVID-19 (Elevated C-reactive protein or IL-6 or lymphopenia and blood oxygen saturation 93% or respiratory rate higher than 24, not connected to mechanical ventilator)	July to Oct 2020	28	Siemieniuk *et al.*
Veiga [46]	Tocilizumab vs Standard Care	Hospitalized patients with severe or critical COVID-19 (pulmonary infiltrates, need for supplemental oxyen to maintain oxygen 93%)	May to July 2020	28	Siemieniuk *et al.* and Selvarajan *et al.*

Fig. 2: *Risk of Bias for Included Studies. All assessments by COVID-NMA Initiative except those indicated. * : assessment by Siemieniuk et al. ^ : assessed for this study.*

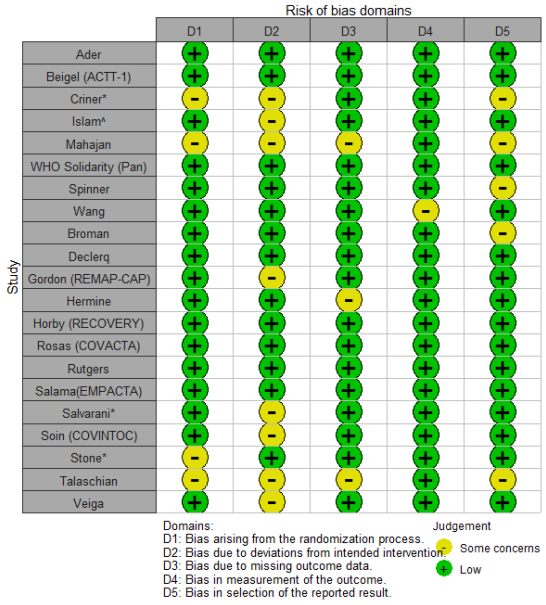
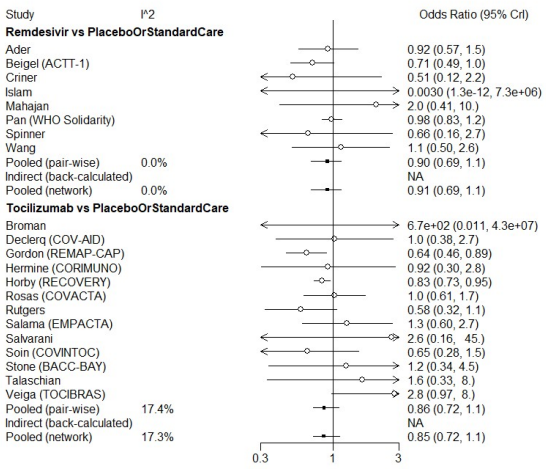


Fig. 3: *Analysis of Heterogeneity*



Results of the PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis are presented in *Appendix 6.6*.

3.2 Non-randomised Evidence

A total of six data partners attempted to run the Cohort Diagnostics phase of data collection to confirm data availability within their databases. Of these, two were unable to run the diagnostics, one found their database did not contain appropriate data, one found their database inappropriately

Fig. 4: *Network Plot*

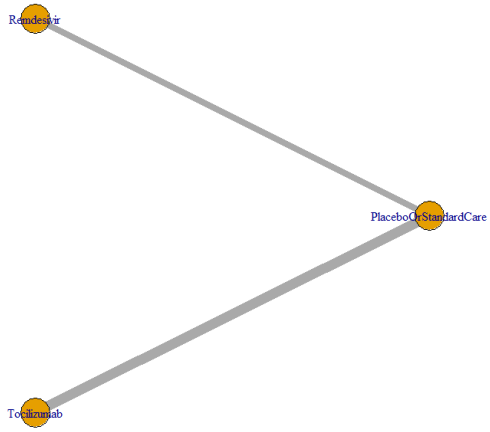
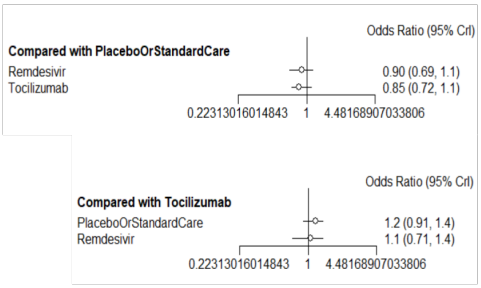


Fig. 5: *NMA Results for Short-term All-cause Mortality*



mapped to the common data model, and two passed the Cohort Diagnostics phase with appropriate data mapped to the common data model. One of these hospitals was unable to complete administrative approval to run the analysis within the set timeframe, and one data partner fully completed the study.

There are currently four data partners still attempting completion of this study, of which one has yet to begin Cohort Diagnostics, two are attempting to run Cohort Diagnostics, and one is awaiting administrative approval to run the full study package.

The following data partner fully completed the study: Hospital del Mar (Spain). From the five target treatments, hospitalised patients with COVID-19 at this site received only remdesivir or tocilizumab. Additionally, only data for patients in the main study group was available, so no subgroup analysis was conducted. There were no negative control outcomes with computable p-values in the collected data, so negative control

TABLE II: *Sensitivity Analyses for Short-term All-cause Mortality. P/SC: Placebo or Standard Care*

Analysis		Odds Ratio vs P/SC	Odds Ratio vs tocilizumab
All 21 trials			
	Remdesivir	0.90 (0.69, 1.1)	1.1 (0.72, 1.4)
	Tocilizumab	0.86 (0.72, 1.1)	
19/21 trials with mortality in all arms	Remdesivir	0.90 (0.70, 1.1)	1.1 (0.73, 1.4)
	Tocilizumab	0.85 (0.75, 1.1)	
19/21 trials with 28-30 day follow-up	Remdesivir	0.89 (0.67, 1.1)	1.0 (0.68, 1.4)
	Tocilizumab	0.85 (0.71, 1.1)	
20/21 trials included in Siemieniuk *et al.*	Remdesivir	0.90 (0.68, 1.2)	1.0 (0.69, 1.4)
	Tocilizumab	0.88 (0.72, 1.2)	
10/20 trials included in Selvarajan *et al.*	Remdesivir 10 days	0.90 (0.61, 1.3)	0.72 (0.40, 1.2)
	Remdesivir 5 days	0.63 (0.27, 1.4)	0.50 (1.9, 1.2)
	Tocilizumab	1.2 (0.83, 1.9)	
Selvarajan results	Remdesivir 10 days	0.78 (0.59, 1.03)	0.66 (0.44–0.99)
	Remdesivir 5 days	0.95 (0.50, 1.78)	0.80 (0.40–1.61)
	Tocilizumab	1.18 (0.88, 1.58)	
Tocilizumab among corticosteroids	Remdesivir	0.90 (0.68, 1.2)	1.1 (0.67, 1.5)
	Tocilizumab in corticosteroids users	0.82 (0.65, 1.2)	

outcomes were not used as study diagnostic criteria.

Table III shows baseline characteristics of patients included in each treatment group in Hospital del Mar. 153 patients were included in the remdesivir group and 322 patients were included in the tocilizumab group. Before propensity score adjustment, the remdesivir group included a similar amount of female patients, a lower percentage of patients aged 55+, and overall lower prevalence of relevant comorbidities compared to the tocilizumab group.

TABLE III: *Baseline Table, Hospital del Mar*

		Remdesivir (n = 153)	**Tocilizumab (n = 322)**
Gender	F	37.9%	33.5%
Age Group	20-34	2.5%	2.10%
	35-39	5.9%	1.90%
	40-44	5.9%	3.40%
	45-49	4.6%	5.60%
	50-54	11.8%	5.90%
	55-59	7.8%	9.90%
	60-64	9.8%	11.80%
	65-69	7.8%	11.20%
	70-74	10.5%	15.20%
	75-79	10.5%	12.10%
	80-84	9.8%	9.60%
	85-89	9.8%	7.80%
	90-94	3.3%	2.80%
	95-99	0.0%	0.60%
Condition	Diabetes Mellitus	34.5%	37.3%
	Obesity	14.3%	16.3%
	Heart Disease	22.1%	26.7%

Tables IV and V show results obtained from comparison of the remdesivir group with the tocilizumab group within Hospital del Mar, including only analyses with enough patients and observed outcomes to generate an odds ratio and p-value. These results indicate lower odds of mortality among the remdesivir group compared to the tocilizumab group. Among the calculable safety outcome results, there was no evidence of a difference in cardiovascular events and respiratory tract infection among the remdesivir group compared to the tocilizumab group. The E-values indicate that at the point estimates, unmeasured confounders would need to be associated with both the treatments and mortality by a risk ratio of at least 2.5 to nullify the calculated effect estimate. At the upper bound of each effect estimate, unmeasured confounders would need to be associated with the treatments and mortality by a risk ratio of at least 1.66 to nullify the calculated effect estimate.

For other specified outcomes, it was not possible to compute an odds ratio or p-value due to lack of outcomes in both groups (length of stay, sepsis, and venous thromboembolic events). In the case of length of stay, the lack of outcome data is likely due to differences in the study definition and hospital definition for the given outcome. Because results for only one major outcome were able to be calculated, no correction for multiple testing has been applied.

Table VI shows results of a risk of bias assessment for this data collection using the Cochrane ROBINS-I tool. This assessment found the non-randomised evidence collection to be at low to moderate risk of bias, out of four possible categories: low, moderate, serious, or critical. This indicates the non-randomised evidence collection methods should provide data that are internally valid and fit for combined analysis with RCTs.

The framework for combination of randomised and non-randomised evidence also asks researchers to assess external validity [16]. Because the current non-randomised evidence comes from just one hospital, it is unclear whether the results are applicable to all hospitalised COVID-19 patients. There is a limited population size and therefore the study may suffer from small-study effects. As such, the available non-randomised evidence is not considered to be feasible for use in meta-analysis under the ISPE framework and thus no meta-analysis was performed.

3.3 Synthesis of Evidence

When more observational evidence is available, application of the ISPE-endorsed framework suggests this scenario to be a medium-evidence bar situation in which non-randomised evidence provides additional complementary information about the effectiveness and safety of medical interventions. Future work should include a three-level hierarchical model in which data is first synthesized by evidence type and then combined between types, leading to three levels: individual study results, results synthesized among one study type, and results synthesized with both randomised and non-randomised evidence.

TABLE IV: *30-day All-cause Mortality, Remdesivir vs Tocilizumab, Hospital del Mar. (OR = odds ratio, HR = Hazard Ratio, LB = lower bound of confidence interval, UB = upper bound of confidence interval, 30 Days = 30 day follow-up period, LR = logistic regression, CPH = Cox Proportional Hazards, (PE, UB) = E-value at Point Estimate, E-value at Upper Bound)*

Analysis	OR/HR	LB, UB	P	E-value (PE, UB)
30 Days, LR, Age + Sex	0.38	0.20, 0.69	0.002	2.63, 2.26
30 Days, LR, CCI + Sex	0.39	0.20, 0.67	0.002	2.58, 1.74
30 Days, CPH, Age + Sex	0.41	0.22, 0.71	0.003	2.50, 1.66
30 Days, CPH, CCI + Sex	0.40	0.22, 0.70	0.002	2.54, 1.68

TABLE V: *Safety Outcomes, Remdesivir vs Tocilizumab, Hospital del Mar. (OR = odds ratio, LB = lower bound of confidence interval, UB = upper bound of confidence interval, 30 Days = 30 day follow-up period, LR = logistic regression.)*

Analysis	OR/HR	LB, UB	P
Cardiovascular Events, 30 Days, LR, Age + Sex	2.10	0.08, 53.38	0.65
Cardiovascular Events, 30 Days, LR, CCI + Sex	2.07	0.08, 52.63	0.66
Cardiovascular Events, 30 Days, CPH, Age + Sex	1.94	0.08, 48.98	0.69
Cardiovascular Events, 30 Days, CPH, CCI + Sex	1.92	0.08, 48.59	0.69
Respiratory Tract Infection, 30 Days, LR, Age + Sex	0.94	0.04, 10.16	0.97
Respiratory Tract Infection, 30 Days, LR, CCI + Sex	0.81	0.04, 8.70	0.88
Respiratory Tract Infection, 30 Days, CPH, Age + Sex	0.78	0.04, 8.12	0.86
Respiratory Tract Infection, 30 Days, CPH, CCI + Sex	0.66	0.03, 6.89	0.76

This step should be completed after the collection of more non-randomised evidence.

This paper conducts a qualitative comparison instead as there is currently a limited set of non-randomised evidence available, including data from just one hospital.

The non-randomised evidence showed lower odds of mortality among remdesivir users compared to tocilizumab users, while the randomised evidence did not show a treatment effect difference. Additionally, the point estimate direction of treatment effect was different between the non-randomised and randomised evidence.

The non-randomised evidence includes a much smaller population (N = 475) compared to the randomised evidence (N = 15,246). Additionally, the non-randomised evidence also includes patients with treatment dates over a wider timespan than the randomised evidence, as the inclusion criteria for non-randomised evidence included dates of treatment from March 2020 to December 2022 while inclusion criteria for randomised evidence included various windows between March 2020 and June 2021. While both the non-randomised and randomised evidence include hospitalised patients with COVID-19, some trials included in the randomised evidence restrict their populations to only patients with more severe COVID-19. There may be different proportions of baseline severities among patients included in the randomised and non-randomised evidence, which could explain part of the observed differences.

TABLE VI: *Results of ROBINS-I Risk of Bias tool to assess risk of bias in non-randomised studies*

Domain	Result	Explanation
Bias due to confounding	Moderate	Confounding is expected, but known important confounding domains have been appropriately measured and controlled for. Measurement of confounders is taken at baseline and is not expected to vary over the course of the intervention as confounders include age, sex, and chronic conditions.
Bias in selection of participants into the study	Low	All participants who would have been eligible for the target trial were included in the study and for each participant, start of follow-up and start of intervention coincided.
Bias in classification of interventions	Low	Intervention status is well defined and intervention definition is based solely on information collected at the time of intervention.
Bias due to deviations from intended intervention	Low	Deviations were not beyond what is expected in normal practice.
Bias due to missing data	Low	Outcome data available for almost all participants and patients were not excluded for missing data. The EHDEN network does not consider missing data as all data is observational and therefore non-recorded events are considered to simply be absent (ie, no diagnosis of obesity indicates not obese). In this case, the outcome mortality is unlikely to be unreported so a minimal amount of missing outcome data is expected.
Bias in measurement of outcomes	Low	Outcome measures not influenced by knowledge of intervention.
Bias in selection of the reported result	Moderate	Multiple analyses of intervention-outcome relationships and selection of subgroups.

4. Discussion

Non-randomised evidence suggests remdesivir is more effective than tocilizumab with regards to prevention of short-term mortality, while randomised evidence does not indicate a difference in treatment effect. Thus the evidence generated by this study is inconclusive.

As there are only data from one participating hospital, the non-randomised evidence may be affected by small-study effects and confounding. To best moderate confounding, an ideal analysis model would include age, sex, obesity, and other underlying comorbidities including heart disease, diabetes, renal diseases, and cancer, as these have been shown to have a strong effect on mortality due to COVID-19 [47]. Within this study, the strong confounders age, sex, diabetes, renal diseases, and some forms of cancer have been controlled for either explicitly or through their inclusion in the Charlson Comorbidity Index (CCI), but obesity and heart disease were not included in either propensity model as it was not possible within the available software. However, as shown in Table III, there is not a large difference between the remdesivir group and tocilizumab group in prevalence of obesity and heart disease. The similarity in results between the model which includes Age and Sex as confounders and the model which includes Age and CCI as confounders also suggests the results are not highly sensitive to the selected confounders.

Another possible confounding factor is that remdesivir is indicated for both severe and non-severe COVID-19, while tocilizumab is indicated only for severe COVID-19 [12]. Because this study focused only on hospitalised patients, baseline severity should have been high enough for all included patients to meet the indication for both remdesivir and tocilizumab. However, it is possible that within the included hospital site patients with less severe illness still received remdesivir at a higher rate than tocilizumab, which would lead to a lower rate of mortality among the remdesivir group.

The E-values for the non-randomised results indicate that an unmeasured confounder must be associated with both the treatments and short-term mortality by a risk ratio of at least 2.50 to nullify the results of the analysis with the least strong effect estimate, or at least 2.63 to nullify the results of the analysis with the strongest effect estimate. There is no cutoff for minimum E-value to consider a calculated association safe from unmeasured confounding, but this E-value is relatively close to 1 and suggests that an unmeasured confounder would not need to have an extremely strong association in order to produce confounding bias equal to the observed OR. It is potentially plausible that unmeasured confounding could be driving the observed treatment effect difference.

Additionally, because this study used routinely recorded data mapped to the OMOP CDM, it is possible that that not all data was accurately recorded within the CDM. The absence of a record of a condition (for example, absence of a cancer diagnosis) was considered to be absence of such condition, but may instead reflect a missed record entry or mismapping.

A limitation for the non-randomised evidence is the lack of direct evidence, as there were no RCTs directly comparing remdesivir and tocilizumab. Also, differences in which comparator treatments were considered "placebo" and "standard care" among different trials were not considered in this NMA, although standard care for COVID-19 actually varied by location and over time. Additionally, while all included trials focused on hospitalised patients with COVID-19, some trials further restricted their population to patients meeting certain criteria for severity. More trials in the tocilizumab group made this restriction than in the remdesivir group.

The time of treatment for included patients in this study also varies both within the randomised evidence and between the randomised and non-randomised evidence. Because dominant COVID strains vary throughout time and relative treatment effectiveness may vary per strain, calculated treatment effect estimates may not be comparable.

A key limitation of this study was the lack of non-randomised data availability. Although over six data partners were interested in the study, only six reached the first study phase of Cohort Diagnostics and only one was able to participate through the full analysis. The lack of a larger pool of non-randomised evidence limited the ability to combine non-randomised and randomised evidence types and so only a more appropriate qualitative synthesis was conducted. This limitation highlights the need for more streamlined data collection processes through the EHDEN network.

Although this study was not able to quantitatively combine non-randomised and randomised evidence, it does have other strengths. The observational data in this study was able to directly compare remdesivir and tocilizumab, which has not been done by any other published work. The use of real-world data provided evidence in the context of real, daily practice, which is not possible through RCTs. This use case ultimately demonstrated the feasibility of collecting data through the EHDEN network to supplement RCT data, and the process of data collection allowed participating hospitals to develop or improve data retrieval processes that will help facilitate future research.

Additionally, the NMA conducted for this study included updated trials in comparison to previously published NMAs. The comparison of remdesivir versus tocilizumab is a novel comparison which complements earlier studies that either separated remdesivir into two treatment courses (5 days versus 10 days), or combined tocilizumab with other IL-6 receptors and corticosteroids to produce treatment effect estimates.

The NMA by Siemieniuk *et al.* does not compare remdesivir versus tocilizumab, but instead estimates the relative treatment effect between remdesivir versus IL-6 receptor antagonists as a group (tocilizumab and sarilumab combined). The results in this NMA align with that of Siemieniuk *et al.*, as neither find evidence of a treatment effect difference between remdesivir and IL-6 receptor antagonists. The NMA by Siemieniuk *et al.* rates this comparison as "low evidence quality", showing that more investigation is valuable.

Unlike the work of Siemieniuk *et al.*, this study does not find a significant difference when considering concomitant

corticosteroid use. Because the comparison in this NMA only considers tocilizumab and not all IL-6 receptor antagonists, there is less available evidence and thus it is more difficult to show significance.

Future work will focus on the recruitment of more hospitals to produce a larger sample of non-randomised evidence. Additionally, further subgroup analyses which focus on patients receiving corticosteroids will provide further complementary evidence to the results of Siemieniuk *et al.* Subgroup analyses which focus on ICU patients and patients receiving oxygen will help to mitigate the effects of baseline differences in severity of disease.

This study demonstrated the feasibility of observational data collection, but also revealed a need for more streamlined processes. Further work investigating the use of non-randomised evidence may build upon the infrastructure developed for this study at participating hospitals.

5. Conclusion

These results provide inconclusive evidence regarding the relative effectiveness of remdesivir and tocilizumab in prevention of short-term mortality among hospitalised COVID-19 patients. More evidence should be collected from hospitals to produce robust non-randomised effect estimates and facilitate the combination of randomised and non-randomised evidence types.

Still, this research demonstrates the feasibility of collecting real-world evidence through EHDEN and synthesizing this observational evidence with randomised evidence.

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6. Appendix

6.1 EMA Authorised COVID-19 Treatments

TABLE VII: *EMA-authorized COVID-19 treatments:*

Treatment	Indication from the EMA	Drug type
tixagevimab / cilgavimab	Prevention of COVID-19 in adults and adolescents. Treatment of COVID-19 in adults and adolescents who do not require supplemental oxygen and who are at increased risk of the disease becoming severe.	Monoclonal antibodies
anakinra	Treatment of COVID-19 in adults with pneumonia requiring supplemental oxygen (low or high flow oxygen) and who are at risk of developing severe respiratory failure, as determined by blood levels of a protein called suPAR (soluble urokinase plasminogen activator receptor) of at least 6 ng per ml.	IL-1 receptor antagonist
ritonavir	Treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of the disease becoming severe.	Protease inhibitor
regdanvimab	Treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of their disease becoming severe.	Monoclonal antibody
tocilizumab	Treatment of COVID-19 in adults who are receiving treatment with corticosteroid medicines by mouth or injection and require extra oxygen or mechanical ventilation (breathing assisted by a machine).	IL-6 receptor antagonist
casirivimab/imdevimab	Prevention of COVID-19 in adults and adolescents. Treatment of COVID-19 in adults and adolescents who do not require supplemental oxygen and who are at increased risk of the disease becoming severe.	Monoclonal antibodies
remdesivir	Treatment of COVID-19 in adults and children, from at least 4 weeks of age and weighing at least 3 kg, with pneumonia requiring supplemental oxygen. Treatment of COVID-19 in adults and children (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of developing severe COVID-19.	RNA Polymerase inhibitor
sotrovimab	Treatment of COVID-19 in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) who do not require supplemental oxygen and who are at increased risk of the disease becoming severe	Monoclonal antibody

6.2 COVID-19 Definitions

Presence of COVID-19 is defined as a measurement of ”SARS-CoV-2 positive test measurement”, a measurement of ”SARS-CoV-2 test measurement” with the value ”Detected”, ”Positive”, or ”Present”, an observation of ”SARS-CoV-2 test measurement” with the value ”Detected”, ”Positive”, or ”Present”, or a condition occurrence of ”COVID-19 conditions”.

Concept sets for ”SARS-CoV-2 positive test measurement”, ”SARS-COV-2 test measurement, ”COVID-19 conditions” are defined below.

TABLE VIII: *SARS-CoV-2 positive test measurement (ATLAS Concept Set ID: 1870583*

Concept	Concept ID
Severe acute respiratory syndrome coronavirus 2 detected	37310282

TABLE IX: *SARS-CoV-2 test measurement (ATLAS Concept Set ID: 1870584*

Concept	Concept ID
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	756055
EXCLUDED: Severe acute respiratory syndrome coronavirus 2 not detected	37310281

TABLE X: *COVID-19 conditions (ATLAS Concept Set ID: 1870581*

Concept	Concept ID
Suspected COVID-19	37311060
Disease due to Coronaviridae	4100065
COVID-19	37311061
Coronavirus infection	439676

6.3 Exposures

Aspirin, Baricitinib, Heparin, Remdesivir, and Tocilizumab were defined by the following concept sets within ATLAS.

TABLE XI: *Exposure definitions in ATLAS:*

Exposure	Included Concept Name	Concept ID
Aspirin		
	Aspirin	1112807
Baritinib		
	baricitinib	958843
	baricitinib	1510627
	Baricitinib	43045764
	Baricitinib	3198592
	Baricitinib	37103776
	Baricitinib	37111518
	Baricitinib	40701753
	baricitinib 1 MG	37497352
	baricitinib 1mg/1 / 2mg/1 ORAL TABLET, FILM COATED [olumiant]	36108881
	baricitinib 1mg/1 / 2mg/1 ORAL TABLET, FILM COATED [olumiant]	37295866
	baricitinib 1mg/1 / 2mg/1 ORAL TABLET, FILM COATED [olumiant]	1207952
	baricitinib 1mg/1 / 2mg/1 ORAL TABLET, FILM COATED [olumiant]	1184818
	baricitinib 1mg/1 / 2mg/1 ORAL TABLET, FILM COATED [olumiant]	43557203
	baricitinib 1mg/1 ORAL TABLET, FILM COATED	36108952
	baricitinib 1 MG [Olumiant]	37497354
	baricitinib 1 MG Oral Tablet	37497353
	baricitinib 1 MG Oral Tablet [Olumiant]	36109358
	baricitinib 1 MG Oral Tablet [Olumiant]	37497355
	baricitinib 2 MG	1510628
	baricitinib 2mg/1 ORAL TABLET, FILM COATED	36189182
	baricitinib 2mg/1 ORAL TABLET, FILM COATED [olumiant]	36160510
	baricitinib 2 MG Delayed Release Oral Tablet	36787582
	baricitinib 2 MG Delayed Release Oral Tablet Box of 28	36787581
	baricitinib 2 MG Delayed Release Oral Tablet Box of 84	36787580
	baricitinib 2 MG Delayed Release Oral Tablet Box of 98	42875510
	baricitinib 2 MG Delayed Release Oral Tablet [Olumiant]	36787579
	baricitinib 2 MG Delayed Release Oral Tablet [Olumiant] Box of 28	36787578
	baricitinib 2 MG Delayed Release Oral Tablet [Olumiant] Box of 28 by Eli Lilly	36787577
	baricitinib 2 MG Delayed Release Oral Tablet [Olumiant] Box of 28 by Orifarm Leverkus	42875511
	baricitinib 2 MG Delayed Release Oral Tablet [Olumiant] Box of 84	36787576
	baricitinib 2 MG Delayed Release Oral Tablet [Olumiant] Box of 84 by Eli Lilly	36787575
	baricitinib 2 MG Delayed Release Oral Tablet [Olumiant] Box of 98	42875512
	baricitinib 2 MG Delayed Release Oral Tablet [Olumiant] Box of 98 by Cc	42875513

TABLE XI: *Exposure definitions in ATLAS:*

Exposure	Included Concept Name	Concept ID
	baricitinib 2 MG Delayed Release Oral Tablet [Olumiant] by Cc	36503766
	baricitinib 2 MG Delayed Release Oral Tablet [Olumiant] by Kohlpharma	36504859
	baricitinib 2 MG Delayed Release Oral Tablet [Olumiant] by Orifarm Leverkus	36504599
	baricitinib 2 MG Delayed Release Oral Tablet [Olumiant] by Paranova Pack	36508742
	baricitinib 2 MG [Olumiant]	1510634
	baricitinib 2 MG Oral Tablet	1510632
	baricitinib 2 MG Oral Tablet Box of 28	44187244
	baricitinib 2 MG Oral Tablet Box of 84	36787574
	baricitinib 2 MG Oral Tablet Box of 98	44187243
	baricitinib 2 MG Oral Tablet [Olumiant]	36175651
	baricitinib 2 MG Oral Tablet [Olumiant]	1510638
	baricitinib 2 MG Oral Tablet [Olumiant]	36175650
	baricitinib 2 MG Oral Tablet [Olumiant] Box of 28	44180263
	baricitinib 2 MG Oral Tablet [Olumiant] Box of 28	40743761
	baricitinib 2 MG Oral Tablet [Olumiant] Box of 28 by Eli Lilly	40743760
	baricitinib 2 MG Oral Tablet [Olumiant] Box of 28 by Lilly	44166708
	baricitinib 2 MG Oral Tablet [Olumiant] Box of 28 by Orifarm Leverkus	42875514
	baricitinib 2 MG Oral Tablet [Olumiant] Box of 84	36787573
	baricitinib 2 MG Oral Tablet [Olumiant] Box of 84 by Eli Lilly	36787572
	baricitinib 2 MG Oral Tablet [Olumiant] Box of 98	44169060
	baricitinib 2 MG Oral Tablet [Olumiant] Box of 98	36421026
	baricitinib 2 MG Oral Tablet [Olumiant] Box of 98 by Cc	42875515
	baricitinib 2 MG Oral Tablet [Olumiant] Box of 98 by Lilly	44185375
	baricitinib 2 MG Oral Tablet [Olumiant] by Abacus Medicine	994801
	baricitinib 2 MG Oral Tablet [Olumiant] by Cc	36508651
	baricitinib 2 MG Oral Tablet [Olumiant] by Eli Lilly	40743762
	baricitinib 2 MG Oral Tablet [Olumiant] by Haematogmbh	37592678
	baricitinib 2 MG Oral Tablet [Olumiant] by Kohlpharma	994802
	baricitinib 2 MG Oral Tablet [Olumiant] by Lilly	2056664
	baricitinib 2 MG Oral Tablet [Olumiant] by Orifarm Leverkus	36508730
	baricitinib 2 MG Oral Tablet [Olumiant] by Paranova Pack	36506007
	Baricitinib 2mg tablets	42523151
	Baricitinib 2mg tablets	37103890
	Baricitinib 2mg tablets	40701752
	Baricitinib 2mg tablets	42520701
	Baricitinib 2mg tablets 28 tablet	40701751
	Baricitinib 2mg tablets 28 tablet	37106183
	baricitinib 4 MG Delayed Release Oral Tablet	36787589
	baricitinib 4 MG Delayed Release Oral Tablet Box of 28	36787588
	baricitinib 4 MG Delayed Release Oral Tablet Box of 84	36787587
	baricitinib 4 MG Delayed Release Oral Tablet [Olumiant]	36787586
	baricitinib 4 MG Delayed Release Oral Tablet [Olumiant] Box of 28	36787537
	baricitinib 4 MG Delayed Release Oral Tablet [Olumiant] Box of 28 by Eli Lilly	36787585
	baricitinib 4 MG Delayed Release Oral Tablet [Olumiant] Box of 84	36787584

TABLE XI: *Exposure definitions in ATLAS:*

Exposure	Included Concept Name	Concept ID
	baricitinib 4 MG Delayed Release Oral Tablet [Olumiant] Box of 84 by Eli Lilly	36787583
	baricitinib 4 MG Delayed Release Oral Tablet [Olumiant] by Kohlpharma	36509872
	baricitinib 4 MG Oral Tablet Box of 28	44176005
	baricitinib 4 MG Oral Tablet Box of 84	40743769
	baricitinib 4 MG Oral Tablet Box of 98	44187242
	baricitinib 4 MG Oral Tablet [Olumiant] Box of 28	44187757
	baricitinib 4 MG Oral Tablet [Olumiant] Box of 28	40743766
	baricitinib 4 MG Oral Tablet [Olumiant] Box of 28 by Eli Lilly	40743765
	baricitinib 4 MG Oral Tablet [Olumiant] Box of 28 by Lilly	44189254
	baricitinib 4 MG Oral Tablet [Olumiant] Box of 84	40743764
	baricitinib 4 MG Oral Tablet [Olumiant] Box of 84 by Eli Lilly	40743763
	baricitinib 4 MG Oral Tablet [Olumiant] Box of 98	36421027
	baricitinib 4 MG Oral Tablet [Olumiant] Box of 98	44161443
	baricitinib 4 MG Oral Tablet [Olumiant] Box of 98 by Lilly	44170432
	baricitinib 4 MG Oral Tablet [Olumiant] Box of 98 by Orifarm Leverkus	42875516
	baricitinib 4 MG Oral Tablet [Olumiant] by Abacus Medicine	37592675
	baricitinib 4 MG Oral Tablet [Olumiant] by Cc	37592676
	baricitinib 4 MG Oral Tablet [Olumiant] by Eli Lilly	40743767
	baricitinib 4 MG Oral Tablet [Olumiant] by Haematogmbh	37592677
	baricitinib 4 MG Oral Tablet [Olumiant] by Kohlpharma	994803
	baricitinib 4 MG Oral Tablet [Olumiant] by Lilly	2056663
	Baricitinib 4mg tablets	40701750
	Baricitinib 4mg tablets	37104009
	Baricitinib 4mg tablets	42523077
	Baricitinib 4mg tablets	42520682
	Baricitinib 4mg tablets 28 tablet	37106363
	Baricitinib 4mg tablets 28 tablet	40701749
	Baricitinib 4mg tablets 84 tablet	42533663
	Baricitinib 4mg tablets 84 tablet	40701748
	Baricitinib-containing product	35622296
	Baricitinib-containing product in oral dose form	35622583
	baricitinib Delayed Release Oral Tablet	36787591
	baricitinib Delayed Release Oral Tablet [Olumiant]	36787590
	Baricitinib only product	36677336
	Baricitinib only product in oral dose form	36680862
	baricitinib; oral	1123897
	baricitinib Oral Product	1510629
	baricitinib Oral Tablet	1510631
	baricitinib Oral Tablet [Olumiant]	1510635
	baricitinib Pill	1510630
	Introduction of baricitinib into lower GI, via natural or artificial opening, new technology group 6	42639793
	Introduction of baricitinib into mouth and pharynx, external approach, new technology group 6	42639791
	Introduction of baricitinib into upper GI, via natural or artificial opening, new technology group 6	42639792
	OLUMIANT - baricitinib tablet, film coated	36151100
	baricitinib 4 MG [Olumiant]	44171917
	baricitinib 4 MG [Olumiant]	40743770

TABLE XI: *Exposure definitions in ATLAS:*

Exposure	Included Concept Name	Concept ID
	baricitinib 4 MG Oral Tablet [Olumiant]	40743768
	baricitinib 4 MG Oral Tablet [Olumiant]	44161444
	baricitinib 4 MG	44160497
	baricitinib 4 MG Oral Tablet	44164714
	Baricitinib	44157647
	Baricitinib 2 MG	44168096
	Baricitinib 2 MG [Olumiant]	44183141
	Baricitinib 2 MG Oral Tablet	44176006
	Baricitinib 2 MG Oral Tablet [Olumiant]	44161445
	Baricitinib Oral Tablet	44183234
	Baricitinib Oral Tablet [Olumiant]	44179594
	Baricitinib	42687705
Remdesivir		
	20 ML remdesivir 5 MG/ML Injectable Solution	36054909
	20 ML remdesivir 5 MG/ML Injectable Solution Box of 1	36054907
	20 ML remdesivir 5 MG/ML Injectable Solution Box of 1 by Gilead	36054865
	20 ML remdesivir 5 MG/ML Injectable Solution by Gilead	36054908
	20 ML remdesivir 5 MG/ML Injectable Solution [Veklury]	36054913
	20 ML remdesivir 5 MG/ML Injectable Solution [Veklury]	35896639
	20 ML remdesivir 5 MG/ML Injectable Solution [Veklury] Box of 1	35896637
	20 ML remdesivir 5 MG/ML Injectable Solution [Veklury] Box of 1	36054911
	20 ML remdesivir 5 MG/ML Injectable Solution [Veklury] Box of 1 by Gilead	35896636
	20 ML remdesivir 5 MG/ML Injectable Solution [Veklury] Box of 1 by Gilead	36054910
	20 ML remdesivir 5 MG/ML Injectable Solution [Veklury] by Gilead	36054912
	20 ML remdesivir 5 MG/ML Injectable Solution [Veklury] by Gilead	35896638
	20 ML remdesivir 5 MG/ML Injection	1146730
	20 ML remdesivir 5 MG/ML Injection [Veklury]	42796750
	20 ML remdesivir 5 MG/ML Injection [Veklury]	37003601
	20 ML remdesivir 5 MG/ML Injection [Veklury]	43550047
	Administration of remdesivir	3655983
	Introduction of Remdesivir Anti-infective into Central Vein, Percutaneous Approach, New Technology Group 5	1781305
	Introduction of Remdesivir Anti-infective into Peripheral Vein, Percutaneous Approach, New Technology Group 5	1781301
	remdesivir	37499271
	remdesivir	957768
	Remdesivir	36080271
	Remdesivir	3658363
	Remdesivir	3666998
	remdesivir 100 MG	37499272
	remdesivir 100mg/1 INTRAVENOUS INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION	35113133
	remdesivir 100mg/1 INTRAVENOUS INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION [veklury]	36395490

TABLE XI: *Exposure definitions in ATLAS:*

Exposure	Included Concept Name	Concept ID
	remdesivir 100mg/1 INTRAVENOUS INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION [veklury]	1212096
	Remdesivir 100mg/20ml concentrate for solution for infusion vials	36080272
	Remdesivir 100mg/20ml concentrate for solution for infusion vials (Gilead Sciences Ltd)	3658357
	Remdesivir 100mg/20ml concentrate for solution for infusion vials (Gilead Sciences Ltd) 1 vial	36080273
	Remdesivir 100mg/20ml concentrate for solution for infusion vials (Gilead Sciences Ltd) 1 vial	3658358
	Remdesivir 100mg/20ml solution for infusion vials	36080274
	Remdesivir 100mg/20ml solution for infusion vials	3658360
	Remdesivir 100mg/20ml solution for infusion vials 1 vial	36080275
	Remdesivir 100mg/20ml solution for infusion vials 1 vial	3658356
	remdesivir 100 MG Injectable Solution	36057821
	remdesivir 100 MG Injectable Solution Box of 1	36057819
	remdesivir 100 MG Injectable Solution Box of 1 by Gilead	36057817
	remdesivir 100 MG Injectable Solution by Gilead	36057820
	remdesivir 100 MG Injectable Solution [Veklury]	36057825
	remdesivir 100 MG Injectable Solution [Veklury]	35896882
	remdesivir 100 MG Injectable Solution [Veklury] Box of 1	36057823
	remdesivir 100 MG Injectable Solution [Veklury] Box of 1	35896880
	remdesivir 100 MG Injectable Solution [Veklury] Box of 1 by Gilead	36057822
	remdesivir 100 MG Injectable Solution [Veklury] Box of 1 by Gilead	35896879
	remdesivir 100 MG Injectable Solution [Veklury] by Gilead	36057824
	remdesivir 100 MG Injectable Solution [Veklury] by Gilead	35896881
	remdesivir 100 MG Injection	37499275
	remdesivir 100 MG Injection Box of 1	36057811
	remdesivir 100 MG Injection Box of 1 by Gilead	36057810
	remdesivir 100 MG Injection by Gilead	36057812
	remdesivir 100 MG Injection [Veklury]	42796858
	remdesivir 100 MG Injection [Veklury]	37002796
	remdesivir 100 MG Injection [Veklury]	35108592
	remdesivir 100 MG Injection [Veklury] Box of 1	36057814
	remdesivir 100 MG Injection [Veklury] Box of 1 by Gilead	36057813
	remdesivir 100 MG Injection [Veklury] by Gilead	36057815
	Remdesivir 100mg powder for concentrate for solution for infusion vials	36080276
	Remdesivir 100mg powder for concentrate for solution for infusion vials (Gilead Sciences Ltd)	3658351
	Remdesivir 100mg powder for concentrate for solution for infusion vials (Gilead Sciences Ltd) 1 vial	3658352
	Remdesivir 100mg powder for concentrate for solution for infusion vials (Gilead Sciences Ltd) 1 vial	36080277
	Remdesivir 100mg powder for solution for infusion vials	3658359
	Remdesivir 100mg powder for solution for infusion vials	36080278
	Remdesivir 100mg powder for solution for infusion vials 1 vial	36080279
	Remdesivir 100mg powder for solution for infusion vials 1 vial	3658350
	Remdesivir 100 mg powder for solution for injection vial	3655947
	remdesivir 100 MG [Veklury]	37002793

TABLE XI: *Exposure definitions in ATLAS:*

Exposure	Included Concept Name	Concept ID
	remdesivir 150 MG	36074072
	remdesivir 150 MG Injectable Solution	36057830
	remdesivir 150 MG Injectable Solution Box of 1	36057828
	remdesivir 150 MG Injectable Solution Box of 1 by Gilead	36057827
	remdesivir 150 MG Injectable Solution by Gilead	36057829
	Remdesivir 150mg powder for concentrate for solution for infusion vials	36080280
	Remdesivir 150mg powder for concentrate for solution for infusion vials (Gilead Sciences Ltd)	3658354
	Remdesivir 150mg powder for concentrate for solution for infusion vials (Gilead Sciences Ltd) 1 vial	36080281
	Remdesivir 150mg powder for concentrate for solution for infusion vials (Gilead Sciences Ltd) 1 vial	3658355
	Remdesivir 150mg powder for solution for infusion vials	36080282
	Remdesivir 150mg powder for solution for infusion vials	3658361
	Remdesivir 150mg powder for solution for infusion vials 1 vial	36080283
	Remdesivir 150mg powder for solution for infusion vials 1 vial	3658353
	remdesivir 5 MG/ML	1145689
	remdesivir 5mg/mL / 100mg/1 INTRAVENOUS INJECTION, INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION	35111796
	remdesivir 5mg/mL / 100mg/1 INTRAVENOUS INJECTION, INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION	35116409
	remdesivir 5mg/mL / 100mg/1 INTRAVENOUS INJECTION, INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION	36373377
	remdesivir 5mg/mL / 100mg/1 INTRAVENOUS INJECTION, INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION	36663421
	remdesivir 5mg/mL / 100mg/1 INTRAVENOUS INJECTION, INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION	42795619
	remdesivir 5mg/mL / 100mg/1 INTRAVENOUS INJECTION, INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION [veklury]	1212480
	remdesivir 5 MG/ML Injectable Solution	36074074
	remdesivir 5 MG/ML Injectable Solution Box of 1	36074073
	remdesivir 5 MG/ML Injectable Solution [Veklury]	35896884
	remdesivir 5 MG/ML Injectable Solution [Veklury]	36074076
	remdesivir 5 MG/ML Injectable Solution [Veklury] Box of 1	36074075
	remdesivir 5 MG/ML Injectable Solution [Veklury] Box of 1	35896883
	remdesivir 5 MG/ML Injection	1145690
	remdesivir 5 MG/ML Injection [Veklury]	37002798
	remdesivir 5mg/mL INTRAVENOUS INJECTION	35113134
	remdesivir 5 MG/ML [Veklury]	37002797
	Remdesivir-containing product	3655943
	Remdesivir-containing product in parenteral dose form	3655945
	remdesivir Injectable Product	37499273
	remdesivir Injectable Solution	36057833
	remdesivir Injectable Solution [Veklury]	36057834
	remdesivir Injectable Solution [Veklury]	35896885
	remdesivir Injection	37499274
	remdesivir Injection [Veklury]	37002794
	Remdesivir only product	3655944
	Remdesivir only product in parenteral dose form	3655946
	VEKLURY - remdesivir injection	36771140

TABLE XI: *Exposure definitions in ATLAS:*

Exposure	Included Concept Name	Concept ID
	VEKLURY - remdesivir injection	37294949
	remdesivir 100 MG Injection [Veklury]	36057816
	remdesivir 100 MG [Veklury]	36057826
	remdesivir 5 MG/ML [Veklury]	36057831
	remdesivir Injection [Veklury]	36057832
	Remdesivir	3574635
	remdesivir 5 MG/ML	36074077
	Remdesivir	32763
Tocilizumab		
	Tocilizumab	40171288

6.4 Outcomes

Outcomes are defined as cohorts within ATLAS. Each outcome cohort is defined below.

6.4.1 30-day all-cause mortality

Any death occurrence from any death. (ATLAS Cohort ID: 1779680)

6.4.2 Length of stay

A visit occurrence or observation of concept set "Discharge from Hospitalization".

TABLE XII: *Discharge from Hospitalization (ATLAS Cohort ID: 1779681)*

Set Name	Concept	Concept ID
Discharge from Hospital	Discharge from Hospital	42303130

6.4.3 Sepsis

A condition occurrence of concept set "Sepsis".

TABLE XIII: *Sepsis (ATLAS Cohort ID: 1779682)*

Set Name	Concept	Concept ID
Sepsis		
	Transient neonatal neutropenia due to neonatal bacterial sepsis	36716754
	Systemic inflammatory response syndrome	434821
	Septic shock	196236
	Sepsis-associated organ dysfunction	4031168
	Sepsis-associated lung injury	4119941
	Sepsis-associated encephalopathy	4046106
	Sepsis syndrome	4029281
	Sepsis	132797
	Puerperal septicemia - delivered with postnatal complication	4066124
	Postprocedural intra-abdominal sepsis	4204036
	Miscarriage with septic shock	4085627
	Menosepsis	4205449
	Clinical sepsis	40487101
	Acute kidney injury due to sepsis	36716312
	Acute kidney injury due to acute tubular necrosis due to sepsis	37395517

6.4.4 Respiratory tract infection

A condition occurrence of concept set "Respiratory Tract Infection".

TABLE XIV: *Respiratory Tract infection (ATLAS Cohort ID: 1779684)*

Set Name	Concept	Concept ID
Respiratory Tract Infection	Respiratory Tract Infection	4170143

6.4.5 Venous thromboembolic events

A condition occurrence of concept set "Venous Thromboembolism (pulmonary embolism and deep vein thrombosis".

TABLE XV: *Venous thromboembolic events (ATLAS Cohort ID: 1779686)*

Set Name	Concept	Concept ID
Venous Thromboembolism		
	Amniotic fluid embolism	435616
	Antepartum deep vein thrombosis	435887
	Budd-Chiari syndrome	196715
	Cerebral venous thrombosis in pregnancy	4062269
	Embolism from thrombosis of vein of lower extremity	40481089
	Obstetric air pulmonary embolism	442055
	Obstetric blood-clot pulmonary embolism	433832
	Obstetric pulmonary embolism	435026
	Obstetric pyemic and septic pulmonary embolism	440477
	Phlebitis and thrombophlebitis of intracranial sinuses	318137
	Portal vein thrombosis	199837
	Postpartum deep phlebothrombosis	438820
	Pulmonary embolism	440417
	Pulmonary infarction	254662
	Septic thrombophlebitis	4235812
	Thrombosed hemorrhoids	195294
	Thrombosis of retinal vein	4187790
	Venous embolism	318775
	Venous thrombosis	444247
	Saddle embolus of pulmonary artery	36713113
	Saddle embolus of pulmonary artery with acute cor pulmonale	35615055

6.4.6 Total cardiovascular disease events

A condition occurrence of concept set "Acute Myocardial Infarction", "Sudden Cardiac Death", "Ischemic Stroke", "intracranial bleed Hemorrhagic stroke", "Heart Failure", with at least 1 visit occurrence of "Inpatient or ER visit" beginning before and ending after the condition occurrence.

TABLE XVI: *Total cardiovascular disease events (ATLAS Cohort ID: 1779685)*

Set Name	Concept	Concept ID
Inpatient or ER visit	Emergency Room and Inpatient Visit	262
	Emergency Room Visit	9203
	Inpatient Visit	9201
Acute myocardial Infarction	Myocardial infarction	4329847
	Old myocardial infarction	314666
Sudden cardiac death	Brainstem death	4048809
	Cardiac arrest	321042
	Death in less than 24 hours from onset of symptoms	442289
	Sudden cardiac death	4317150
	Sudden death	4132309
	Ventricular fibrillation	437894
Ischemic stroke	Cerebral artery occlusion	372924
	Cerebral embolism	375557

TABLE XVI: *Total cardiovascular disease events (ATLAS Cohort ID: 1779685)*

Set Name	Concept	Concept ID
	Cerebral infarction	443454
	Cerebral thrombosis	441874
Heart Failure	Congestive rheumatic heart failure	315295
	Heart failure	316139
intracranial bleed Hemorrhagic stroke	Cerebral hemorrhage	376713
	Intracranial hemorrhage	439847
	Spontaneous cerebellar hemorrhage	43530674
	Spontaneous cerebral hemorrhage	43530727
	Spontaneous hemorrhage of cerebral hemisphere	42535425
	Spontaneous subarachnoid hemorrhage	4148906
	Subarachnoid hemorrhage	432923

6.5 Negative Controls

Negative controls and corresponding ATLAS IDs are defined below.

TABLE XVII: *Negative controls (Concept Set ID: 1870598).*

Concept	Concept ID
Postmature infancy	437369
Problem related to lifestyle	46286594
Retinopathy of prematurity stage 0	45772079
Open anterior occlusal relationship	45770922
Urethral intrinsic sphincter deficiency	45757504
Disproportion of reconstructed breast	45757370
Problem with artificial heart	44790844
Open wound of thumb with damage to nail	44789003
Transplanted heart valve present	42538119
Bladder stoma present	42537740
Opioid in blood specimen positive	40481365
Myopic choroidal neovascularization	37116419
Sequela of trachoma	36716521
Somatic dysfunction of lumbar region	36713918
Prematurity of infant	36675035
Non-healing surgical wound	36683375
Prematurity of infant	36675035
Limitation of movement of temporomandibular joint	4318718
Intracranial space-occupying lesion	4309779
Complications of attempted introduction of embryo in embryo transfer	4309151
Foot-drop	4264617
Somatic dysfunction of rib	4219138
Bizarre personal appearance	4216219
Sensory disturbance in limb	4215568
Cervical somatic dysfunction	4213540
O/E - hearing	4205383
Gastrostomy present	4201388
Tracheostomy present	4201387
Flail elbow	4193774
Late effect of epidural hematoma due to trauma	4176310
Absence of lung	4170145
Genetic disorder carrier	4168318
Intra-abdominal and pelvic swelling, mass and lump	4168222
Genetic predisposition	4166231

TABLE XVII: *Negative controls (Concept Set ID: 1870598).*

Concept	Concept ID
Localized swelling, mass and lump, trunk	4166126
Complete disruption of pelvic ring	4155077
Patient condition resolved	4153217
Baby birth weight 1 to 1.5 kilogram	4150397
Birth weight 999 g or less	4149610
Impaired intestinal carbohydrate absorption	4147614
Normal uterine cervix	4129479
Fetal problem	4126571
Slurred speech	4125590
Fetal or neonatal effect of maternal oligohydramnios	4118057
Balanced rearrangement and structural marker	4114976
Primary gonarthrosis, bilateral	4114585
Sequelae of malnutrition and other nutritional deficiencies	4101286
Foreskin deficient	4096540
Pregnancy test equivocal	4094911
Sequelae of leprosy	4093636
Polyarticular joint involvement	4094163
Absent kidney	4092879
Absent nipple	4088768
Ptosis of eyebrow	4087800
Excess subcutaneous fat	4086512
Irregular eye movements	4081461
Callosity	4067069
Clicking hip	4066505
Sample organism cultured	4056128
Sequelae of injuries of lower limb	4052226
Malingering	4051630
Sequelae of open wound of upper limb	4050690
Autoimmune reaction mediated by cell-mediated immunity	4045471
Severe systemic illness tissue wasting	4031170
Electrocerebral silence	4028689
Discord with counselor	4022078
Patient dependence on care provider	4022076
Convalescence	4022071
Discord in school	4019971
Social exclusion	4019836
Stenosis due to any device, implant AND/OR graft	4008710
Psychostimulant dependence	443274
Incoordination	441417
Wristdrop	440193
Descemet's membrane fold	438759
Complication of renal dialysis	438624
Chyluria	438262
Exhaustion due to excessive exertion	437448
Physiological development failure	437092
Malleus mobility reduced	436426
Delayed milestone	436233
Leech infestation	436041
Adverse anesthesia outcome	435720
Jaw to cranial base anomaly	434063
Late effect of accident due to natural and environmental factors	433681

TABLE XVII: *Negative controls (Concept Set ID: 1870598).*

Concept	Concept ID
Ill-defined disease	433605
Precipitate labor	433542
Excess skin of eyelid	374358
Oxygen supply absent	313601
Foreign body in orifice	259995
Hypermobility of coccyx	77364

6.6 PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis

TABLE XVIII: *Results of PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis*

Section	Checklist Item	Explanation
Title	Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis).	Yes
Abstract	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis. Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity. Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name	Yes
Introduction	Describe the rationale for the review in the context of what is already known, including mention of why a network metaanalysis has been conducted	Yes
	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Yes
Methods	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Not included - no such protocol exists
	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).	Yes
	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Yes
	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Yes
	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Yes
	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Yes

	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Yes
	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	Not included - network geometry not explorable
	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Yes
	State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.	Yes
	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: Handling of multi-arm trials; Selection of variance structure; Selection of prior distributions in Bayesian analyses; and Assessment of model fit	Yes
	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	N/A
	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Yes
	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: Sensitivity or subgroup analyses; Meta-regression analyses; Alternative formulations of the treatment network; and Use of alternative prior distributions for Bayesian analyses (if applicable)	Yes
Results	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Yes
	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Yes
	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure	
	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Yes
	Present data on risk of bias of each study and, if available, any outcome level assessment.	Yes

	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. Modified approaches m	
	Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	Yes
	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network	N/A
	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Not included according to Cochrane standards
	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth)	Yes