Anti-Interleukin-6 therapies for hospitalised patients with COVID-19: A protocol for a prospective meta-analysis of randomised trials

On Behalf of the WHO Covid- Clinical Management Characterization Working Group

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1. INTRODUCTION

1.1. Rationale

We are in the midst of a COVID-19 pandemic, which has seen numerous randomized clinical trials (referred to as trials in this document) of similar interventions, but with differences in eligibility criteria and design, being conducted simultaneously and globally. The heightened need for rapid reliable information to guide the clinical management of patients with COVID-19 creates a compelling case for prospective meta-analyses (PMA), as PMA can provide timely evidence of efficacy with maximal precision and minimum risk of bias, to inform clinical practice guidelines[1,2]. The key design feature for PMA is that the study selection criteria, hypotheses, and analyses are specified before the results of the studies are known. We recently used this model to evaluate the role of corticosteroids in COVID-19[3].

We present a PMA protocol of anti-interleukin-6 (IL6-) therapy trials recruiting patients hospitalized with COVID-19. It is based on the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 statement[4]. It will be registered on the PROSPERO international prospective register of systematic reviews, and published online before outcome data are received.

1.2. Objectives

The overall objective of this PMA is to estimate the effect of anti-IL-6 therapy compared with usual care in hospitalised patients with suspected or confirmed COVID-19. The primary comparison is of the class effect of anti-IL-6 therapies. We will also estimate the effects of specific anti-IL-6 therapies.

The primary objective is to estimate the effect of anti-IL-6 therapies compared with usual care or to corticosteroids on mortality up to 28 days after randomization. Therefore, treatment comparisons will be:

- Anti-IL-6 therapy + usual care (+/- other additional treatment)* versus usual care (+/- placebo) (+/- other additional treatment)*
- Anti-IL-6 therapy + usual care versus systemic corticosteroid + usual care

*provided these are the same for the anti-IL-6 and usual care arms

The secondary objectives are to estimate the overall and individual-drug-specific effects of anti-IL-6 therapy compared with usual care or corticosteroids:

(i) on preventing development of severe COVID-19 illness (see section 2.4.1);

(ii) within subgroups defined a priori using baseline characteristics (see section 2.4.2).

2. METHODS

2.1. Search strategy, trial eligibility criteria and invitations to participate

Trials were identified through systematic searching of clinicaltrials.gov, EudraCT, and the WHO ISRCTN registry using the term "random*" AND “COVID" in the Title or Abstract, along with terms for all IL6-antagonists individually (“tocilizumab”; “sarilumab”; “clazakizumab”; “siltuximab”; “olokizumab”) and for the term "Interleukin 6”. Individual searches were then combined. Searches were not

restricted by language, trial status (ongoing or completed); publication status, date or language. Additional relevant trials were sought through contact with research and WHO networks, and by full text screening of cited references from relevant published systematic reviews or randomized trials on IL-6 therapies in COVID-19.

Searches were initially carried out on 7th October 2020, and updated on 25th November 2020 and 11-January-2021. Searches will continue to be updated with weekly alerts. Additional eligible trials identified will be invited to participate until the start of data collection for the prospective meta-analysis. No additional trials will be included after outcome data are shared.

Additionally, research and WHO networks were asked for relevant trials. Table-1 shows a summary of trial eligibility criteria. We will include randomized controlled trials that recruited hospitalized patients. Note that trials without mortality data will be eligible if they recorded data on secondary outcomes.

Table-1: Trial Eligibility Criteria Summary

Parameter	Inclusion	Exclusion
Population	Hospitalised with suspected or proven COVID-19, including patients admitted and not admitted to critical care at the time of randomization	Non-COVID trials; Trials restricted to patients with advanced cancer
Intervention	Anti-IL-6 therapies	Trials in which anti- IL-6 therapies are combined with other active agents
Comparator	Usual care or placebo or systemic corticosteroids	Trials with active comparators other than systemic corticosteroids
Outcome (primary)	All-cause mortality up to 28 days after randomization	
Outcomes (secondary)	See section 2.4.1	
Study design	Randomized clinical trials (both blinded and open-label) including platform trials testing multiple interventions; Phase-2, -3 and -4 trials	Observational cohort studies, including matched cohorts; Phase-1 studies

Invitations offering participation in this PMA will be sent to the Principal Investigators of eligible trials by the WHO Chief Scientist on behalf of the Clinical Characterization and Management Working Group of the WHO. Participation will be based on this protocol. If further eligible trials are located while the PMA is in progress (but before sharing of outcome data), the PIs of these trials will be sent the protocol and invited to participate. Participation will be confirmed when the trial Principal Investigator indicates their willingness to participate, subject to the procedures described in this protocol. No additional trials will be included after outcome data are shared.

2.2. Study selection, data items and data synthesis

The appendix summarises details of the trials identified for potential inclusion in this PMA, including their trial registration identifiers and the number of participants. Trial protocols will be compared to make final decisions on those for which data pooling appears justifiable, based on recruitment of sufficiently similar patient groups, treatment with similar anti-IL-6 therapy interventions, and employing

similar comparator interventions. All such decisions will be made in advance of sharing of outcome data.

2.3. Risk of bias assessment

We will assess the risk of bias in the overall effect on mortality reported by each trial, based on the Cochrane Risk of Bias Assessment Tool (RoB 2)[5]. We will assess the effect of assignment to intervention (the 'intention-to-treat' effect), for the primary outcome. Risk of bias assessments will be based on the trial protocols and CONSORT flow charts together with the following information, which will be supplied by each trial:

- Methods used to generate the allocation sequence and conceal randomized allocation.
- Whether patients and health professionals were blinded to assigned interventions.
- Methods used to ensure that patients received their allocated intervention.
- Methods used to measure 28-day mortality.

Risk of bias assessments will be done by at least two individuals independently. Disagreements will be resolved through discussion, with consensus assessments reported.

2.4. Data synthesis

We will collect trial results, not individual-participant data. Trial investigators will provide summary tables showing numbers of participants who did and did not experience each outcome according to intervention group, overall and in the following specified subgroups. They will also provide estimated hazard ratios and 95% confidence intervals, for 90-day outcomes. Reporting of outcomes in the main manuscript will be restricted to those for which data are available for at least 1000 randomised patients.

2.4.1. Outcomes

The primary outcome is all-cause mortality up to 28 days after randomization. Shorter-term mortality (e.g., 21 days) will be acceptable if longer-term mortality is not available.

Secondary outcomes to be addressed are defined as:

1. Other mortality time-points from randomization date
    - in-hospital mortality
    - 90-day mortality
2. Other outcomes
    - Progression to invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) or death by 28 days, in those not receiving invasive mechanical ventilation (IMV) at randomization
    - Progression to requiring cardiovascular system (CVS) support or death by 28 days in those who did not require CVS support at randomization

- Progression to renal replacement therapy (RRT) or death by 28 days in those who did not require RRT at randomization. Patients with underlying dialysis dependence or Stage-III or above chronic kidney disease will be excluded from this analysis
- Duration of IMV up to 28 days (in those receiving IMV at baseline), accounting for survival status by treating patients who died as having 28 days of invasive mechanical ventilation.
- Proportion of patients discharged from hospital (alive) by day 28 (accounting for survival status by treating patients who died as having remained hospitalised for 28 days).

3. Secondary infection rates at both 28-days and 90-days after randomisation. In addition, serious adverse events (SAEs) or serious adverse reactions (SARs) as defined in each trial will be reported but no meta-analysis will be conducted.

2.4.2. Subgroups

We will estimate intervention effects across trial-level subgroups relating to anti-IL6 dosing and risk of bias. Providing that sufficient outcome data are available, we will also estimate intervention effects across patient-level subgroups relating to disease severity and treatment at randomization, and patient characteristics at the time of randomization for anti-IL-6 therapy overall and, additionally, for specific anti-IL-6 therapies.

Subgroups related to disease severity or treatment at the time of randomization:

1. Assigned dose of anti-IL-6 therapy:
    - Low (Tocilizumab: min to 4mg/kg; or Sarilumab min to 200mg)
    - High (Tocilizumab: >4mg/Kg, 8mg/Kg or multiple doses (regardless of number of doses received); or Sarilumab >200mg or multiple doses)
2. Receipt of systemic corticosteroids. The minimum dose considered as receipt of corticosteroids is defined as ≥ 30mg prednisone in a calendar day or 4.5 mg of dexamethasone or 150 mg of hydrocortisone in a calendar day (referred to as lower threshold dose). Corticosteroid subgroups will be compared as follows:
    - Meta-analysis restricted to trials that conducted factorial randomization to corticosteroids and anti-IL-6 agents up to June 2020, including examination of evidence for effect modification.
    - Corticosteroid treatment at randomization (yes vs no).
    - Corticosteroid treatment at randomization (yes vs no) within the four subgroups defined by respiratory support at randomization (see 3 below).
3. Respiratory support:
    - No supplemental oxygen therapy
    - Supplemental oxygen therapy (O2 flow ≤ 15l/min e.g. by face mask or nasal cannula) only
    - Non-invasive ventilation (O2 flow >15l/min e.g. by face mask, ‘High Flow’ devices (e.g. HFNC), CPAP or Non-invasive ventilation including BiPAP and other devices)
    - Invasive mechanical ventilation (IMV) including ECMO.

4. Severity of systemic inflammation at baseline (C-Reactive Protein (CRP):
    - <75 mg/L
    - ≥75 to <150 mg/L
    - ≥150 mg/L
5. *Acute organ support at randomization, in the following four groups:
    - Patients **not requiring** respiratory support (or requiring respiratory support with supplemental oxygen therapy only) **and not requiring** cardiovascular system (CVS) support (defined as receipt of vasoactive medications).
    - Patients **not requiring** respiratory support (or requiring respiratory support with supplemental oxygen therapy only) **and requiring** cardiovascular system (CVS) support (defined as receipt of vasoactive medications).
    - Patients **requiring** respiratory support via non-invasive ventilation (including HFNC) or invasive mechanical ventilation (IMV) **and not requiring** cardiovascular system (CVS) support (defined as receipt of vasoactive medications)
    - Patients **requiring** respiratory support via non-invasive ventilation (including HFNC) or invasive mechanical ventilation (IMV) **and requiring** cardiovascular system (CVS) support (defined as receipt of vasoactive medications).

** Respiratory support as defined above*

Subgroups related to patient characteristics:

1. Age (<70 years vs ≥70 years age).
2. Sex.
3. Race/Ethnicity (where available and supplied as defined in each trial).

Subgroups related to risk of bias

4. Low risk of bias, some concerns, high risk of bias. If appropriate, we will present sensitivity analyses (1) restricted to trial results at low risk of bias and (2) excluding trial results at high risk of bias.
5. Placebo controlled trials vs open label trials.

2.4.3. Other data

Trial investigators will also provide summary information on characteristics of patients at the time of randomization and numbers of patients lost to follow up, which will be tabulated (and provide useful contextual information) but will not be used in analyses.

2.5. Analyses

Characteristics of trials, and of patients recruited to the trials, will be summarised in descriptive tables. The proportion of patients receiving post-randomization corticosteroids and who received second/further doses of anti-IL-6 therapy will be reported.

The primary analyses will be based on inverse-variance weighted meta-analyses of overall and subgroup effects. We will quantify inconsistency in effects between trials heterogeneity using I^2 statistics. We will report precise p values and will not use a threshold for statistical significance.

Providing sufficient trial data are available for each comparison, we will make two separate meta-analysis comparisons (1) anti-IL6 + usual care/placebo with or without corticosteroids versus usual care/placebo with or without corticosteroids and (2) anti-IL6 versus corticosteroids. Factorial trials of anti-IL6 and corticosteroids will contribute all participants to the first comparison and half their participants to the second comparison.

Random-effects meta-analyses (with restricted maximum likelihood (REML) estimate of heterogeneity[6] and Hartung-Knapp adjustment) will be reported as a sensitivity analysis for the primary outcome of overall mortality, in the text of the paper but not in forest plots or results tables[7,8]. Random-effects meta-analyses estimate the mean treatment effect across trials, based on the assumption that the true treatment effect varies between trials. The confidence interval for this mean reflects both imprecision in estimating the mean and the estimated amount of between-trial variance. The latter is subject to considerable sampling variation when there are not many trials, so the mean treatment effect estimated using random-effects meta-analysis may not be estimated precisely even when treatment effects are estimated with precision within individual trials.

Evidence for subgroup effects will be quantified by ratios of odds ratios comparing effects in the subgroups, and corresponding interaction p-values. Comparisons between subgroups defined by trial characteristics will be made using random-effects meta-regression ('across-trial' approach). Interpretation of meta-regression results will be cautious because of the potential for confounding by other trial characteristics. Where subgroup comparisons are made both across trials and within trials (e.g. different trials use different IL6 agents, but some trials also make a randomised comparison between these agents directly), we will use a hybrid approach in which subgroup (indirect) comparisons from meta-regression are combined with direct, statistically independent, within-trial comparisons where available, using fixed-effect meta-analysis. Comparisons between subgroups defined by patient characteristics (for example, age and sex) will be made following recommendations by Fisher et al.[9], by estimating trial-specific ratios of odds ratios comparing intervention effects between subgroups ('within-trial' approach), then combining these. For characteristics that vary between participants in some but not all trials, we will use a within-trial approach restricted to the trials where this is possible, and compare this with an approach in which effects in subgroups are estimated in separate meta-analyses, and ratios of odds ratios derived from the overall effect in each subgroup. Interpretation will be cautious because of the potential for confounding of across-trial comparisons by other trial characteristics. Treatment effects in each patient subgroup in each trial will be combined across trials using fixed-effect meta-analysis, in order to obtain subgroup-specific treatment effects. In sensitivity analyses, we will additionally compute subgroup-specific estimates that are adjusted so that they correspond with the ratios of odds ratios derived from the within-trial approach.

For 90-day outcomes, estimated log hazard ratios and their standard errors, estimated using Cox regression, will be reported by individual trials and meta-analysed using inverse-variance weighting.

2.6. Certainty of the evidence

We will use the GRADE approach[10] to rate the certainty of the evidence for the overall effect of anti-IL-6 therapy across the included trials for the primary outcome[11].

3. What will an agreement to participate in this PMA entail?

Trials that agree to participate in this PMA will agree to the following:

- To share their protocol in advance.
- To share summary data in a prespecified format. These data will be limited to a small number of agreed upon elements, including key aspects of the trial design to inform ROB assessments and GRADE assessments, a CONSORT 2010 flow diagram (Figure-1), summary trial characteristics (Table 2), baseline demographics (Table 3), 2×2 tables (overall and in specified subgroups) for the association of interventions with outcomes, and hazard ratios with 95% confidence intervals for 90-day outcomes. Unblinded pooled data will be analysed according to this protocol.
- To agree to a pre-specified process for reporting results to decision-makers and submitting pooled results for publication.

4. Consequences for individual trials

Trial PIs/Steering committees (usually with input from their DMCs) will consider whether to suspend ongoing patient enrolment (on the basis of benefit, harm or futility) from the time of the first communication of the results to the trial Principal Investigator. Subsequent trial management will be at the discretion of each trial PI and his/her trial steering committee, and is likely to be guided by a number of factors including the consistency of the findings across trials and the perceived relevance to the question addressed in their trial. A trial might opt to continue recruitment if the population, the intervention, or the efficacy signal differed substantively from the overall pooled data. A decision to terminate or continue the trial would be communicated to the appropriate REBs and to the study funder, with a detailed rationale for the decision made.

5. Reporting of results

As soon as the analyses are complete, they will be released to:

- Trial PIs, for sharing as appropriate with research ethics boards overseeing each trial.
- Each trial sponsor who will have 48 hours to review the results and discuss them with the PIs of the other included trials, prior to releasing them.
- The Secretary-General of the WHO, or their designate, for sharing with the relevant guideline development committee.

A paper reporting these findings will be prepared and submitted for publication. The paper will be published using an agreed group title. A writing committee including one or more representatives from each trial as well as individuals involved in conducting and reporting the PMA will be established, and its members listed. A list of all Trial Steering Committee (TSC) members for each trial will be provided as supplementary material.

Table-2: Trial summary characteristics

Trial Descriptors:	Trial title
	Trial Acronym
	Trial Identifier No. (NCT, EudraCT, ChiCTR, other)
	Countries in which trial took place
Details of interventions:	IL-6 Intervention (drug name, planned dose and planned number of doses)
	Usual Care / Placebo (Control)
	Additional treatment(s) used on both arms of the trial
Principal investigator(s) Details	
Status of trial (e.g. in recruitment; in follow-up; completed and analyzed etc)	
Trial design details	Random allocation sequence generation method
	Method used to conceal allocation
	Extent of blinding to assigned intervention
	Method used to ensure that patients received their allocated intervention
	Proportion of patients allocated not receiving allocated intervention
	Outcomes available
	Method used to record outcomes

Table-3: Baseline Demographics (data collection form)

		αIL-6 + Usual Care	Usual care / Placebo
Number of patients randomized			
Median age in years (IQR)			
Unknown (n, %)			
Ethnicity / Race Please supply details as recorded for your trial			
Unknown (n, %)			
Sex	Male (n, %)		
	Female (n, %)		
	Unknown (n, %)		
SARS-Co-V-2 Status by PCR	+ve (n, %)		
	-ve (n, %)		
	Unknown (n, %)		
Median C-reactive protein level (IQR) Please supply units			
Unknown (n, %)			
Median IL-6 (IQR) Please supply units			
Unknown (n, %)			
Median neutrophil count (IQR) Please supply units			
Unknown (n, %)			
Median lymphocyte count (IQR) Please supply units			
Unknown (n, %)			

Receipt of additional treatments at the time of randomization			
NB. All categories are mutually exclusive (totals across all categories should equal the total patients randomised)		**αIL-6 + Usual Care N (%)**	**Usual care / Placebo N (%)**
Respiratory support	No supplemental oxygen therapy		
	Supplemental oxygen therapy (O2 flow ≤15l/min e.g. by face mask, nasal cannula)		
	Non-invasive ventilation (O2 flow >15l/min, e.g. by face mask, 'High Flow' devices (e.g. HFNC), CPAP or Non-invasive ventilation including BiPAP and other devices)		
	Invasive mechanical ventilation (IMV) including ECMO		
	Unknown		
Vasoactive medication	Receiving vasoactive medication		
	Not receiving vasoactive medication		
	Unknown		
Renal replacement therapy (RRT)	Receiving RRT		
	Not receiving RRT		
	Unknown		
Remdesivir	Receiving remdesivir		
	Not receiving remdesivir		
	Unknown		
Corticosteroids	Prednisone (≥ 30mg/ day)		
	Dexamethasone (≥ 4.5 mg/ day)		
	Hydrocortisone (≥150 mg/day)		
	Other (please specify)		
	Not receiving corticosteroids		
	Unknown		
Convalescent plasma	Receiving convalescent plasma		
	Not receiving convalescent plasma		
	Unknown		
Anticoagulation at therapeutic dose *(please specify and provide minimum dose)*	Receiving anticoagulant therapy		
	Not receiving anticoagulant therapy		
	Unknown		
Other *(e.g colchicine; please specify)*	Receiving		
	Not receiving		
	Unknown		

6. Logistics, management, and co-ordination

Data will be securely transferred to a central repository at the World Health Organization for statistical analyses.

7. Status

- Trial registers including www.clinicaltrials.gov: most recent search completed on 18th November 2020
- Principal Investigators contact – ongoing
- Meetings of trial PIs – weekly from 23rd November until 21st December 2020; and from 4th January 2021 until date of this protocol.

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Appendix

Table 1: Trials potentially eligible for comparison 1 (IL-6 + Usual care vs Usual care +/- Placebo)

NCT number / Acronym	Participants	Treatment	Control / Comparison	Outcomes	Status	Potential patients to contribute to PMA (n)
IL-6 agent: Tocilizumab						
NCT04320615 **COVACTA**	Hospitalized with COVID-19 Pneumonia	Tocilizumab 8 mg/kg, up to a maximum dose 800 mg. Up to 1 additional dose if clinical symptoms worsen or show no improvement.)	Matched Placebo Up to 1 additional dose if clinical symptoms worsen or show no improvement	Various incl. Mortality Rate [Days 7, 14, 21, 28, and 60]	Completed and pre-print reported	452
NCT04356937 **BACC Bay**	Hospitalized COVID-19 adult patients with elevated inflammatory measures	Tocilizumab 8mg/kg single dose	Placebo/ Soc	Various incl 28d mortality	Completed and reported	243
NCT04331808 **CORIMUNO-TOCI**	Non-ICU patients only Hospitalized with COVID-19 either diagnosed with moderate or severe pneumonia requiring no mechanical ventilation or critical pneumonia requiring mechanical ventilation	Tocilizumab 8mg/kg D1 and if no response (no decrease of oxygen requirement) a second injection at D3.	Standard of care	Various including survival at 28d	Completed and reported	131
	ICU patients only	Tocilizumab 8mg/kg D1 and if no response (no decrease of oxygen requirement) a second injection at D3.	Standard of care	Various including survival at 28d	Not yet reported	97

NCT04372186 **EMPACTA**	Hospitalized participants with COVID-19 pneumonia	Tocilizumab 8 mg/kg, with a maximum dose of 800 mg. Up to one additional dose may be given.	Placebo	Various including mortality at 28d	Completed and reported	379
NCT04479358 **COVIDOSE-2 (sub-study A)**	COVID-19 Pneumonitis Not Requiring Invasive Ventilation	Tocilizumab 40mg Vs Tocilizumab 120mg	Standard of care	Various incl. Mortality at 28 days	Still Recruiting (will submit data for PMA for those recruited by end Jan 2021)	30
NCT04412772 **ARCHITECTS**	Severe COVID-19	Tocilizumab 8mg/kg IV (not to exceed 800 mg) Up to 1 additional dose if clinical symptoms worsen	Matched Placebo Up to 1 additional dose if clinical symptoms worsen	Various incl. Mortality at 28 days	Recruiting	300
NCT04435717 **COVITOZ-01**	Covid19 with mild-moderate pneumonia	Tocilizumab 8 mg / kg (with a maximum of 800 mg) in single dose + usual care Vs Tocilizumab 8 mg / kg in two doses at 0 and 12 hours (with a maximum of 800 mg per dose) + soc	Usual care	Various incl. Mortality to 28 days after started treatment [Day3, Day7 and Day28]	Stopped recruitment	26
NCT04377750	Severe COVID-19 with suspected pulmonary hyper-inflammation	Tocilizumab 8mg/kg IV (not to exceed 800 mg)	Placebo (intravenous administration of 100 ml of normal saline)	Mortality at 28 days	Recruiting	500
NCT04412291	COVID-19 and Respiratory Distress Not Requiring Mechanical Ventilation	Tocilizumab 8mg/kg for up to max 800 mg. If no clinical response another dose of 8mg/kg may be given	SoC	Lots incl. Mortality to 29 days	Recruiting (Est completion February 2021)	120

NCT04577534 **COVIDSTORM**	Hospitalized with COVID-19 disease	Tocilizumab One infusion according to weight of patient	SoC	Lots incl Mortality at 28 days	Recruiting Intent is to recruit 310. Will submit data on pts recruited by end Jan 2021 for PMA	60
NCT04330638 **COV-AID**	Hospitalized with severe COVID-19 disease	Tocilizumab Single iv infusion at 8mg/kg with a maximum of 800mg	Usual care	Time to Clinical Improvement [at day 15]; all-cause mortality (up to D28) and also longer term (10-20 weeks follow up) plus others	Recruiting	342
NCT02735707 **REMAP-CAP**	Community-acquired Pneumonia, Influenza, COVID-19	Tocilizumab Single dose of 8mg/kg - maximum total dose of 800mg Vs Sarilumab (400mg single dose)	SoC (no immune modulation treatment)	Various including all-cause mortality at 90d	Completed recruitment – pre-print available – full report in press	755
NCT04381936 **RECOVERY**	Severe Acute Respiratory Syndrome – Patients with progressive COVID-19	Tocilizumab Dose determined by body weight	Standard of care	28 day mortality plus others	Completed recruitment – preprint available	4116
NCT04332094 **TOCOVID**	COVID-19	Tocilizumab 162mg x 2 doses at 12 hours + Hydroxychloroquine 400 mg day 1 followed by 200 mg for 6 days + Azithromycin (500 mg / day x 3)	Hydroxychloroquine 400 mg day 1 followed by 200 mg for 6 days + Azithromycin 500 mg / day x 3 days	2 incl In-hospital mortality [average timeframe of 14 days	Recruiting - data on patients randomised by end Jan 2021 will be available for PMA	260
NCT04409262 **REMDACTA**	Hospitalized with COVID-19 pneumonia	Tocilizumab + Remdesivir	Placebo + Remdesivir	Lots incl. Mortality up to Day 28 and Day 60	Recruitment completed – data will be available for PMA	650

NCT04476979 **TOCIDEX**	Coronavirus Infection	Tocilizumab 8mg/kg d1 and if no response a second fixed dose of 400mg wil be administered at d3 + Dexamethasone	Dexamethasone	Survival without needs of ventilator utilization at day 14 / Overall survival at 14, 28, 60 and 90 days + others	Recruitment ongoing – Data on patients included by end Jan 2021 will be available for PMA	295
NCT04403685 **TOBRICAS**	Moderate to severe COVID-19 with increased inflammatory markers	Tocilizumab 8 mg/kg (maximum dose of 800mg)	Best supportive care alone	All cause mortality at D28 plus others	Published	129
CTRI/2020/05/025369 **COVINTOC**	Moderate to severe COVID 19 infection	Tocilizumab 6 mg/kg (up to a maximum of 480 mg), Frequency: Once,	Standard of care	unknown	In Press	180
IL-6 agent: Sarilumab						
NCT04315298 **SANOFI P2/P3 Trial**	Patients hospitalized with COVID-19	Single or multiple intravenous (IV) doses of Sarilumab. Additional doses may be administered if the patient meets protocol defined criteria. (NB seems to be at least 2 different dose options – low and high dose)	Placebo	Many! including % deaths at 29d	Completed	1912
NCT04327388 **SANOFI TRIAL**	Patients hospitalized with severe or critical COVID-19	Sarilumab IV up to 2 doses. NB 2 Sarilumab arms at 2 different doses	Matching placebo	Various including % alive at D29	Completed – accepted for publication – data on all pts available for PMA	420
NCT04359901	Hospitalized patients with COVID-19 infection of moderate severity	Sarilumab 400mg subcutaneous injection plus standard of care	Standard of care	Intubation or death at D14	Recruiting	120
NCT02735707	Community-acquired Pneumonia, Influenza, COVID-19	Sarilumab 400mg single dose	SoC (no immune modulation treatment)	Various including all-cause mortality at 90d	Completed recruitment – pre-print available	48 Pts randomised to Sarilumab in addition to

REMAP-CAP						shared 402 SOC arm with Toci comparison
EudraCT Number: 2020-002037-15 **SARTRE**	SARS-CoV-2 infected patients with pneumonia	Sarilumab 200mg single dose IV	Placebo	Severe respiratory failure; mortality and survival at 15d	Recruitment ongoing – 16/02/2021 decision re continuation 170 pts to date – able to provide data on ~140 early March	140
NCT04357808 **SARCOVID**	Hospitalised patients with moderate to early severe COVID-19	Sarilumab 2 X 200mg SC injection (single dose)	Standard of care	Mean change in clinical status assessment; Deaths within 30d; Duration of hospitalisation	Active, not recruiting	30
NCT04324073 **CORIMUNO-SARI**	Non ICU patients only Hospitalized patients with COVID-19 and either moderate or severe pneumonia requiring no mechanical ventilation or critical pneumonia requiring mechanical ventilation	Sarilumab 1 x IV injection 400mg	Standard of care	Ventilator-free survival at 14d; Survival at 14, 28 and 90d plus others	Recruitment completed – all pts available for PMA	148
	ICU patients only	Sarilumab 1 x IV injection 400mg	Standard of care	Ventilator-free survival at 14d; Survival at 14, 28 and 90d plus others	Active, not recruiting	91
NCT04357860 **SARICOR**	Hospitalised adults with COVID-19 presenting cytokine release syndrome.	Sarilumab (200 and 400 mg) plus best available therapy (BAT)	Best available therapy	Various including 28d mortality	Was not yet recruiting as of April 2020 (NB Protocol was published Nov 2020)	120
IL-6 agent: Clazakizumab						

NCT04494724 **Pro00025969**	Patients with COVID-19 and pulmonary manifestations	Clazakizumab - 25mg IV infusion	Placebo	Various including survival at 28d	Recruiting	60
NCT04363502 **IRB00247932**	Patients with life-threatening COVID-19 infection manifest by pulmonary failure and a clinical picture consistent with a cytokine storm syndrome	Clazakizumab 25mg (second dose no later than D3 if CRP has not decreased by 50% within 36-48hr)	Placebo	Change in CRP level up to 3 days only	Recruiting	30
NCT04348500	Patients with COVID-19 disease and signs of pulmonary involvement who have not yet required mechanical ventilation and/or ECMO	Clazakizumab 25 mg IV infusion x 1 dose	Placebo	Various including survival at 28d	Active, not recruiting	17
NCT04381052	Patients with life-threatening pulmonary failure secondary to COVID-19 disease	Clazakizumab 25 mg IV infusion 1 dose (second dose no later than D3 if CRP has not decreased by 50% within 36-48hr)	Placebo	Various including survival at 28d	Not yet recruiting (May 2020)	30
NCT04343989 **s20-00392**	Patients with life-threatening pulmonary failure secondary to COVID-19 disease	Clazakizumab 12.5 mg, OR Clazakizumab 25mg	Placebo	Various including survival at 28d	Active not recruiting	90
Il-6 agent: Olokizumab						
NCT04380519 **CL04041078**	Patients with severe SARS-CoV-2 infection	Olokizumab 64 mg	Placebo	Various including mortality at 29d	Completed	372
NCT04452474 **CL04041080**	Patients with severe SARS-CoV-2 infection	Olokizumab 64 mg	Placebo	Various including 28-day case fatality rates	Not yet recruiting (as of 30/06/2020)	376

Il-6 agent siltuximab						
NCT04330638 COV-AID	COVID-19 coronavirus infection and acute hypoxic respiratory failure and systemic cytokine release syndrome	Siltuximab 11 mg/kg	Usual Care	Various including mortality at 28d and at 10-20 weeks	Active, not recruiting	342

Table 2: Trials potentially eligible for comparison 2 (IL-6 + Usual care vs Corticosteroid + Usual care)

NCT number / Acronym	Population	Intervention	Control	Outcomes	Status	Planned recruitment
NCT04519385	Severe Covid-19	Tocilizumab 4mg/kg – 2 doses 24h apart).	Dexamethsone pulse therapy	Survival 14 days from admission date Change in Fio2/Pao2	Completed	69
NCT02735707 REMAP-CAP	Community-acquired Pneumonia, Influenza, COVID-19	Tocilizumab Single dose of 8mg/kg - maximum total dose of 800mg).	Hydrocortisone	Various including all-cause mortality at 90d	This comparison completed recruitment	Tbc*
NCT04381936 RECOVERY	Severe Acute Respiratory Syndrome – Patients with progressive COVID-19	Tocilizumab	Corticosteroid	28 day mortality plus others	Recruiting	Tbc*
NCT04345445 TVCS-COVID19	COVID-19 patients with moderate COVID-19 disease at risk for complications of cytokine storm	Tocilizumab 8 mg/kg single dose	Methylprednisolone 120mg/day for 3 days	Various including overall 28d survival	Not yet recruiting (as of April 14th 2020)	310
NCT04377503 **COVID-19 HSD**	Patients with COVID-19	8mg/kg repeated once after 12h	Methylprednisolone: 1.5 mg / kg / day divided into 2 daily doses for 7 days. Then 1 mg / kg / day for 7 days in two daily doses. Finally 0.5 mg / kg / day for 7 days.	Patient clinical status 15 days after randomization (composite of death, ventilation status, etc)	Not yet recruiting (May 2020)	40

***Only those patients randomised between the active arms within the same time frame eligible**