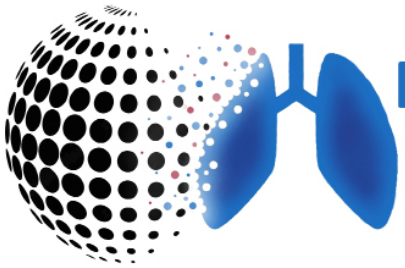

Protocol Amendment to COVID-19 Immune Modulation Therapy Domain-Specific Appendix

Summary of changes

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

---

REMAP-CAP COVID-19 Protocol Amendment Summary Version 1 dated 08 April 2020

TABLE OF CONTENTS

1. CURRENT VERSIONS OF PROTOCOL DOCUMENTS

1.1. The current versions of pandemic specific protocol documents:

- REMAP-CAP Core Protocol Version 3, dated 10 July 2019
- Pandemic Appendix to Core Version 1.1, dated 12 February 2020
- Domain-Specific Appendices
    - COVID-19 Antiviral Therapy Domain-Specific Appendix Version 2, dated 01 April 2020
    - COVID-19 Immune Modulation Domain-Specific Appendix Version 1, dated 11 March 2020

2. AMENDMENT 1

The COVID-19 Immune Modulation Therapy DSA protocol document underwent an amendment in April 2020.

2.1. Summary of changes

Section	Original text	New Text	Reason
Front page and whole document header	REMAP-CAP COVID-19 Antiviral Therapy Domain-Specific Appendix Version 1.0 dated 11 March 2020	REMAP-CAP COVID-19 Antiviral Therapy Domain-Specific Appendix Version 2.0 dated 04 April 2020	Administrative change
Summary Page 2	In this domain of the REMAP-CAP trial, participants meeting the platform entry criteria for REMAP-CAP admitted to participating intensive care units with suspected or microbiological testing-confirmed COVID-19 infection will be randomized to receive one of up to three interventions depending on availability and acceptability: • No immune modulation for COVID-19 (no placebo) • interferon-beta-1a (IFN-β1a) • anakinra i.e. interleukin-1 receptor antagonist (IL1Ra)	In this domain of the REMAP-CAP trial, participants meeting the platform entry criteria for REMAP-CAP admitted to participating intensive care units with suspected or microbiological testing-confirmed COVID-19 infection will be randomized to receive one of up to five interventions depending on availability and acceptability: • No immune modulation for COVID-19 (no placebo) • interferon-beta-1a (IFN-β1a) • anakinra ~~i.e.~~ (interleukin-1 receptor antagonist; IL1Ra) • tocilizumab (IL-6 receptor antagonist; IL6Ra) • sarilumab (IL-6 receptor antagonist; IL6Ra)	Addition of new interventions
Summary table Page 3 Analysis and strata	Blank	Unit of analysis may be further modified by application of a biomarker strata.	Team members with expertise regarding the new interventions has raised the possibility that the treatment effect of

			these interventions may be influenced by status with respect to biomakers. This modification permits the introduction of a biomarker-based stratum within this domain.
Nesting	None	There is one nest, comprising tocilizumab and sarilumab, which are both interleukin-6 inhibitors.	Both agents have a similar mechanism of action, so creation of a nest allows evaluation of their combined similar treatment effect as well as evaluation of each individual agent.
Domain-Specific Exclusions	• Patient has already received any dose of any form of interferon or anakinra, or is on long-term therapy with any of these agents prior to this hospital admission	• Patient has already received any dose of one or more of any form of interferon, anakinra, tocilizumab, or sarilumab, or is on long-term therapy with any of these agents prior to this hospital admission	Domain-level exclusion criteria updated for tocilizumab and sarilumab
Intervention-Specific Exclusions	Receiving an agent that is specified as an intervention in this domain as a usual medication prior to this		Removed as intervention-level exclusion criteria. This is

	hospitalization will exclude a patient from receiving that agent.		already covered by a domain level-exclusion for long-term pre-hospital use of any agent specified as an intervention in this domain
Intervention-Specific Exclusions	• Known or suspected pregnancy will result in exclusion from the anakinra and IFN-β1a interventions.	• Known or suspected pregnancy will result in exclusion from the anakinra, IFN-β1a, tocilizumab and sarilumab interventions. • A baseline alanine aminotransferase or an aspartate aminotransferase that is more than five times the upper limit of normal will result in exclusion from receiving tocilizumab or sarilumab • A baseline platelet count < 50 x 109 / L will result in exclusion from receiving tocilizumab and sarilumab	Intervention-level exclusion criteria updated for tocilizumab and sarilumab
SECTION 1 ABBREVIATIONS	**Original text**	**New Text**	**Reason**
Page 8	AE Adverse Event ARDS Acute Respiratory Distress Syndrome CCP Clinical Characterization Protocol DSA Domain-Specific Appendix DMSB Data Safety and Monitoring Board DSWG Domain-Specific Working Group	AE Adverse Event ARDS Acute Respiratory Distress Syndrome CCP Clinical Characterization Protocol DSA Domain-Specific Appendix DMSB Data Safety and Monitoring Board DSWG Domain-Specific Working Group	Administrative update

	ICU Intensive Care Unit IFN Interferon IL Interleukin ISIG International Statistics Interest Group ITSC International Trial Steering Committee MAS Macrophage Activation Syndrome MERS-CoV Middle East respiratory syndrome coronavirus MMF Mycophenolate mofetil OTD Optimal Tolerated Dose PAtC Pandemic Appendix to the Core Protocol PISOP Pandemic infection is suspected or proven REMAP-CAP Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia RSA Region-Specific Appendix SAE Serious Adverse Event SARS Serious Acute Respiratory Syndrome SOBI Swedish Orphan Biovitrum WHO World Health Organization	FDA U.S Food and Drug Administration ICU Intensive Care Unit IFN Interferon INTEREST trial Efficacy and Safety of FP-1201-lyo (Interferon Beta-1a) in Patients Having Acute Respiratory Distress Syndrome (ARDS) IL Interleukin ISIG International Statistics Interest Group ITSC International Trial Steering Committee LFT Liver Function Tests MAS Macrophage Activation Syndrome MERS-CoV Middle East respiratory syndrome coronavirus MIRACLE trial The MERS-CoV Infection tReated With A Combination of Lopinavir/Ritonavir and IntErferon-β1b trial MMF Mycophenolate mofetil OTD Optimal Tolerated Dose PAtC Pandemic Appendix to the Core Protocol PISOP Pandemic infection is suspected or proven PY Patient Years REMAP-CAP Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia	

		RO Receptor Occupancy RSA Region-Specific Appendix SAE Serious Adverse Event SARS Serious Acute Respiratory Syndrome SOBI Swedish Orphan Biovitrum WHO World Health Organization	
SECTION 3 COVID-19 ANTIVIRAL THERAPY DOMAIN-SPECIFIC APPENDIX VERSION	**Original text**	**New Text**	**Reason**
3.1. Version History Page 11	Version 1: Approved by the COVID-19 Domain Specific Working Group (DSWG) on 11 March, 2020	Version 1: Approved by the COVID-19 Domain Specific Working Group (DSWG) on 11 March, 2020 Version 2: Approved by the COVID-19 DSWG on 07 April, 2020	Administrative change
SECTION 4 COVID-19 ANTIVIRAL DOMAIN GOVERNANCE	**Original text**	**New Text**	**Reason**
4.1. Domain members Page 10	Professor Derek Angus Dr Kenneth Baillie Professor Richard Beasley A/Prof Scott Berry Professor Marc Bonten Professor Frank Brunkhorst Professor Allen Cheng Professor Menno de Jong	Professor Derek Angus Dr Kenneth Baillie Professor Richard Beasley A/Prof Scott Berry Professor Marc Bonten Professor Frank Brunkhorst Professor Allen Cheng Dr Nichole Cooper	Addition of investigators

	Dr Lennie Derde Dr Rob Fowler Professor Herman Goossens Professor Anthony Gordon Mr Cameron Green Dr Ed Litton Professor John Marshall Dr Colin McArthur Professor Susan Morpeth Dr Srinivas Murthy Dr Mihai Netea Professor Alistair Nichol A/Prof Rachael Parke Ms Jane Parker Professor Kathy Rowan Dr Steve Tong Dr Tim Uyeki Dr Frank van de Veerdonk Professor Steve Webb	Professor Menno de Jong Dr Lennie Derde Dr Rob Fowler Mr James Galea Professor Herman Goossens Professor Anthony Gordon Dr Thomas Hills Mr Cameron Green Prof Andrew King Dr Ed Litton Professor John Marshall Dr Colin McArthur Dr Susan Morpeth Dr Srinivas Murthy Dr Mihai Netea Professor Alistair Nichol Dr Kayode Ogungbenro A/Prof Rachael Parke Ms Jane Parker Professor Kathy Rowan Dr Steve Tong Dr Tim Uyeki Dr Frank van de Veerdonk Professor Steve Webb	

		Dr Taryn Youngstein	
SECTION 5 BACKGROUND AND RATIONALE	**Original text**	**New Text**	**Reason**
5.2.2.1. Current clinical trials and interventions being evaluated Page 16	This domain will evaluate two active interventions that are designed to modify host immune responses to viral infection, particularly around the severity of viral pneumonitis and progression to ARDS. These agents are IFN-β1a and anakinra which acts as interleukin-1 receptor antagonist. The inclusion of IFN-β1a will allow evaluation of combination therapy with lopinavir/ritonavir with the use of this antiviral agent being specified in a separate DSA	At launch, this domain will evaluate two active interventions that are designed to modify host immune responses to viral infection, particularly around the severity of viral pneumonitis and progression to ARDS. These agents are IFN-β1a and anakinra which acts as interleukin-1 receptor antagonist. The inclusion of IFN-β1a will allow evaluation of combination therapy with lopinavir/ritonavir with the use of this antiviral agent being specified in a separate DSA. Additional agents may be added subsequently.	Minor additions for clarity
5.2.3. Intervention strategy for this domain Page 18	Although this domain will commence with a two active immune modulation therapies agent, it is intended that additional agents can be added (allowing evaluation of several agents against a common control intervention) as well as allowing introduction of combinations of agents (to evaluate potential synergy). Any changes to the intervention structure of the domain will be specified using one or more amendments to this DSA with implementation occurring only after ethical approval has been obtained. The initial selection of antiviral agents to be evaluated is a combination of IFN-	Although this domain will commence with two active immune modulation therapies, it is intended that additional agents can be added (allowing evaluation of several agents against a common control intervention) as well as allowing introduction of combinations of agents (to evaluate potential synergy). Any changes to the intervention structure of the domain will be specified using one or more amendments to this DSA with implementation occurring only after ethical approval has been obtained. The initial selection of agents to be evaluated are IFN-β1a and anakinra.	Correction of grammatical errors and clarification of when additional agents were commenced

	β1a and anakinra. Commencing with Version 2.0, additional agents have been added and are outlined below.	Commencing with Version 2.0, additional agents have been added and are outlined below.	
5.2.4.4. IFN-β1a dosing Page 22	The dose selected for this study (10 µg) is based on information from the previous studies, where the maximum tolerated dose was found to be 22 µg. In some regions IFN-β1a is available in a preparation containing 22µg in a 0.5ml syringe. Therefore the dose in this trial will be 10-11µg, depending on the preparation available.	The dose selected for this study is based on information from the previous studies, where the maximum tolerated dose was found to be 22 µg. In some regions IFN-β1a is available in a preparation containing 22µg in a 0.5ml syringe. Therefore the dose in this trial will be 10-11µg, depending on the preparation available.	The dose change to a range is required due to the different total amount of IFN-beta in different preparations available in different trial locations.
5.2.5.3. Anakinra dosing Page 25	To neutralize IL-1 signaling completely, IL-1Ra must be present in at least a concentration 1000 times higher than IL-1 (Arend et al., 1990). When this occurs, signaling is blocked for at least 4-6 hours, but continuous blockade is not needed for biological efficacy. The trial will use a dose of 300 mg intravenously once daily to reach the amount of IL-1Ra that can completely block IL-1 signaling. This is a much lower dose than 2 mg/kg per hour administered in previous clinical and pre-clinical studies that recruited patients with severe sepsis and septic shock, which did not report serious side effects.	To neutralize IL-1 signaling completely, IL-1Ra must be present in at least a concentration 1000 times higher than IL-1 (Arend et al., 1990). When this occurs, signaling is blocked for at least 4-6 hours. The trial will use a dose of 300 mg intravenously once initially to reach the amount of IL-1Ra that can completely block IL-1 signaling. It will then continue at a maintenance dose of 100 mg intravenously every 6 hours to maintain adequate drug levels to block IL-1. This is a much lower dose than 2 mg/kg per hour administered in previous clinical and pre-clinical studies that recruited patients with severe sepsis and septic shock, which did not report serious side effects.	Modification of dose from original version of protocol noting that, at time of submission of this amendment, no patients have yet been recruited using V1 of the protocol. The change in dose is based on new information provided to team members by researchers with expertise in use of anakinra.

	The mean plasma clearance of anakinra in subjects with mild (creatinine clearance 50-80 ml / min) and moderate (creatinine clearance 30-49 ml/min) renal failure was reduced by 16% and 50%, respectively, and it is stated that anakinra can be given once daily in a similar dose as for normal renal function. However, with severe renal failure, end stage renal disease (creatinine clearance < 30 ml/min), and renal replacement therapy, anakinra should be given on alternate days, instead of daily (https://www.ema.europa.eu/en/medicines/human/EPAR/kineret).	The mean plasma clearance of anakinra in subjects with mild (creatinine clearance 50-80 ml / min) and moderate (creatinine clearance 30-49 ml/min) renal failure was reduced by 16% and 50%, respectively, and it is stated that anakinra can be given once daily in a similar dose as for normal renal function. However, with severe renal failure, end stage renal disease (creatinine clearance < 30 ml/min), and renal replacement therapy, maintenance anakinra doses should be given at 12 hourly intervals (https://www.ema.europa.eu/en/medicines/human/EPAR/kineret	
5.2.6. IL-6 receptor antagonists Page 25	Blank	5.2.6. IL-6 receptor antagonists	Administrative update – new heading
5.2.6.1. Biological rationale Page 25	Blank	Experimental models of Coronavirus infection support a role for IL-6 in pathogenesis. In SARS, high levels of interleukin (IL)-6 are released from monocytes and macrophages in response to interaction between the viral spike (S) protein and cell-surface TLR- 2 (Jacques et al., 2009). In this model, the release of IL-6 and TNF-a was mostly dependent on the activation of the ERK-1/2 MAPK and JNK pathways and, to a lesser extent, the p38 MAPK and NF-jkB pathways. The pathology induced by in a mouse Coronavirus model, utilizing the Mouse	Updated to include rationale for new interventions

		Hepatitis Virus, was mediated by the release of intrahepatic IL-6 and TNF-a via the TLR2 receptor, as demonstrated in TLR2 knockout mice and by histopathological observations. In a mouse model of SARS, excessive secretion of IL-6 and IL-8 exacerbate pulmonary pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. These cytokines may also facilitate a mechanism for evading the host immune response by delaying and inhibiting the ability of dendritic cells to prime naïve T cells. This provides a dual rationale for the potential benefit of IL-6 blockade in Coronavirus infection. In patients with COVID-19, increased secretion of IL-6 was observed in monocytes and CD4+ cells of patients who developed a severe clinical course, in comparison with patients who had uncomplicated infection or healthy controls (Zhou et al., 2020b). These preclinical findings together suggest that IL-6 may be a key mediator in severe COVID-19 and is a suitable target for immunomodulatory therapy	
5.2.6.2. Tocilizumab	Blank	5.2.6.2. Tocilizumab	Administrative update – new heading

5.2.6.2.1. Clinical studies of Tocilizumab Page 26	Blank	Tocilizumab is a humanized monoclonal antibody that inhibits both membrane-bound and soluble interleukin-6 (IL-6) receptors. IL-6, which is secreted by monocytes and macrophages, is one of the main drivers of immunologic response and symptoms in patients with cytokine-release syndrome (CRS). While tocilizumab was first approved by the FDA in 2010 for the treatment of rheumatoid arthritis, it has received additional approval for treatment of patients with giant cell arteritis, and systemic and juvenile forms of idiopathic arthritis. In 2017, Tocilizumab received additional approval for the treatment of severe or life-threatening CAR T-associated CRS due to its efficacy and safety profile. While criteria for grading CRS severity varies by cancer center, it has been proposed to administer tocilizumab to CRS patients with any of the following: oxygen requirement < 40%, hypotension responsive to fluids or a low dose of a single vasoactive agent, or Grade 2 organ toxicity as defined by the Common Terminology Criteria for Adverse Events.(Lee et al., 2018) Hyperinflammatory states and cytokine storming, including elevated IL-6, has been reported in patients with severe COVID-19 and were associated with increased mortality in patients in China.(F. Zhou et al.,	Addition to background information with recent trial results

		2020b) A pre-print (non-peer reviewed) case series of 21 patients treated with tocilizumab between February 5-14, 2020 in China reported clinical success, with rapid resolution of fever and C-reactive protein, decreased oxygen requirements, and resolution of lung opacities on computerized tomography imaging. The authors state the patients all had "routine treatment for a week" before tocilizumab, which was described as "standard care according to national treatment guidelines" including lopinavir, methylprednisolone, and other supportive care. All patients had IL-6 analyzed prior to tocilizumab administration with a mean value of 132.38 ± 278.54 pg/mL (normal < 7 pg/mL). No adverse events were described in this case-series although no assessment of long-term outcomes was reported. If effective, there is uncertainty regarding optimal timing of administration or of possible differential treatment effect depending on stage of disease. There are several clinical studies of tocilizumab in COVID019 underway. NCT04317092 is a single arm study of 330 participants who are hospitalized due to COVID-19 and have either low oxygen saturations (<93% on air) or have been intubated for <24 hours. All patients will be treated with tocilizumab (8mg/kg) and	

		the primary outcome is one-month mortality. NCT04320615 will evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of tocilizumab (8mg/kg) compared with a matching placebo in combination with standard of care (SOC) in hospitalized patients with severe COVID-19 pneumonia. Participants will be hospitalized patients due to COVID-19 with oxygen saturations ≤93% or a PaO2 / FiO2 ratio of 300mmHg. The primary outcome is Clinical Status Assessed Using a 7-Category Ordinal Scale at day 28. There are also anecdotal reports of the off-trial use of tocilizumab in several countries including Italy, United Kingdom, and Australia. As outlined earlier WHO guidance and CMO guidance in the United Kingdom (ref to CMO letter), there is an imperative that interventions that are being used by clinicians, without evidence of the balance between risks and harms, are incorporated within controlled clinical trials as rapidly as possible.	
5.2.6.2.2. Safety profile Page 27	Blank	There is extensive experience with the use of tocilizumab for ambulatory patients with rheumatoid arthritis and other inflammatory diseases as part of pivotal clinical trials or post-marketing surveillance. For patients who participated pivotal phase III trials for rheumatoid arthritis and were treated with 4 to 8mg/kg	Updated to include information on new intervention

		of intravenous tocilizumab, the most common adverse effects (incidence range 3-8%) over a follow-period of 6 months were upper respiratory tract infections, nasopharyngitis, headache, hypertension, and transaminitis (https://www.actemrahcp.com/ra/clinical-study-safety/clinical-study-safety.html). The incidence of these adverse events was slightly higher compared to patients treated with methotrexate or other disease modifying agents. The most common serious adverse events were infections (cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, and bacterial arthritis). The cumulative incidence of serious infections was 5 per 100 patient years (PY) compared to 4 per 100 PY for other disease modifying agents. Less commonly observed serious adverse events were new medically confirmed malignancies (1.3 per 100 PY), myocardial infarctions (0.3 per 100 PY), hepatic events (0.04 per 100 PY), and medically confirmed gastrointestinal perforations (0.2 per 100 PY). IL-6 antagonism has been associated with neutropenia and thrombocytopenia in patients receiving chronic therapy with tocilizumab for giant cell arteritis or rheumatoid arthritis (https://www.medicines.org.uk/emc/product/6673/smpc#PRODUCTINFO).	

		In a case series of 53 adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia, Grade 3 CRS or higher was associated with increased risk of subsequent infection but it was unclear whether tocilizumab or corticosteroid use promoted this risk.(Park et al., 2018) There were no reported adverse events in the 60 tocilizumab-treated patients submitted to the FDA for the CRS indication, which recommends a maximum of 4 doses for treatment.(Lee et al., 2018) To date, to the best of our knowledge, only an uncontrolled case series of 21 patients (17 assessed as severe and 4 as critical) treated with tocilizumab has been published as a pre-print (chinaXiv:202003.00026v1). In this case series, 18 patients received one dose (400mg) and 3 patients had a repeat dose within 12 hours. All patients had a return to normal body temperature. Fifteen patients had reduced oxygen requirements, and two were extubated within 5 days. CT scans were reported as showing improvement in 19 patients. At the time of the report 90% of the patients had been discharged from the hospital. There were no reports of secondary pulmonary infections or other deteriorations. No adverse drug reactions were reported during the treatment. It should	

		also be noted that pharma sponsored trials of IL-6 blockade have been registered. Although it is clear that Tocilizumab can increase the risk of infection, and it is acknowledged that patients who are critically ill are at risk of secondary bacterial infections, these risks should be interpreted in the context of short-term treatment in patients with COVID-19 who have high reported mortality. As such, it is reasonable to conclude that the potential benefits of treatment with tocilizumab as anti-inflammatory agent outweigh the known potential risks.	
5.2.6.2.3. Tocilizumab dosing Page 28	Blank	Immunotherapy with tocilizumab is listed as a treatment option for severe or critical cases of COVID-19 with elevated IL-6 in the 7th edition of the National Health Commission of the People's Republic of China COVID-19 Diagnosis and Treatment Guide (http://kjfy.meetingchina.org/msite/news/show/cn/3337.html) The recommended dose is 4-8 mg/kg with the option to repeat a dose in 12 hours.	Updated to include information on new intervention
5.2.6.3. Sarilumab	Blank	5.2.6.3. Sarilumab	Administrative update – new heading
5.2.6.3.1. Pre-clinical studies of sarilumab Page 28	Blank	Sarilumab is a recombinant humanized monoclonal antibody (IgG1) that binds to both soluble and membrane-bound human interleukin-6 receptor alpha	Updated background information

		(IL-6R) to inhibit IL-6 mediated signaling. Three phase I randomized, double-blind, placebo-controlled trials of sarilumab in rheumatoid arthritis were carried out in a total of 83 active treatment and 24 placebo patients using ascending doses of 50, 100, 150, and 200 mg (June, 2016). A dose-dependent reduction in levels of acute phase reactants was observed, with a greater than 90% reduction in high sensitivity c-reactive protein (hs-CRP) and serum amyloid A after administration of the 200 mg dose of sarilumab. Compared to tocilizumab, the in vitro binding affinity of sarilumab (K 61.9 pM) for the human interleukin-6 receptor (IL-6R) is 15–22-fold higher (June and Olsen, 2016)	
5.2.6.3.2. Clinical studies of Sarilumab Page 28	Blank	Safety and efficacy of sarilumab was evaluated in a combined phase II /III multicenter, randomized, double-blind placebo-controlled studies in 1588 patients with rheumatoid arthritis (Huizinga et al., 2014; Genovese et al., 2015). Patients were randomized to placebo or five different subcutaneous dosing regimens (100/150/200 mg every 2 weeks; 100/150mg every week). Significant clinical responses compared to placebo were seen after 12 weeks of treatment across all doses of 150 mg Q2 weeks or greater. Disease activity at day 28 combined with c-reactive protein levels responses showed a dose	Addition to background information with recent trial results

		response relationship with sarilumab and the highest remission response was seen in the 150 mg weekly regimen. An adaptive phase 2/3, randomized, double-blind, placebo-controlled study assessing efficacy and safety of sarilumab for hospitalized patients with COVID-19 (NCT04315298) is currently enrolling with a planned sample size of 400 patients. The trial evaluates a single dose of 400mg intravenous sarilumab, in comparison with placebo. At this time, the rate of recruitment into this trial is not known. Simulations conducted to support the development of the pandemic component of REMAP-CAP indicate that 200 patients enrolled to active treatment would have sufficient power to detect only a very strong treatment effect. Additional trials comparing the efficacy and safety of alternative dosing regimens are in planning (NCT 04324073, NCT 04322773, NCT 04321993).	
5.2.6.3.3. Safety profile of Sarilumab Page 29	Blank	The safety profile of sarilumab in ambulatory patients is well established. No dose-limiting toxicities were observed in the phase II/III trials of sarilumab. In phase II/part A trial of 306 patients with active rheumatoid arthritis, who also received concurrent treatment with methotrexate, dose-related neutropenia was observed.	Updated to include information on new intervention

		The level of ALT increased to more than three times the upper limit of normal in 4% of patients and there was elevation of serum cholesterol levels in 10 to 20% of patients after 12 weeks of treatment (June, 2016). In the phase III/part B of the trial, which included 1282 patients in the safety analysis, AEs and SAEs were more common in the sarilumab group (11.3% in the 200-mg group vs. 5.4% placebo). The most common AEs and SAEs were related to infections. Injection site reactions were reported in approximately 10% of patients treated with sarilumab. Eight malignancies occurred, with a higher incidence reported among patients treated with sarilumab. Neutropenia in the range of 0.5–1.0 × 109 /L was observed in 5.1% of the sarilumab 150-mg and 7.8% of the 200-mg groups and occurred in a dose-dependent manner. Increase in liver function parameters occurred in 9.5% of the 150-mg sarilumab group subjects versus 2.1% of the placebo group subjects. Increase in serum cholesterol occurred in 43% of the sarilumab group subjects versus 18% of placebo group subjects.	
5.2.6.3.4. Sarilumab dosing Page 29	Blank	To allow comparison with the other ongoing clinical trial for hospitalized patients with COVID-19 (NCT04315298) a single dose of 400mg sarilumab will be administered.	Updated to include information on new intervention
SECTION 6 DOMAIN OBJECTIVES	**Original text**	**New Text**	**Reason**

Page 30	We hypothesize that the probability of occurrence of the primary endpoint specified from the PAtC will differ based on the allocated immune modulation strategy. The following interventions will be available: • No immune modulation for COVID-19 (no placebo) • interferon-β1a (IFN-β1a) • anakinra Each participating site has the option to opt-in to two or more interventions to be included in the randomization schedule depending on local clinical preference, usual practice, acceptable practice, and the availability of the intervention at that site. At launch, participation in the 'no immune modulation for COVID-19 intervention' is mandatory.	We hypothesize that the probability of occurrence of the primary endpoint specified from the PAtC will differ based on the allocated immune modulation strategy. The following interventions will be available: • No immune modulation for COVID-19 (no placebo) • interferon-β1a (IFN-β1a) • anakinra • tocilizumab • sarilumab We hypothesize that the treatment effect of different immune modulation strategies is different depending on whether COVID-19 infection is confirmed to be present or absent. We hypothesize that the treatment effect of different immune modulation strategies is different depending on biomarker strata status. Each participating site has the option to opt-in to two or more interventions to be included in the randomization schedule depending on local clinical preference, usual practice, acceptable practice, and the availability of the intervention at that site. At launch, and continuing at	Addition of new interventions and related hypothesis

		time of Version 2.0, participation in the 'no immune modulation for COVID-19 intervention' is mandatory.	
SECTION 7 TRIAL DESIGN	**Original text**	**New Text**	**Reason**
7.2.2. Domain exclusion criteria Page 31	Patients will be excluded from this domain if they have any of the following: • More than 24 hours has elapsed since ICU admission • Patient has already received any dose of any form of interferon or anakinra, or is on long-term therapy with any of these agents prior to this hospital admission	Patients will be excluded from this domain if they have any of the following: • More than 24 hours has elapsed since ICU admission • Patient has already received any dose of one or more of any form of interferon, anakinra, tocilizumab, or sarilumab during this hospitalisation or is on long-term therapy with any of these agents prior to this hospital admission	Clarification of an existing exclusion criteria to confirm that prior adminstration of these agents that results in exclusion only applies to this hospitalisation. Addition of new agents.
7.2.3. Intervention exclusion criteria Page 32	• Receiving an agent that is specified as an intervention in this domain as a usual medication prior to this hospitalisation will exclude a patient from receiving that agent	• ~~Receiving an agent that is specified as an intervention in this domain as a usual medication prior to this hospitalisation will exclude a patient from receiving that agent~~	Removed intervention-level exclusion criteria for clarification. This criteria duplicates a domain-level exclusion criteria, which excludes patients who are recieveing long-term pre-hospital therapy with any agent specified as an intervention in this domain

7.2.3. Intervention exclusion criteria Page 32	• Known or suspected pregnancy will result in exclusion from the anakinra and IFN-β1a interventions. It is normal clinical practice that women admitted who are in an age group in which pregnancy is possible will have a pregnancy test conducted. The results of such tests will be used to determine interpretation of this exclusion criteria.	• Known or suspected pregnancy will result in exclusion from the anakinra, IFN-β1a, tocilizumab, and sarilumab interventions. It is normal clinical practice that women admitted who are in an age group in which pregnancy is possible will have a pregnancy test conducted. The results of such tests will be used to determine interpretation of this exclusion criteria. • A baseline an alanine aminotransferase or an aspartate aminotransferase that is more than five times the upper limit of normal will result in exclusion from receiving tocilizumab or sarilumab • A baseline platelet count < 50 x 10^9 / L will result in exclusion from receiving tocilizumab or sarilumab	Addition of new agents, as determined to be appropriate, for pregnancy as an intervention-level exclusion for tocilicumab and sarilumab.
7.3.1. Immune modulation interventions Page 33	Patients will be randomly assigned to receive one of the following open-label strategies. All interventions will be commenced immediately after allocation status is revealed. ☐ No immune modulation for COVID-19 (no placebo) ☐ interferon beta-1a (IFN-β1a)	Patients will be randomly assigned to receive one of the following open-label strategies. All interventions will be commenced immediately after allocation status is revealed. ☐ No immune modulation for COVID-19 (no placebo) ☐ interferon beta-1a (IFN-β1a)	Addition of new interventions

	☐ anakinra	☐ anakinra ☐ tocilizumab ☐ sarilumab	
7.3.2.1. Dosing Page 33	IFN-β1a 10 µg will be diluted in 1 mL of sterile water.	IFN-β1a 10 or 11 µg will be diluted in 4.5mL of 0.9% saline.	The dose change to a range is required due to the different total amount of IFN-beta in different preparations.
7.3.3.1. Dosing Page 34	300 mg of anakinra will be administered as an intravenous bolus injection via a central or peripheral line as an initial dose. In patients with creatinine clearance of less than 30 ml/min or receiving renal replacement therapy, anakinra will be dosed on alternate days.	Anakinra will be administered as an intravenous bolus injection via a central or peripheral line. A loading dose of 300 mg will be administered, followed by maintenance doses of 100 mg of anakinra administered every 6 hours. In patients with creatinine clearance of less than 30 ml/min or receiving renal replacement therapy, anakinra will be dosed every 12 hours.	Updated with new dosing information based on advice that previous dosing regimen may not have been sufficient to result in sustained suppression of IL-1 activity.
7.3.3.2. Duration of therapy Page 34	Anakinra will be administered once daily until the patient has been breathing without receiving invasive mechanical ventilation for more than 24 hours or for 14 days in patients who continue to receive invasive mechanical ventilation.	Anakinra will be administered four times daily until the patient has been breathing without receiving invasive mechanical ventilation for more than 24 hours or for 14 days in patients who continue to receive invasive mechanical ventilation. For patients not receiving invasive mechanical ventilation the drug will stop on ICU discharge or after 14 days, whichever occurs first.	Updated to cover the possibility that a participant may not have ever received invasive mechanical ventilation which was not covered adequately with previous version of protocol.

7.3.4. Discontinuation of study drug Page 34		Section moved to 7.3.6. on page 35	Moved as an administrative change
7.3.4. Tocilizumab Page 34	Blank	7.3.4. Tocilizumab	Administrative update – new heading
7.3.4.1. Dosing Page 34	Blank	Tociluzimab will be administered at a dose of 8mg/kg based on measured or estimated body weight with total dose not exceeding 800mg. Tocilizumab will be administered as an intravenous infusion via a central or peripheral line over a one-hour period. The appropriate dose of drug will be mixed in a 100 ml bag of 0.9% saline, after removing an equivalent volume of saline, 0.4ml/kg, to match the added drug, so that the total volume is 100 mls. The infusion speed must be 10 mls per hour for 15minutes and then increased to 130 mls per hour for the next 45 minutes. After completion of the infusion of active study drug, at least 20 mls of 0.9% saline should be used to flush the drug through the giving set.	Updated to include information on new intervention
7.3.4.2. Duration of therapy Page 35	Blank	A single dose will be administered. If the treating clinician believe there has not been sufficient clinical improvement, repeat administration of the same dose can be administered between 12 and 24 hours after the initial dose.	Updated to include information on new intervention

7.3.5. Sarilumab Page 35	Blank	7.3.5. Sarilumab	Administrative update – new heading
7.3.5.1. Dosing Page 35	Blank	Sarilumab will be administered as a single dose of 400 mg as an intravenous infusion via a central or peripheral line over a one-hour period. The drug will be mixed in a 100 ml bag of 0.9% saline, after removing an equivalent volume of saline so that the total volume is 100 mls. The infusion speed must be 10 mls per hour for 15 minutes and then increased to 130 mls per hour for the next 45 minutes. After completion of the infusion of active study drug, at least 20 mls of 0.9% saline should be used to flush the drug through the giving set.	Updated to include information on new intervention
7.3.5.2. Duration of therapy Page 35	Blank	A single dose of 400mg will be administered	Updated to include information on new intervention
7.3.6. Discontinuation of study drug Page 35	Section moved from 7.3.4. on page 34		Moved as an administrative change
SECTION 9 TRIAL CONDUCT	**Original text**	**New Text**	**Reason**
8.1.1 Microbiology Page 36	This protocol specifies the collection of biological samples from patients with COVID-19. Samples collected in patients who are enrolled in the CCP may be made available to REMAP-CAP investigators to evaluate aspects of host or pathogen biology associated with	This protocol specifies the collection of biological samples from patients with COVID-19. If additional sampling is required, beyond that specified in the CCP, for example for studies of pharmacokinetics this is permitted but will occur via separate protocol. Samples	Allows for possibility of sampling regimens that are different or extend beyond that provided for in the ISARIC Clinical

	assignment in this domain. Ethical approval at such sites and agreement from patients to undertake the CCP will be obtained separately.	collected in patients who are enrolled in the CCP or other studies may be made available to REMAP-CAP investigators to evaluate aspects of host or pathogen biology associated with assignment in this domain. Ethical approval at such sites and agreement from patients to undertake the CCP and other studies will be obtained separately.	Characterisation Protocol. Investigators at a UK site are particularly interested in writing a seaprate protocol for studying pharmacolinetic/pharma codynamic properties of agents in this domain.
SECTION 9 STATISTICAL CONSIDERATIONS	**Original text**	**New Text**	**Reason**
9.2. Unit-of-analysis and strata Page 38	Blank	An additional strata may be applied to the unit-of-analysis which will be determined by status with respect to one or more biomarkers comprising d-dimer, ferritin, C-reactive protein, neutrophil count, and lymphocyte count collected from samples collected closest to the time of randomization and not more than 2 hours after randomization. The exact biomarker strata structure will be specified in an operational document that will be finalized before the first interim analysis that applies the biomarker strata. It is believed that there is insufficient information regarding the biology of the disease to set the composition, categories and thresholds for this biomarker at the time of this amendment.	Allows for the creation of a new strata, within the PISOP stratum, to identify sub-groups of patients with differential treatment effect in this domain. There is insufficient information regarding the basic biology of this disease but new reports are emerging on a frequent basis. The assays that

			may contribute to the biomarker have been specified but the way in which these assays will contribute will be determined as new information becomes available and be specified in an operational document prior to the first interim analysis that applies the biomarker.
9.5. Nesting of interventions Page 40	Nesting is not applicable in this domain.	There is one nest within this domain, comprising Tocilizumab and Sarilumab. The rationale for this is that the mechanism of action of these agents is similar.	Both agents have a similar mechanism of action, so creation of a nest allows evaluation of their combined similar treatment effect as well as evaluation of each individual agent.
9.6. Threshold probability for superiority and inferiority Page 40	The threshold odds ratio delta for superiority and inferiority in this domain are those specified as the default threshold from the PAtC.	The threshold odds ratio delta for superiority and inferiority in this domain are those specified in the Operating Characteristics document derived from the	Provides an update to the protocol, reflected as an operational decision,

		PAtC. It is noted that the threshold for superiority and inferiority in the current model has been modified from 0.95 to 0.99 to provide adequate control of type I error, following the evaluation of simulations. It is also noted that asymmetric probabilities may be specified for harm, to allow early cessation and declaration of a Platform Conclusion for interventions that are unlikely to be effective and may be harmful. If so, this will be specified in the Operating Characteristics document which is placed in the public domain. It is also noted that the requirements for declaration of a Platform Conclusion for inferiority for the 'no immune modulation' intervention is modified so that such a declaration will be made if this intervention is inferior to one or more active interventions. The consequence of this is that the 'no immune modulation' intervention no longer needs to be inferior to all other interventions before a Platform conclusion is reached. This is necessary because of the increasing number of interventions within the domain and serves to remove the 'no immune modulation' intervention at the earliest possible time, if there are one or more effective interventions within the domain.	to make more stringent the statistical trigger threshold based on evaluation of simulations that evaluated frequency of type I error.
SECTION 10	**Original text**	**New Text**	**Reason**

ETHICAL CONSIDERATIONS			
10.1. Data Safety and Monitoring Board Page 42	Blank	Safety secondary outcomes will be reported to the DSMB who are empowered to require additional analyses regarding these outcomes as required.	Added to include specific reporting of occurrence of serious ventricular dysrhythmias to the DSMB.
10.2. Potential domain-specific adverse events Page 42	Blank	For patients assigned to tocilizumab or sarilumab • Severe thrombocytopenia, out of keeping with clinical disease • Severe neutropenia, out of keeping with clinical disease • Increase in LFTs to 5x upper limit of normal • Gastro-intestinal perforation • Allergic reactions, including anaphylactic reactions and angio-edema • Secondary opportunistic Infections, out of keeping with clinical disease	Updated to include information on new interventions
SECTION 11 GOVERNANCE ISSUES	**Original text**	**New Text**	**Reason**
11.2. Funding of domain interventions and outcome measures Page 43	The cost of IFN-β1a will be reimbursed or supplied by the study sponsor or supplied to participating sites by Faron Pharmaceuticals. The study is seeking support from Faron Pharmaceuticals for the cost or supply of	The supply and cost re-imbursement of the drugs will be vary by region and possibly even within different countries in a region. The options will include purchase of the drugs by individual recruiting sites or centrally by health bodies. In some cases, the drugs may be donated	Updated because reimbursement arrangements may vary between regions and to summarise in a single

	IFN-β1a. Faron Pharmaceuticals will have no role in the design, conduct, analysis, or reporting of this domain. The cost of anakinra will be reimbursed or supplied by the study sponsor or supplied to participating sites by Swedish Orphan Biovitrum AB (SOBI). The study is seeking support from SOBI for the cost or supply of anakinra. SOBI will have no role in the design, conduct, analysis, or reporting of this domain. Costs unrelated to study drug may be sought from one or more of pending grant applications, Faron Pharmaceuticals and SOBI.	for trial use by the relevant company (e.g. Roche UK have donated the tocilizumab for use in the UK). In other cases, the costs may be reimbursed by other companies (e.g. Faron Pharmaceuticals for the cost or supply of IFN-β1a). These companies will have no role in the design, conduct, analysis, or reporting of this domain. Costs unrelated to study drug may be sought from one or more of pending grant applications, Faron Pharmaceuticals and SOBI.	paragraph what had been previously stated on an intervention-by-intervention level.