



UMC Utrecht



MEDICAL RESEARCH
INSTITUTE
OF NEW ZEALAND



CCCTG
Canadian Critical Care
Trials Group



GLOBAL COALITION
FOR ADAPTIVE RESEARCH



REMAP-CAP
JAPAN



National University
Hospital



Domain-Specific Appendix: INFLUENZA IMMUNE MODULATION DOMAIN

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

In this domain ~~of the REMAP-CAP trial~~, participants meeting the platform entry criteria with microbiological testing-confirmed influenza virus infection will be randomized to receive one of up to three interventions depending on availability and acceptability:

- No immune modulation (no placebo)
- Tocilizumab
- Baricitinib

At this participating site the following interventions have been selected within this domain:

- ☐ No immune modulation (no placebo)
- ☐ Tocilizumab
- ☐ Baricitinib

This domain includes patients aged ≥ 2 years old. In this region, this domain will be offered to eligible participants aged:

- ☐ ≥ 2 years old and <12 years old
- ☐ ≥ 12 years and < 18 years old
- ☐ ≥ 18 years old

In this region:

- ☐ Patients who are known or suspected of being pregnant will be eligible for the tocilizumab intervention
- ☐ Patients who are known or suspected to be pregnant will be excluded from the tocilizumab intervention

<u>Age Stratum</u>	<u>≥ 2 years old and <12 years old</u>		<u>≥ 12 years and < 18 years old</u>		<u>≥ 18 years old</u>	
<u>Illness Severity State</u>	<u>Moderate State</u>	<u>Severe State</u>	<u>Moderate State</u>	<u>Severe State</u>	<u>Moderate State</u>	<u>Severe State</u>
<u>Domain-specific strata</u>	<u>N/A</u>	<u>N/A</u>	<u>N/A</u>	<u>N/A</u>	<u>N/A</u>	<u>N/A</u>
<u>Interventions specified in this DSA</u>	<u>Domain not available</u>	<ul style="list-style-type: none"> <u>No immune modulation</u> <u>Tocilizumab</u> <u>Baricitinib</u> 	<u>Domain not available</u>	<ul style="list-style-type: none"> <u>No immune modulation</u> <u>Tocilizumab</u> <u>Baricitinib</u> 	<u>Domain not available</u>	<ul style="list-style-type: none"> <u>No immune modulation</u> <u>Tocilizumab</u> <u>Baricitinib</u>
<u>Interventions submitted for approval in this jurisdiction</u>	<u>Domain not available</u>	<input type="checkbox"/> <u>No immune modulation</u> <input type="checkbox"/> <u>Tocilizumab</u> <input type="checkbox"/> <u>Baricitinib</u>	<u>Domain not available</u>	<input type="checkbox"/> <u>No immune modulation</u> <input type="checkbox"/> <u>Tocilizumab</u> <input type="checkbox"/> <u>Baricitinib</u>	<u>Domain not available</u>	<input type="checkbox"/> <u>No immune modulation</u> <input type="checkbox"/> <u>Tocilizumab</u> <input type="checkbox"/> <u>Baricitinib</u>

REMAP-CAP: Influenza Immune Modulation Domain Summary	
Interventions	<p><u>The following interventions are offered in this domain:</u></p> <ul style="list-style-type: none"> • No immune modulation (no placebo) • Tocilizumab • Baricitinib
Timing of Reveal	Randomization with Immediate Reveal <u>and initiation</u> , or Delayed Reveal and Initiation
<u>Population</u>	<p><u>This domain will be offered to the following patient categories:</u></p> <ul style="list-style-type: none"> • <u>Pediatric, Adolescent, and Adult Age Strata</u> • <u>Severe Illness Severity State</u>
<u>Domain-Specific Inclusions</u>	<p>Patients will be eligible for this domain if:</p> <ul style="list-style-type: none"> • <u>Patient is aged ≥ 2 years</u> • Influenza virus infection has been confirmed by microbiological testing. • <u>In the opinion of the treating clinician, the primary contributor to the patient's Severe Illness State is a respiratory tract infection</u> • <u>Patient has a community-acquired respiratory tract infection</u> • <u>Patient has pneumonia</u>
Domain-Specific Exclusions	<p>Patients will be excluded from this domain if they have any of the following:</p> <ul style="list-style-type: none"> • SARS-CoV-2 infection has been confirmed by microbiological testing • Known condition or treatment resulting in ongoing immune suppression including neutropenia prior to this hospitalization • A neutrophil count $< 1.0 \times 10^9 / L$ • Confirmed or strongly-suspected active mycobacterial infection or invasive fungal infection • Patient has already received any dose of one or more of any form of tocilizumab or another IL-6 receptor antagonist (e.g. sarilumab), baricitinib or another JAK inhibitor (e.g. tofacitinib, ruxolitinib or upadacitinib) during this hospitalization or is on long-term therapy with any of these agents prior to this hospital admission. • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	<p>Criteria that exclude a patient from a one or more interventions are:</p> <ul style="list-style-type: none"> • Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent. • Known or suspected pregnancy will result in exclusion from the baricitinib intervention. • It is recognised that there is a wide range of regulatory approaches and attitudes to the evaluation of interventions in pregnant trial participants across participating regions and sites. Known or suspected pregnancy is not an intervention-level exclusion for the tocilizumab intervention by default; however, if a site does not have regulatory approval to enrol pregnant patients to the tocilizumab intervention, known or suspected pregnancy will be applied as an intervention-specific exclusion and will result in exclusion from the tocilizumab intervention. • 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 • A platelet count $< 50 \times 10^9 / L$ will result in exclusion from receiving tocilizumab • <u>For adults and children ≥ 9 years of age, a baseline eGFR $< 15 \text{ mL/min/1.73m}^2$ and/or receipt of renal replacement therapy (including long-term renal replacement therapy) at baseline will result in exclusion from receiving baricitinib</u> • <u>For children ≥ 2 years and < 9 years of age, a baseline eGFR $< 30 \text{ mL/min/1.73m}^2$ and/or receipt of renal replacement therapy (including long-term renal replacement therapy) at baseline will result in exclusion from receiving baricitinib</u>

Outcome measures	<p>Primary endpoint: as specified in the REMAP-CAP Core Protocol <u>Core Protocol documents</u></p> <p>Secondary REMAP endpoints: refer to REMAP-CAP Core Protocol <u>Core Protocol documents</u></p> <p>Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment):</p> <ul style="list-style-type: none"> • Positive blood culture for pathogenic bacteria and/or fungus during this hospitalization and more than 48 hours following randomization • <u>Pulmonary aspergillosis, during this hospitalization and more than 48 hours following randomization, defined as culture of Aspergillus species from tracheal aspirate or bronchoalveolar lavage or invasive pulmonary aspergillosis diagnosed and treated with one or more systemic antifungal agent</u> • <u>Serious Adverse Events (SAE) as defined in Core Protocol documents</u>
<u>Platform Conclusions</u>	<p><u>The following Platform Conclusions are possible for this domain:</u></p> <ul style="list-style-type: none"> • <u>Efficacy of any active immune modulation intervention compared with ‘no immune modulation’ intervention</u> • <u>Superiority of any intervention within the domain</u> • <u>Inferiority of any intervention within the domain</u> • <u>Futility of one or more active immune modulation interventions compared with ‘no immune modulation’ intervention</u> • <u>Equivalence among active immune modulation interventions</u>
Unit of Analysis, Strata, and State	<p>This domain is analyzed in the interpandemic model, or its successor (as defined in relevant Core Protocol documents). The unit-of-analysis for this domain <u>corresponds to all patients who receive an allocation in this domain.</u> is the influenza-confirmed stratum. Within this stratum, the unit-of-analysis is further defined subdivided by the Severe illness-severity State and the presence or absence of bacterial co-infection <u>Bacterial Infection Diagnosed strata (defined as Bacterial Infection Diagnosed or Bacterial Infection Not Diagnosed).</u> Borrowing is permitted between strata.</p> <p>Response-adaptive randomization may be applied. No other strata contribute to the unit-of-analysis for this domain.</p>
Evaluable treatment-by-treatment Interactions	No interactions will be evaluated with any domain.
Nesting	None.

TABLE OF CONTENTS

1.	ABBREVIATIONS	8
2.	PROTOCOL APPENDIX STRUCTURE	9
3.	INFLUENZA IMMUNE MODULATION DOMAIN-SPECIFIC APPENDIX VERSION	10
3.1.	Version history	10
4.	INFLUENZA IMMUNE MODULATION DOMAIN GOVERNANCE.....	10
4.1.	Domain members.....	10
4.2.	Contact Details.....	12
5.	INFLUENZA IMMUNE MODULATION DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION 12	
6.	BACKGROUND AND RATIONALE.....	12
6.1.	Domain definition	12
6.2.	Domain-specific background.....	13
6.2.1.	Influenza.....	13
6.2.2.	Intervention strategy for this domain.....	15
6.2.3.	Tocilizumab	16
6.2.4.	Baricitinib	21
7.	DOMAIN OBJECTIVES.....	25
8.	TRIAL DESIGN	26
8.1.	Population.....	26
8.1.1.	Age Strata.....	26
8.1.2.	Illness Severity State	26
8.1.3.	Domain-specific strata	26
8.2.	Eligibility criteria.....	26
8.2.1.	Domain inclusion criteria	27
8.2.2.	Domain exclusion criteria	27
8.2.3.	Intervention exclusion criteria	27
8.3.	Interventions.....	28
8.3.1.	Influenza Immune Modulation Domain Interventions	28
8.3.2.	No Influenza Immune Modulation therapy	29
8.3.3.	Tocilizumab	29
8.3.4.	Baricitinib	29
8.3.5.	Discontinuation of study intervention	30

8.4.	Concomitant care	30
8.5.	Endpoints	31
8.5.1.	Primary endpoint	31
8.5.2.	Secondary endpoints	31
9.	TRIAL CONDUCT	31
9.1.	Microbiology	31
9.2.	Domain-specific data collection	31
9.3.	Criteria for discontinuation	32
9.4.	Blinding	32
10.	STATISTICAL CONSIDERATIONS	32
10.1.	Domain-specific stopping rules	32
10.2.	Unit-of-analysis and strata	34
10.3.	Application of Response-Adaptive Randomization	34
10.4.	Timing of revealing of randomization status	34
10.5.	Interactions with interventions in other domains	34
10.6.	Nesting of interventions	35
10.7.	Threshold probability for superiority, effectiveness, and inferiority	35
10.8.	Threshold odds ratio delta for equivalence and futility	35
10.9.	Statistical management of patients with intervention-specific exclusion	35
10.10.	Informative priors	36
10.11.	Post-trial sub-groups	36
11.	ETHICAL CONSIDERATIONS	37
11.1.	Data Safety and Monitoring Board	37
11.2.	Potential domain-specific adverse events	37
11.3.	Domain risk assessment	37
11.4.	Domain-specific consent issues	37
12.	GOVERNANCE ISSUES	38
12.1.	Funding of domain	38
12.2.	Funding of domain interventions and outcome measures	38
12.3.	Domain-specific declarations of interest	38
13.	REFERENCES	39

1. ABBREVIATIONS

ARDS	Acute respiratory distress syndrome
CRP	C- reactive protein
CRS	Cytokine release syndrome
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
eGFR	Estimated glomerular filtration rate
FDA	(US) Food and Drug Administration
ICU	Intensive Care Unit
ITSC	International Trial Steering Committee
PINSNP	Pandemic infection is neither suspected nor proven
PISOP	Pandemic infection is suspected or proven
PY	Patient-years
RCT	Randomized controlled trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see Glossary, Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study); a Statistical Analysis Appendix (principles of statistical analysis and models); a Patient, Pathogen and Disease Appendix to the Core Protocol (PANDA); multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain); and multiple Region-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s) within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions within each domain is covered in the relevant DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject to a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analytic model will also change over time in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis Appendix and an operational document referred to as the Current State. These documents are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the Statistical Design Team and Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a

RSA. This includes information related to local management, governance, and ethical and regulatory aspects. Within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the relevant Core Protocol, DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (~~www.remapcap.org~~).

3. INFLUENZA IMMUNE MODULATION DOMAIN-SPECIFIC APPENDIX

VERSION

The version of the Influenza Immune Modulation Domain-Specific Appendix is in this document's header and on the cover page.

3.1. *Version history*

Version 1: Approved by the Influenza Immune Modulation Domain-Specific Working Group (DSWG) on 29th September, 2023

Version 1.1: Approved by the Influenza Immune Modulation DSWG on 29th September, 2023. This version was developed for regions who were only able to include adult participants.

Version 2: Approved by the Influenza Immune Modulation DSWG on 5th November 2024

4. INFLUENZA IMMUNE MODULATION DOMAIN GOVERNANCE

4.1. *Domain members*

Chair: Dr Thomas Hills

Deputy Chair: Associate Professor Srinivas Murthy
Professor Frank van de Veerdonk

Members:
Professor Djillali Annane
Dr Alexandra Binnie
Dr Aidan Burrell
Professor Paul Dark
Professor Lennie Derde

Professor Anthony Gordon
Mr Cameron Green
Dr Antoine Guillon
Dr Andrea Haren
Dr Ken Hodson
Dr Anthony Jordan
Dr Karuna Keat
Professor Marian Knight
Dr Patrick Lawler
Professor David Lye
Dr Florian Mayr
Dr Colin McArthur
Professor Danny McAuley
Associate Professor Bryan McVerry
Dr Susan Morpeth
Dr Lyle Murray
Professor Alistair Nichol
Professor Asad Patanwala
Associate Professor Jason Phua
Professor Mathias Pletz
Dr Padmanabhan Ramanarayan
Associate Professor Luis Felipe Reyes
Dr Johnathan Luke Richardson
Dr Manoj Saxena
Professor Ian Seppelt
Professor Manu Shankar-Hari
Professor Wendy Sligl
Professor Steve Tong
Ms Anne Turner
Professor Tim Uyeki
Dr Gloria Vazquez-Grande
Professor Steve Webb

4.2. Contact Details

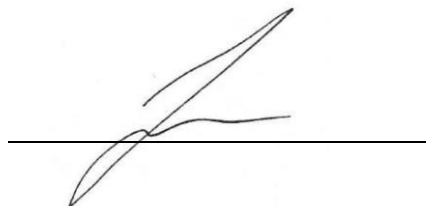
Chair: Dr Thomas Hills
Medical Research Institute of New Zealand
Wellington Hospital
Riddiford Street
Wellington 6021
New Zealand

~~Phone +64274277037~~
~~Email thills@adhb.govt.nz~~

5. INFLUENZA IMMUNE MODULATION DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The Influenza Immune Modulation Domain-Specific Working Group have read this appendix and authorize it as the official Influenza Immune Modulation Domain-Specific Appendix ~~for the study entitled REMAP-CAP~~. Signed on behalf of the committee

Chair
Dr Thomas Hills



Date 5th November, 2024

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain ~~within the REMAP-CAP platform~~ to test the effectiveness of immune modulation for ~~critically severely~~ ill hospitalized patients ~~admitted to hospital~~ with microbiological testing confirmed influenza virus infection.

6.2. Domain-specific background

6.2.1. Influenza

6.2.1.1. Introduction

Seasonal influenza is estimated to cause approximately 300,000 to 650,000 respiratory deaths worldwide each year (Iuliano et al., 2018). Reducing influenza mortality is a key focus of public health agencies around the world, through improvements in prevention, diagnostics and therapeutics. To date, there is limited evidence to support the use of pharmacological interventions for hospitalized patients with influenza virus infection. Uncertainty remains regarding the utility of influenza antiviral agents in hospitalized influenza patients (see Influenza Antiviral DSA). The role of corticosteroids in patients with pneumonia caused by or occurring in association with influenza virus infection has been a longstanding controversy (see Corticosteroid DSA). Several key clinical management research questions and evidence gaps have been described, including the role of immune modulation and other anti-inflammatory agents in severe influenza (Uyeki et al., 2022). This DSA seeks to understand the utility of immune modulation treatments in influenza patients with and without bacterial co-infection and to assess for the risk of secondary infections occurring following receipt of immune modulation therapy.

6.2.1.2. Hyperinflammation in influenza

Immune modulation, with corticosteroids, baricitinib, and IL-6 receptor antagonists, has been shown to improve survival in hospitalized patients with COVID-19 (Remap-Cap Investigators et al., 2021, Recovery Collaborative Group, 2021, Angus et al., 2020, Recovery Collaborative Group et al., 2021, Group, 2022). Severe influenza and severe COVID-19 share features of a cytokine release syndrome (CRS) or ‘hyperinflammatory’ response, at least in a subset of patients (Liu et al., 2016, Bain et al., 2021). Levels of specific pro-inflammatory cytokines have been compared in bronchoalveolar lavage fluid from patients with severe COVID-19, severe influenza, moderate influenza, and controls. Elevated levels of IL-1, IL-6, IL-8, MCP-1, MIG, IP-10, IL-12, and MIP-1 β were seen in those with severe COVID-19 or severe influenza when compared with moderate influenza and control patients (Reynolds et al., 2021). Levels of IL-1 in bronchoalveolar lavage fluid were higher in severe influenza than severe COVID-19 (Reynolds et al., 2021). [In children hospitalized with H1N1 influenza, plasma IL-1 \$\beta\$ and IL-6 correlate with disease severity \(Chiaretti et al., 2013\).](#) The similarity of the hyperinflammatory response observed in influenza and COVID-19 provides a rationale for the evaluation of immune modulation strategies with demonstrated efficacy for the treatment of severe

COVID-19 in severe influenza. The utility of immune modulation in severe influenza is not known and clinical trials are necessary to determine efficacy.

6.2.1.1. *Influenza and bacterial pneumonia*

Influenza may be associated with concomitant bacterial infection that is present at the time a patient with influenza is hospitalized (termed 'bacterial co-infection' here) or bacterial infection that occurs during hospitalization and treatment for severe influenza (termed bacterial 'secondary infection' here).

6.2.1.2. *Influenza and bacterial co-infection*

Patients presenting with severe influenza may or may not have bacterial co-infection at the time of hospitalization. The reported rates of bacterial co-infection in influenza vary widely (2% to 65%) but the proportion of hospitalized influenza patients with proven bacterial co-infection probably lies between 11% and 35% (Klein et al., 2016). When bacterial co-infection exists, it can be clinically evident (e.g. lobar pneumonia) or indistinguishable from severe influenza virus infection alone. Bacterial co-infection is associated with an increased risk of death (Chertow and Memoli, 2013), however, it is unclear whether developing organ dysfunction occurs as a result of influenza virus infection, bacterial infection, or both. It is plausible that immune modulation interventions have differential treatment effects in patients with and without bacterial co-infection and studying immune modulation interventions in these two groups is important.

6.2.1.3. *Bacterial secondary infection and immune modulation*

Much of the experience with immune modulation for viral pneumonia comes from COVID-19. Some reports describe bacterial infection as relatively rare with COVID-19, although data are inconsistent and empiric broad-spectrum antibiotic use, including prior to the identification of a bacterial infection, was initially very common (Russell et al., 2021, Manohar et al., 2020, Kitsios et al., 2021). Bacterial secondary infections have specifically been reported to be more common with COVID-19 than influenza, although interpretation of these data is limited by the pandemic context where COVID-19 patients in a critical care unit may be more unwell than historic comparators with influenza (Shafran et al., 2021). Randomized clinical trial evidence has helped clarify the safety of immune modulation in COVID-19, in terms of secondary infections. For example, in a recent WHO meta-analysis of IL-6 receptor antagonists in COVID-19, secondary infections occurred in 21.9% of patients treated with IL-6 receptor antagonists vs 17.6% of patients treated with usual care or placebo (OR accounting for trial sample sizes, 0.99; 95% CI, 0.85-1.16) (WHO Rapid Evidence

Appraisal for COVID-19 Therapies Working Group et al., 2021). Thus, it will be important to identify bacterial secondary infection, plausibly related to immune modulatory interventions (occurring at least 48 hours post-enrolment), and to distinguish this from bacterial co-infection.

6.2.1.4. *Influenza infection and subsequent cardiovascular events*

CAP and influenza virus infection are associated with an increased risk of cardiovascular events (Kwong et al., 2018, Warren-Gash et al., 2009, Barnes et al., 2015, Kulick et al., 2021). This risk is most pronounced in the period immediately following the acute illness but may persist for years. For example, the incidence of myocardial infarction, stroke, and fatal coronary heart disease was elevated in the first year after hospitalization with CAP (HR 4.07; 95% CI, 2.86-5.27) but remained elevated out to 10 years (HR 1.86; 95% CI, 1.18-2.55). Randomized trial evidence demonstrate that influenza vaccination reduces the risk of cardiovascular events in at risk populations (Frobert et al., 2021, Barnes et al., 2015, Warren-Gash et al., 2009). The mechanisms that underpin the increased risk of cardiovascular events following influenza are unknown although it has been hypothesized that the inflammatory response to influenza virus infection, including elevated levels of pro-inflammatory cytokines such as IL-6, predisposes to cardiovascular events (Guan et al., 2012).

6.2.1.1. Severe influenza in children

Influenza is responsible for significant morbidity and mortality in children, especially children less than 5 years of age and those with underlying medical conditions, although the burden varies considerably with influenza season (Doyle and Campbell, 2019). Data guiding influenza therapies in the pediatric population are lacking, leaving clinicians to extrapolate findings from studies in adults to pediatric patients. Pediatric immune modulator dosing is included in this DSA to allow for recruitment of pediatric participants at sites where the approved Core Protocol permits the recruitment of children.

6.2.2. *Intervention strategy for this domain*

This domain will evaluate the potential benefits of immune modulation for influenza.

If at any stage, external evidence of harm or definitive evidence of absence of effectiveness in critically ill or ward patients or both emerges for one or more interventions specified in this domain, the ITSC, as advised by the DSWG, may remove the intervention(s) prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to the intervention will occur, so as to contribute additional weight of evidence in the public domain.

6.2.3. Tocilizumab

6.2.3.1. *Tocilizumab – biological rationale and pre-clinical studies*

Tocilizumab is a humanized monoclonal antibody that inhibits both membrane-bound and soluble 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. While tocilizumab was first approved by the Food and Drug Administration (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 cytokine release syndrome (CRS) associated with chimeric antigen receptor T cell cancer therapy due to its efficacy and safety profile.

REMAP-CAP recently demonstrated efficacy of IL-6 receptor antagonists , along with systemic corticosteroids , for critically ill COVID-19 patients. The RECOVERY trial has also shown that tocilizumab is effective in hospitalized patients with COVID-19 (Recovery Collaborative Group, 2021). A recent WHO meta-analysis noted that IL-6 receptor antagonist treatment of COVID-19 may only reduce 28-day all-cause mortality when given with concomitant corticosteroids (WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group et al., 2021). In December 2022, the FDA approved tocilizumab for treatment of hospitalized adults with severe COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (<https://www.fda.gov/news-events/press-announcements/fda-roundup-december-23-2022#:~:text=On%20Wednesday%2C%20the%20FDA%20approved,invasive%20mechanical%20ventilation%2C%20or%20extracorporeal>).

It is now imperative that we understand whether IL-6 receptor antagonist treatment is effective in severe pneumonia, including acute respiratory distress syndrome (ARDS) caused by other viral pathogens. Patients with ARDS due to severe COVID-19 have blood IL-6 levels that are comparable with levels seen with ARDS due to influenza and other viral pathogens, but lower than bacterial ARDS, confirming that elevated IL-6 levels are not unique to COVID-19 (Bain et al., 2021). The role of immune modulation strategies in severe pneumonia/ARDS due to pathogens other than SARS-CoV-2 remains unclear.

IL-6 is a pleiotropic cytokine that drives much of the hyperinflammatory response seen in cytokine release syndromes. Signaling through the IL-6 pathway is activated in response to influenza virus infection (Wang et al., 2015). In a human challenge model of influenza A(H1N1) virus infection, IL-6

levels in nasal lavage fluid were correlated with symptoms and signs of influenza virus infection and with viral shedding (Skoner et al., 1999, Gentile et al., 1998). High IL-6 levels were noted in bronchoalveolar lavage fluid from severe influenza (and severe COVID-19 patients) when compared with moderate influenza patients and controls (Reynolds et al., 2021). Levels of IL-6 are elevated in patients with severe influenza due to influenza A(H1N1)pdm09 virus infection (Hagau et al., 2010), and IL-6 has been identified as a biomarker of disease severity (Paquette et al., 2012). IL-6 levels were associated with mortality in patients hospitalized with influenza A(H1N1)pdm09 virus infection (Paquette et al., 2012). Further, IL-6 expression was inversely associated with arterial oxygen levels in hospitalized patients with influenza infection (Bermejo-Martin et al., 2009).

It is unclear whether IL-6 is elevated as a marker of disease severity or whether it contributes to the pathogenesis of severe disease following influenza virus infection. The pre-clinical evidence on the role of IL-6 in the pathophysiology of severe influenza infection is conflicting. For example, IL-6 has been shown to drive muscle dysfunction in a mouse model of influenza and this was attenuated by treatment with tocilizumab (Radigan et al., 2019). In a lethal mouse model of influenza A(H1N1)pdm09 virus infection, a pronounced IL-6-associated inflammatory response was demonstrated. However, using an IL-6 knockout mouse model, there was no significant difference in viral load, pathology, weight loss, or survival observed between IL-6^{-/-} and wild-type mice (Paquette et al., 2012). Other animal work has suggested a protective role for IL-6 (Dienz et al., 2012, Yang et al., 2017).

The relevance of mouse models of severe influenza virus immunopathology is uncertain. For example, it was postulated that TLR3 signaling would be critical for a protective host response to influenza virus infection and that TLR3 knockout mice would be more likely to succumb following challenge with influenza virus. TLR3 signaling drives the production of IL-6 and other cytokines. However, it was observed that TLR3 knockout mice had a reduced inflammatory response (including reduced IL-6 levels in bronchoalveolar lavage fluid) but, contrary to the hypothesis, survival was improved (Le Goffic et al., 2006).

Data from human studies are lacking. There are no data on tocilizumab as a treatment for influenza. There are no clinical trials of IL-6 receptor antagonists in influenza registered on www.clinicaltrials.gov. Whether immune modulation strategies for the treatment of influenza could prolong viral shedding is also unknown.

6.2.3.2. *Tocilizumab – safety profile*

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 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>). There were no reported adverse events in the 60 tocilizumab-treated patients submitted to the FDA for cytokine release syndromes associated with chimeric antigen receptor T cell cancer therapies which recommends a maximum of 4 doses for treatment (Lee et al., 2019).

Tocilizumab has an established role, and an established safety profile, in the management of children with JIA. For example, in a pivotal trial of 112 children (2 to 17 years of age) with active systemic JIA, clinical improvement was observed in significantly more in patients given tocilizumab (8 mg/kg if weight \geq 30 kg and 12 mg/kg if weight <30 kg) every two weeks for 12 weeks than in the placebo group (64 of 75 [85%] vs. 9 of 37 [24%], $P<0.001$) (De Benedetti et al., 2012). Adverse events were similar to those seen in adults. In the double-blind phase, 159 adverse events, including 60 infections (2 serious), occurred in the 75 participants in the tocilizumab group, as compared with 38, including 15 infections, in the 37 participants in the placebo group (De Benedetti et al., 2012). A similar safety profile was observed with four weekly tocilizumab dosing of JIA patients, where serious infections or occurred at a rate of 4.9/100 PY, comparable to the rate seen in adults, and no deaths were reported during the study (Brunner et al., 2015). Further, tocilizumab is increasingly

used for the acute treatment of cytokine release syndrome associated with Chimeric Antigen Receptor T Cell Therapy for pediatric leukemia (Fitzgerald et al., 2017).

Observational data from a small cohort of patients treated with tocilizumab for juvenile idiopathic arthritis (10 patients with a mean age of 14 years) did not identify an increased risk of severe disease following influenza virus infection (Kawada et al., 2013). Compared to patients with JIA on non-biologic treatments, those who developed influenza on tocilizumab had less fever, a shorter duration of fever when it occurred, and a lower C-reactive protein (CRP), although numbers were small. No patients in either group developed severe complications. The relevance of this long-term tocilizumab treatment data from patients with juvenile idiopathic arthritis who developed influenza, when considering the potential short duration of treatment for severe influenza, is unknown.

Finally, and most importantly as it pertains to the proposed study, tocilizumab has been used extensively for the treatment of severe COVID-19 with clear evidence of a mortality benefit (Remap-Cap Investigators et al., 2021, Recovery Collaborative Group, 2021). A meta-analysis noted improved survival with IL-6 receptor antagonist treatment and no significant increase in secondary bacterial infections, which occurred in 21.9% of patients treated with IL-6 antagonists vs 17.6% of patients treated with usual care or placebo (OR accounting for trial sample sizes, 0.99; 95% CI, 0.85-1.16) (WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group et al., 2021).

6.2.3.3. *Tocilizumab in pregnancy*

Pregnancy is associated with poor clinical outcomes in both COVID-19 and influenza (Zambrano et al., 2020, Martinez-Portilla et al., 2021, Uyeki et al., 2019). Based on the efficacy in non-pregnant patients, it is recommended that “tocilizumab should be strongly considered” for pregnant women with severe COVID-19 (<https://www.rcog.org.uk/guidance/coronavirus-covid-19-pregnancy-and-women-s-health/coronavirus-covid-19-infection-in-pregnancy/>). Identifying effective treatments for severely unwell pregnant women with influenza is a priority.

Data on the safety of tocilizumab in pregnancy continue to accrue, both from the use of tocilizumab to treat chronic conditions and as an acute treatment for COVID-19. Human pregnancy safety data are provided by case reports/series which collectively describe 367 pregnancies among women with chronic conditions who were receiving regular treatment with tocilizumab at the time of conception (Saito et al., 2019, Tada et al., 2019, Weber-Schoendorfer and Schaefer, 2016, Hoeltzenbein et al., 2016, Nakajima et al., 2016, Cruz-Machado et al., 2021, Saito et al., 2021, Imaizumi et al., 2022, Konagai et al., 2023, Gotestam Skorpen et al., 2016, Kaneko et al., 2016, Rubbert-Roth et al., 2010, Ishikawa et al., 2012). An additional 51 cases of gestational tocilizumab exposure have been

reported in case reports/series which describe acute tocilizumab treatment of severe COVID-19 (Easterlin et al., 2020, Naqvi et al., 2020, San-Juan et al., 2020, Abdullah et al., 2021, Chinen et al., 2021, Isaac et al., 2023, Guiritan and Cataluna, 2023, Jimenez-Lozano et al., 2021). For these uncontrolled data, where details were provided, most women discontinued tocilizumab use early in pregnancy. As such, evidence is generally lacking regarding the safety of long-term use in pregnancy. Few controlled studies exist and have only been conducted using non-denominator based adverse drug event datasets containing 357 adverse reaction reports where maternal tocilizumab use was used in pregnancy (Ghalandari et al., 2022, Deroncourt et al., 2023).

Although adverse pregnancy outcomes have been described following in utero exposure to tocilizumab, including cases of congenital anomaly, miscarriage, low birth weight and preterm delivery, the crude rates of these events do not appear to be notably increased above their respective expected background rates, and no pattern of malformation has been observed. Of note, no adverse events considered attributable to the tocilizumab exposure were described among the small number of women with acute treatment of severe COVID-19. Additionally, the studies of adverse drug events did not identify any signals of disproportionality for any specific adverse pregnancy outcome. Conversely, tocilizumab has been shown to improve morbidity and mortality from acute, severe COVID-19 in a non-pregnant population (Group, 2021) which is beneficial to both the pregnant woman and her baby. There are theoretical concerns that immunosuppressant antibodies which actively cross the placenta during pregnancy could result in neonatal/infant immunosuppression and increase the risk of neonatal/infant infection. There is a lack of safety data investigating these specific concerns, but currently no reports indicating such associations exist following exposure in human pregnancy. As a precaution, live vaccines should not be routinely used until the infant is 6 months old following in utero biologic immunosuppressant exposure.

The United Kingdom Tetralogy Information Service will continue to provide up-to-date information about safety data on the use of tocilizumab in pregnancy:

<https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-TOCILIZUMAB-IN-PREGNANCY/>

6.2.3.4. *Tocilizumab – dosing*

Adult participants

Tocilizumab will be administered using similar dosing to the REMAP-CAP COVID-19 Immune Modulation DSA, which aligns with the dosing used for longer-term tocilizumab treatment in

rheumatological diseases. A single dose of 8mg/kg, based on measured or estimated body weight, with total dose not exceeding 800mg, will be administered.

Pediatric participants

Tocilizumab will be administered using similar dosing to that used in the management of JIA. For children weighing at least 30 kg, a single dose of 8mg/kg, based on measured body weight, with total dose not exceeding 800mg, will be administered. For children weighing less than 30kg, the tocilizumab dose is 12mg/kg.

6.2.4. Baricitinib

6.2.4.1. *Baricitinib – biological rationale, pre-clinical studies, and clinical studies*

Baricitinib is an oral selective Janus kinase (JAK)1/JAK2 inhibitor that has been widely used for autoimmune and atopic diseases. There is a biological rationale for baricitinib therapy in severe influenza virus infection. Baricitinib inhibits the intracellular signaling of cytokines known to be elevated in severe influenza (and severe COVID-19), including the key inflammatory cytokine interleukin-6 (see section 6.2.4.1). In summary, signaling through the IL-6 pathway is activated in response to influenza virus infection (Wang et al., 2015). IL-6 levels correlate with influenza symptoms, signs, disease severity, and mortality (Skoner et al., 1999, Gentile et al., 1998, Reynolds et al., 2021, Hagau et al., 2010, Paquette et al., 2012). It is unclear whether IL-6 is elevated as a marker of disease severity or whether it drives the pathogenesis of severe disease following influenza virus infection. JAK1/JAK2 inhibition with baricitinib modulates the effect and reduces the levels of IL-6 and a number of other pro-inflammatory cytokines. For example, detailed biomarker studies from patients with COVID-19 demonstrate that baricitinib treatment can rapidly reduce the levels of cytokines associated with the hyperinflammatory response seen in severe SARS-CoV-2 infection (e.g. IL-1, IL-6, and MCP-1 – cytokines also elevated in severe influenza) (Sims et al., 2021, Reynolds et al., 2021).

While immune modulation effects are hypothesized to be the potential mechanism of action for baricitinib in severe influenza, JAK1/JAK2 inhibition may also have anti-viral effects. It has been shown that the NS1 protein of the influenza A(H1N1) virus activates the PI-3 kinase pathway and inhibits virus-induced apoptotic signaling responses leading to increased virus replication (Ehrhardt et al., 2007). Targeting this pathway inhibits influenza A virus replication in vitro (Wang et al., 2020). Recent studies using genome-wide screening to search for host factors as potential antiviral targets

have identified molecules that play important roles in influenza virus replication. Among them, JAK1 and JAK2 are leading drug target candidates (Watanabe et al., 2014).

Importantly, baricitinib is an effective therapy in adults hospitalized with severe COVID-19. The placebo-controlled phase 3 Adaptive COVID-19 Treatment Trial 2 (ACTT-2) enrolled 1033 participants (Kalil et al., 2021). Patients receiving corticosteroids were excluded from ACTT-2. Combination therapy with baricitinib and remdesivir was superior to remdesivir alone in reducing the time to recovery (rate ratio 1.16, 95% CI 1.10-1.32, $p=0.03$). In the ACTT-2 study, baricitinib did not reduce the secondary outcome of 28-day mortality (5.1% vs 7.8%, hazard ratio 0.65, 95% CI 0.39-1.09).

The COV-BARRIER study was a phase 3 double-blind randomized clinical trial of baricitinib in addition to standard of care (which could include corticosteroids) in hospitalized adults with COVID-19 who did not require mechanical ventilation (Marconi et al., 2021). 1525 participants were randomly assigned to receive baricitinib ($n=764$) or placebo ($n=761$). 1204/1518 (79.3%) of participants with available data were receiving systemic corticosteroids at baseline. There was no difference in disease progression; 27.8% of participants receiving baricitinib and 30.5% of those receiving placebo progressed to meet the composite primary endpoint including increased oxygen support or death by day 28 (odds ratio 0.85, 95% CI 0.67-1.08, $p=0.18$). However, 28-day all-cause mortality (a secondary outcome) was significantly lower (8% vs 13%) with baricitinib therapy (hazard ratio 0.57, 95% CI 0.41-0.78, $p=0.0018$). In those requiring high flow oxygen or non-invasive ventilation at baseline, the hazard ratio for all-cause 28-day mortality was 0.52 (95% CI 0.33-0.80). An addendum to the COV-BARRIER trial enrolled patients who required invasive mechanical ventilation (Ely et al., 2022). In this critically ill population, studied later in the pandemic, standard of care included corticosteroids at baseline in 86% of participants. The 28-day all-cause mortality was again significantly lower with baricitinib than placebo (39% vs 58%, hazard ratio 0.54, 95% CI 0.31-0.96, $p=0.03$).

The largest study of baricitinib in hospitalized adults with COVID-19 is the RECOVERY trial, which randomized 8156 patients to either baricitinib or usual care (Recovery Collaborative Group, 2022). At baseline, 95% of patients were receiving corticosteroids and 23% were receiving tocilizumab. Death within 28 days was lower with baricitinib (12%) compared with usual care (14%); age-adjusted rate ratio 0.87 (95% CI 0.77-0.99, $p=0.028$). A meta-analysis including the results from RECOVERY and eight other completed trials, involving 11 888 randomly assigned patients and 1485 deaths, allocation to baricitinib or another JAK inhibitor was associated with a 20% proportional reduction in mortality (rate ratio 0.80, 95% CI 0.72-0.89, $p<0.0001$) (Recovery Collaborative Group, 2022).

Taken together, these data indicate baricitinib is an effective therapy for severe COVID-19, with greater treatment effects seen in critically ill patients. There are no studies of baricitinib for severe influenza.

6.2.4.2. *Baricitinib – safety profile*

There is extensive experience with long-term outpatient baricitinib use. Baricitinib is generally well-tolerated and long-term follow-up of phase one, two, and three studies have assessed for important relevant safety signals, including serious infections (Winthrop et al., 2020). Studies of baricitinib use in rheumatoid arthritis patients demonstrated no increased risk of serious infection with long term use of 2mg daily or 4mg daily for a 1-year period but found an increase in treatment-related infection from 75 to 88 per 100-person years with long-term 4 mg dosing (Winthrop et al., 2020). Further analyses have found an increased rate of herpes zoster infection with long-term use of 4 mg of baricitinib; an increased risk of herpes zoster infection appears to be a class effect also observed with other JAK inhibitors (Alvaro-Gracia et al., 2021, Genovese et al., 2020). Safety data from long-term baricitinib use may not be relevant when considering short courses of baricitinib as therapy for acute influenza virus infection.

There are no published safety or pharmacokinetic data available on baricitinib treatment of hospitalized influenza patients but the safety of baricitinib has been demonstrated in hospitalized, including critically-ill, COVID-19 patients. For example, ACTT-2 enrolled 1033 hospitalized patients with COVID-19 and found that serious adverse events were less common in the baricitinib group than in the control group (16% vs. 21%) (Kalil et al., 2021). Further, ACTT-2 demonstrated no increased risk of new infections with a 14-day treatment course of baricitinib compared with placebo (5.9% vs. 11.2%). The COV-BARRIER study enrolled 1525 hospitalized COVID-19 patients and found that serious adverse events occurred in 110 (15%) participants in the baricitinib group and 135 (18%) participants in the placebo group). Serious infections occurred in 64 (9%) participants randomized to baricitinib and 74 (10%) participants randomized to placebo (Marconi et al., 2021). In the 101-participant addendum to the COV-BARRIER trial, recruiting participants who required invasive mechanical ventilation or extracorporeal membrane oxygenation, serious adverse events occurred in 25 (50%) participants in the baricitinib group and 35 (71%) participants in the placebo group (Ely et al., 2022). Serious infections were reported for 22 (44.0%) participants who received baricitinib and 26 (53.1%) who received placebo. In the 8156 patient RECOVERY trial of baricitinib, there were no new safety concerns and no significant difference in the rates of non-SARS-CoV-2 infection with baricitinib (9.8%) vs usual care (9.9%) (Recovery Collaborative Group, 2022).

Venous thromboembolism has been reported with long-term baricitinib use in rheumatoid arthritis (0.5 events per 100 patient-years) (Genovese et al., 2020). However, there was no increased rate of venous thromboembolism with baricitinib treatment in COV-BARRIER (occurring in 3% of those assigned to placebo and 3% of those assigned to baricitinib), in critically ill participants in the addendum to COV-BARRIER (occurring in 6% of those assigned to placebo and 6% of those assigned to baricitinib), or in RECOVERY, where thrombotic events occurred in 4.6% of those assigned to usual care and 4.4% of those assigned to baricitinib (Marconi et al., 2021, Ely et al., 2022, Recovery Collaborative Group, 2022).

Long-term use of JAK inhibitors (JAKi) has been described for children with alopecia areata and JIA. When administered for the treatment of alopecia areata, JAKi were well-tolerated with only mild adverse effects (Hamilton and Craiglow, 2020). When used at varied doses in the management of rheumatological conditions, such as JIA, interferonopathies, and pediatric cancers, potential adverse effects such as infections were reported in some case series (Hamilton and Craiglow, 2020). In a phase 3 multicenter, double-blind, withdrawal, efficacy, and safety study of baricitinib in 163 children with JIA, the proportion of patients with a flare was significantly lower for baricitinib vs placebo (14 [17.1%] vs 41 [50.6%], $p < 0.001$) (Ramanan et al., 2022). In the placebo and baricitinib groups, 38 (46.9%) and 54 (65.9%) of participants reported treatment emergent adverse respectively, SAEs occurred in 3 (3.7%) of those receiving placebo and 4 (4.9%) of those receiving baricitinib, and there were no deaths (Ramanan et al., 2022). In the RECOVERY trial, 33 children were randomly assigned to receive baricitinib or usual care. Given the low numbers relative to the 8123 adults in the RECOVERY trial of baricitinib for patients hospitalized with COVID-19, outcomes in these 33 children were reported descriptively and the authors did not report any new safety signals in this population (Recovery Collaborative Group, 2022). The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization to permit the use of baricitinib for COVID-19 in hospitalized pediatric patients at least 2 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (<https://www.fda.gov/media/143823/download>).

6.2.4.3. *Baricitinib in pregnancy*

Baricitinib is a small molecule expected to readily cross the placenta; recommendations on the safety of baricitinib in pregnancy are not available due to a lack of data (Sammaritano et al., 2020). Patients who are pregnant or breastfeeding will not be eligible for randomization to baricitinib within this domain.

6.2.4.4. Baricitinib – dosing

Adult participants

Baricitinib is rapidly absorbed after enteral administration. Clearance is via renal elimination of the parent compound and dosing is dependent on renal function. Baricitinib will be administered at the same dose used for COVID-19. The daily baricitinib dose depends on the most recent eGFR.

Baricitinib will be given at a dose of 4 mg daily if the eGFR is ≥ 60 mL/min. Baricitinib will be given at a dose of 2 mg daily if the eGFR is 30 to <60 mL/min. Baricitinib will be administered at a dose of 1 mg daily if the eGFR is 15 to <30 mL/min. Baricitinib will be withheld if the eGFR is <15 mL/min or the patient is receiving renal replacement therapy.

Pediatric participants

In children 9 years of age and older, the same dose of baricitinib used in adults will be administered. In children 2 years to <9 years of age with an eGFR ≥ 60 mL/min, the baricitinib dose will be 2mg daily. In children 2 years to <9 years of age with an eGFR of 30 to <60 mL/min, baricitinib will be given at a dose of 1 mg daily. In children 2 years to <9 years of age, baricitinib will be withheld if the eGFR is <30 mL/min or the patient is receiving renal replacement therapy.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of immune modulation interventions for critically/severely ill hospitalized patients with confirmed influenza virus infection.

We hypothesize that the probability of the occurrence of the primary endpoint specified in the relevant Core Protocol documents will differ based on allocation to influenza immune modulation therapy. The following interventions will be available:

- No immune modulation (no placebo)
- Tocilizumab
- Baricitinib

We hypothesize that the treatment effect of immune modulation therapy is different depending on the presence or absence of diagnosed bacterial co-infection at the time of enrollment.

8. TRIAL DESIGN

~~This domain will be conducted as part of the REMAP-CAP trial. Treatment allocation will be based on response adaptive randomization, as described in Core Protocol documents.~~

8.1. *Population*

~~This domain enrolls patients who are admitted to hospital with microbiological testing confirmed influenza virus infection.~~

~~8.1.1.~~ Age Strata

~~This domain is available to patients in the Pediatric, Adolescent, or Adult Age Stratum, as defined in Core Protocol documents. Eligibility within these strata may be further constrained by domain-specific eligibility criteria specified below. Participating sites may chose to offer this domain to patients in one or more (or all) of these Age Strata~~

~~8.1.1-8.1.2.~~ Illness Severity State

~~This domain is available for patients who are in the Severe State, as defined in Core Protocol documents.~~

~~8.1.2-8.1.3.~~ Domain-specific strata

Domain-specific strata are not applied to patients at the time of assessment for this domain.

~~8.1.2.1.~~ Bacterial Co-Infection Strata

~~Bacterial Co-infection Strata are applied within the unit of analysis of this domain. Patients diagnosed with probable or confirmed bacterial co-infection will be categorized as members of the Bacterial Co-infection Diagnosed Stratum. Patients with possible or unlikely bacterial co-infection will be categorized as members fo the Bacterial Co-infection Not Diagnosed Stratum. At the time of launch of this domain, these strata will be domain-specific but it is anticipated that bacterial infection strata may be incorporated into the Platform in the future.~~

8.2. *Eligibility criteria*

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified In relevant Core Protocol Documents. Patients eligible

for the REMAP-Platform may have conditions that exclude them from the Influenza Immune Modulation Domain.

8.2.1. Domain inclusion criteria

Patients are eligible for this domain if:

- Patient is aged ≥ 2 years
- Influenza virus infection has been confirmed by microbiological testing
- In the opinion of the treating clinician, the primary contributor to the patient's Severe Illness State is a respiratory tract infection
- Patient has community-acquired respiratory tract infection
- Patient has pneumonia

8.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- SARS-CoV-2 infection has been confirmed by microbiological testing
- Known condition or treatment resulting in ongoing immune suppression, including neutropenia, prior to this hospitalization
- A neutrophil count $< 1.0 \times 10^9 / L$
- Confirmed or strongly-suspected active mycobacterial infection or invasive fungal infection
- Patient has already received any dose of one or more of any form of tocilizumab or another IL-6 receptor antagonist (e.g. sarilumab), baricitinib or another JAK inhibitor (e.g. tofacitinib, ruxolitinib or upadacitinib) during this hospitalization or is on long-term therapy with any of these agents prior to this hospital admission.
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

8.2.3. Intervention exclusion criteria

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons. In such cases, patients will be randomly allocated a remaining intervention from among those available at that site.

Patients who are eligible for only a single intervention at a site (i.e. all other interventions are contraindicated) are not eligible for this domain. Patients in whom all interventions are contraindicated will be treated according to the current standard of care at the clinician's discretion.

Criteria that exclude a patient from a one or more interventions are:

- Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent.
- Known or suspected pregnancy will result in exclusion from the baricitinib intervention. 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.
- It is recognised that there is a wide range of regulatory approaches and attitudes to the evaluation of interventions in pregnant trial participants across participating regions and sites. Known or suspected pregnancy is not an intervention-level exclusion for the tocilizumab intervention by default; however, if a site does not have regulatory approval to enrol pregnant patients to the tocilizumab intervention, known or suspected pregnancy will be applied as an intervention-specific exclusion and will result in exclusion from the tocilizumab intervention.
- 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
- A platelet count $< 50 \times 10^9 / L$ will result in exclusion from receiving tocilizumab
- In adults and in children ≥ 9 years of age, a baseline eGFR $< 15 \text{ mL/min/1.73m}^2$ and/or receipt of renal replacement therapy (including long-term renal replacement therapy) at baseline will result in exclusion from receiving baricitinib
- In children aged > 2 years and < 9 years, a baseline eGFR $< 30 \text{ mL/min/1.73m}^2$ and/or receipt of renal replacement therapy (including long-term renal replacement therapy) at baseline will result in exclusion from receiving baricitinib

8.3. Interventions

8.3.1. Influenza Immune Modulation Domain Interventions

Patients will be randomly assigned to receive either of the following open-label strategies. The interventions will be commenced immediately after allocation status is revealed.

☐ No immune modulation (no placebo)

☐ Tocilizumab

☐ Baricitinib

8.3.2. No Influenza Immune Modulation therapy

Patients assigned to this intervention are not to receive any additional targeted immune modulation therapy until the end of study day 28 or hospital discharge, whichever occurs first. Corticosteroids can be administered, either by enrolment in the Corticosteroid Domain of REMAP-CAP or as determined by the treating clinician.

8.3.3. Tocilizumab

The dose of tocilizumab is dependent on age and weight. Tocilizumab will be administered as a single dose of 8mg/kg based on measured body weight (or estimated body weight in adults if measured body weight is unavailable) with the total dose not exceeding 800mg. In children weighing less than 30 kg, the tocilizumab dose will be 12mg/kg. Tocilizumab will be commenced as soon as possible following reveal of allocation and 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 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.

8.3.4. Baricitinib

The dose of baricitinib is dependent on age and renal function. The dose of baricitinib administered will depend on the most recent eGFR, including modification of dose for change in renal function during the treatment period.

In adults and in children 9 years of age and older, baricitinib ~~Baricitinib~~ will be administered enterally at a dose of 4 mg daily if the eGFR is at least 60 mL/min/1.73m². Baricitinib will be given at a dose of 2 mg daily if the eGFR is at least 30 and less than 60. Baricitinib will be given at a dose of 1 mg daily if the eGFR is at least 15 and less than 30 mL/min/1.73m². Baricitinib will be withheld if the eGFR is

less than 15 mL/min/1.73m² and in patients who are receiving intermittent or continuous renal replacement therapy

In children 2 years to <9 years of age, the baricitinib dose will be 2mg daily if the eGFR is at least 60 mL/min/1.73m². In children 2 years to <9 years of age, baricitinib will be given at a dose of 1 mg daily if the eGFR is at least 30 and less than 60 mL/min/1.73m². In children 2 years to <9 years of age, baricitinib will be withheld if the eGFR is <30 mL/min/1.73m² or the patient is receiving renal replacement therapy

For patients who are unable to swallow whole tablets, baricitinib may be dispersed in water and delivered via an enteral feeding tube. If 1 mg tablets are not available, a 2 mg tablet can be split using a tablet splitter that has a razor blade to administer half a 2 mg tablet once daily. Alternatively, 2 mg of baricitinib can be given every second day. Baricitinib will be commenced as soon as possible following reveal of allocation and will be administered for 10 days or until hospital discharge, whichever occurs first. For patients who are discharged or transferred from the participating clinical area (e.g. discharged from ICU to a ward) before completion of the 10-day course of baricitinib, it is the responsibility of the randomizing team to prescribe any doses of baricitinib to complete the 10-day course. However, continued administration of the course of baricitinib after discharge from the participating clinical area is a clinical decision that is at the discretion of the treating clinician. Under such circumstances, discontinuation of baricitinib prior to the end of the 10-day course is not a protocol deviation.

8.3.5. Discontinuation of study intervention

An immune modulation intervention for influenza should be discontinued if there is development of a SAE which, in the opinion of the treating clinician, could be related to participation in this domain. The study interventions can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

8.4. Concomitant care

Additional agents, other than those specified in the platform, that are intended to modulate the immune response to influenza should not be permitted. Commencement of such an agent in the absence of an accepted clinical indication is a protocol deviation. The use of corticosteroids, other than those specified by assignment within the platform, for a new indication (e.g. bronchospasm or septic shock) can be determined by the treating clinician. All other treatment that is not specified by assignment within the platform will be determined by the treating clinician.

8.5. Endpoints

8.5.1. Primary endpoint

The primary endpoint for this domain is the primary outcome specified in the ~~REMAP-CAP~~ Core Protocol.

8.5.2. Secondary endpoints

All secondary endpoints as specified in the ~~REMAP-CAP~~ Core Protocol

The domain-specific secondary outcome measures (from randomization, during the index hospitalization, censored 90 days after enrollment) will be:

- Positive blood culture for pathogenic bacteria and/or fungus during this hospitalization and more than 48 hours following randomization
- Pulmonary aspergillosis, during this hospitalization and more than 48 hours following randomization, defined as culture of *Aspergillus* species from tracheal aspirate or bronchoalveolar lavage or invasive pulmonary aspergillosis diagnosed and treated with one or more systemic antifungal agent
- Serious adverse event (SAE) as defined in Core Protocol

An additional endpoint, that will be reported as it becomes available and only from sites where linked data is available, is occurrence of major adverse cardiovascular events.

9. TRIAL CONDUCT

9.1. Microbiology

Microbiological testing will be performed as per local practice, including bacterial and viral testing to guide clinical care. Results of these tests will be collected but no additional clinical testing is specified in this protocol.

9.2. Domain-specific data collection

Additional domain-specific data will be collected.

- Virologic endpoints, at selected sites:

- Change from baseline in influenza virus levels, measured from upper or lower respiratory tract specimens taken while the patient remains in hospital at baseline, D3 and at D7 ~~or ICU discharge (whichever occurs first) in upper and lower respiratory tract specimens.~~
- Results of culture of blood for pathogenic bacteria and/or fungus during this hospitalization
- Hospitalization or death due to major adverse cardiovascular events (at sites where linked data are available)
- Pregnancy outcomes will be collected for patients who are pregnant at the time of randomization to this domain.

Data on the identification of Aspergillus species from respiratory tract specimens is collected at a platform level.

9.3. Criteria for discontinuation

Refer to relevant Core Protocol documents for criteria for discontinuation of participation in ~~the REMAP-CAP~~ this trial.

9.4. Blinding

~~9.4.1. Blinding~~

All medication will be administered on an open-label basis.

~~9.4.2. Unblinding~~

~~Not relevant.~~

10. STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

The following Platform conclusions are possible in this domain:

- ~~Effectiveness~~ Efficacy ~~for of~~ any active immune modulation intervention compared with 'no immune modulation' intervention
- Superiority ~~for of~~ any intervention within the domain
- Inferiority ~~for of~~ any intervention within the domain

- Futility ~~for~~of one or more active immune modulation interventions compared with 'no immune modulation' intervention
- Equivalence among active immune modulation interventions

One or more active immune modulation interventions can be declared to be futile in comparison with the no immune modulation intervention. If this occurs there will be a public declaration of futility with the likely adaptation being removal of futile immune modulation interventions from the randomization schedule. This will be an operational decision and will not require an amendment to the DSA, noting that if the point estimate of a futile intervention is in the direction of worse outcome than the no immune modulation comparator, that removal from the randomization schedule is pre-specified to be mandatory. A harm threshold is not necessary in this domain, as a futility trigger will be achieved before harm thresholds in the setting of regular adaptive analyses.

~~Any statistical trigger for equivalence that occurs before a declaration of effectiveness efficacy or futility will not be communicated to the ITSC until there is a declaration of either futility or effectiveness efficacy involving the equivalent interventions. Prior to a declaration of effectiveness efficacy or futility, if interventions that are nested trigger for equivalence, further analysis will be undertaken with the nested interventions being pooled, until a declaration of futility or effectiveness efficacy.~~

In the event of one or more active immune modulation interventions being declared effective, the no immune modulation intervention will be removed from the randomization schedule. This is pre-specified, via this version of the DSA, and can occur without further amendment of this DSA. In this situation, the domain will continue to randomize to the active immune modulation interventions to determine the comparative efficacy of active immune modulation interventions. The trigger for equivalence may be applied following removal of the no immune modulation intervention. If the trigger for equivalence is to be applied, this will be *a priori* operational decision specified in the Current State document. The decision regarding the reference control can only be made after having achieved a trigger for efficacy as this decision is dependent on patterns of clinical practice at that time. Following removal of the no immune modulation intervention the triggers of superiority and inferiority among the remaining active interventions will be available. If a trigger occurs for inferiority when two or more additional active interventions remain within the randomization schedule, the inferior intervention will be removed from the randomization schedule and will be subject of public disclosure. It is noted that public disclosure may also require identification of the active intervention against which the inferiority trigger occurred.

In all other respects the stopping rules for this domain are those outlined in the relevant Core Protocol documents.

10.2. Unit-of-analysis and strata

The domain is analyzed in the interpandemic model or its successor model (specified in relevant Core Protocol documents). The eligibility criteria for this domain correspond to the Influenza ~~Infection Confirmed Stratum~~ ~~Present Stratum specified in the Core Protocol~~ (i.e. microbiological testing-confirmed influenza) and ~~the~~ Severe ~~Illness Severity~~ State. Within this stratum and state, the unit-of-analysis is defined by the ~~presence of absence of bacterial infection (i.e., Bacterial Co-infection Strata)~~ Bacterial Infection Diagnosed Strata (defined as Bacterial Infection Diagnosed or Bacterial Infection Not Diagnosed). Borrowing is permitted between strata. No other strata will contribute to the unit-of-analysis, although this may be modified as an operational decision as specified in the Current State document.

10.3. Application of Response-Adaptive Randomization

~~Response Adaptive Randomization may be applied. If RAR is applied, the cap on the maximum or minimum proportion of patients assigned to an intervention that is specified in core protocol documents may be modified by the Statistical Analysis Committee (SAC) if needed to reduce the likelihood of sites being unblinded or to improve power. If required, any such modifications will be an operational decision of the Design Team specified in the Current State document and applied by the SAC.~~

~~10.3.~~10.4. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal and Initiation if prospective agreement to participate is required for this domain (see relevant Core Protocol documents) or if the results of microbiological testing for influenza or SARS-CoV-2 or both are unavailable at the time of eligibility.

~~10.4.~~10.5. Interactions with interventions in other domains

An *a priori* interaction with the Corticosteroid Domain or Influenza Antiviral Domain are considered possible but will only be investigated in post-trial subgroup analyses. It is noted that interaction with

these other domains that include patients with confirmed influenza as part of their unit-of-analysis will be evaluated as post-platform conclusion sub-groups.

Interactions with all other domains are either not evaluable or not considered possible and will not be incorporated into the statistical model or models in which this domain is evaluated.

If an interaction is specified with a future domain, it is sufficient for the interaction to be specified only in the DSA of such a future domain.

~~10.5.~~10.6. *Nesting of interventions*

Nesting is not applicable to this domain.

~~10.6.~~10.7. *Threshold probability for superiority, effectiveness, and inferiority*

The threshold probability for statistical triggers for superiority, effectiveness, and inferiority are those specified in the relevant Core Protocol documents. The threshold probability for the statistical trigger of effectiveness will be the same as that applied for superiority.

~~10.7.~~10.8. *Threshold odds ratio delta for equivalence and futility*

If two interventions within this domain, for a unit-of-analysis, have at least a 0.90 probability of being within a pre-specified delta for the primary endpoint then these interventions will be deemed as being equivalent. The size of the pre-specified odds ratio delta is 0.10~~The threshold odds ratio delta for equivalence and futility in this domain will be those specified in the Core Protocol. At the time of launch of this domain the Core Protocol does not include a trigger for futility. The threshold probability of a statistical trigger for futility will be those specified in future versions of the Core Protocol documents.~~

~~10.8.~~10.9. *Statistical management of patients with intervention-specific exclusion*

The analysis for this domain will incorporate a variable for eligibility to baricitinib based on intervention-specific exclusion criteria related to severe impairment of renal function. This variable adjusts for expected differences in outcome for participants randomized to other interventions in the domain based on their eligibility for baricitinib. Specific details of the definition of this adjustment variable and the associated prior distribution will be provided in the Current State document. The intention of this adjustment is to compare baricitinib patients to other patients in the

domain that were eligible to receive baricitinib. This baricitinib eligibility variable will only be defined for participants that are randomized within the Influenza Immune Modulation domain. This approach will not be applied to any other intervention-specific exclusion factor because of the anticipated low incidence of such exclusions or the anticipated low likelihood of the exclusion being independently associated with outcome or both.

~~10.9.10.10.~~ Informative priors

This domain will launch with priors that are uninformative for main effects.

~~10.10.10.11.~~ Post-trial sub-groups

Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The *a priori* patient sub-groups of interest are:

- Bacterial co-infection at baseline ~~ultimately confirmed on microbiological testing~~
- Shock ~~s~~Strata
- Receiving invasive mechanical ventilation at baseline
- CRP level at baseline
- Ferritin level at baseline
- IL-6 level at baseline (where available, at sites participating in the Biological Sampling Appendix)
- Treatment-by-treatment interaction with the Corticosteroid and Influenza Antiviral Domains
- All remaining potentially evaluable treatment-by-treatment interactions with other domains; *a priori*
- Any component of the unit-of-analysis for which borrowing was permitted but pooled analysis was utilized

If there are potentially important results within one or more of these pre-specified post-platform conclusion subgroups, after the occurrence of a pre-specified threshold for the unit-of-analysis described above, this domain may re-start (new stage) without necessarily requiring a subsequent amendment with eligibility restricted to a sub-group with possible beneficial treatment effect. This will be an operational decision of the ITSC, as advised by the DSWG.

Heterogeneity of treatment effect ~~will~~may also be evaluated by multiple methods including machine learning techniques (such as causal forest).

11. ETHICAL CONSIDERATIONS

11.1. *Data Safety and Monitoring Board*

The DSMB is convened under the guidance provided in the Core Protocol and DSMB Charter. The statistical triggers that apply to this domain are specified in this DSA. If requested by the DSMB, domain-specific safety secondary endpoints will be provided to the DSMB as part of the regular safety reports.

11.2. *Potential domain-specific adverse events*

The occurrence of the following should be screened for and reported as SAEs for all patients in this domain, irrespective of intervention allocation:

- 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
- Gastrointestinal perforation

Other SAEs should be reported only where, in the opinion of the site-investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see relevant Core Protocol documents).

11.3. *Domain risk assessment*

Participating sites will have reviewed the interventions in this domain and their clinical appropriateness for evaluation in this population. Enrolment in this domain will only occur if the treating clinician believes participation is not contrary to the best interests of the patient. The risks and benefits of participation will be outlined in local consent documentation. It is plausible that the effect of immune modulation in influenza differs depending on whether bacterial co-infection exists. The structure of this domain, with stratification by the presence or absence of bacterial co-infection, seeks to identify divergent treatment effect, should this occur.

11.4. *Domain-specific consent issues*

In the absence of evidence of effectiveness of any interventions specified in this DSA or alternative intervention that lies within this domain, the use of a usual care control is both appropriate and ethical.

Clinicians may choose not to enroll individual patients if they feel that participation is not in patient's best interests, and safety criteria are used to exclude patients from this domain for appropriate clinical reasons.

For patients who are not competent to consent, and in accordance with local jurisdictional requirements, where permitted entry into this domain is preferred to be via waiver-of-consent or some form of delayed consent. In any jurisdiction in which prospective agreement is necessary, reveal of assignment status will only occur after prospective agreement has been obtained.

During a pandemic, including an influenza pandemic, visiting by relatives of affected patients may not be possible. In such situations, alternative methods for confirming consent including electronic and telephone communication, as permitted by an appropriate ethical review body, may be acceptable methods for confirming agreement to participate in this (and other) domains of the platform.

12.GOVERNANCE ISSUES

12.1. *Funding of domain*

Funding sources for the ~~REMAP-CAP trial~~Platform are specified in ~~the REMAP-CAP~~ Core Protocol documents. This domain has not received any additional domain-specific funding but such funding, from any source, may be obtained during the life-time of the domain.

12.2. *Funding of domain interventions and outcome measures*

The supply and cost re-imbursement of the interventions included in this domain will vary by region and possibly even within different countries in a region. Options will include purchase of the drugs by individual recruiting sites or centrally by health bodies. In some cases, the drugs may be donated for trial use by the relevant company. Companies that supply drug will have no role in the design, conduct, analysis, or reporting of this domain.

12.3. *Domain-specific declarations of interest*

~~All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAPA registry of interests for all members of the International Trial Steering Committee is maintained on the trial website. These are updated periodically and publicly accessible on the study website.~~

13. REFERENCES

- ABDULLAH, S., BASHIR, N. & MAHMOOD, N. 2021. Use of intravenous tocilizumab in pregnancy for severe coronavirus disease 2019 pneumonia: two case reports. *J Med Case Rep*, 15, 426.
- ALVARO-GRACIA, J. M., GARCIA-LLORENTE, J. F., VALDERRAMA, M., GOMEZ, S. & MONTORO, M. 2021. Update on the Safety Profile of Tofacitinib in Rheumatoid Arthritis from Clinical Trials to Real-World Studies: A Narrative Review. *Rheumatol Ther*, 8, 17-40.
- ANGUS, D. C., DERDE, L., AL-BEIDH, F., ANNANE, D., ARABI, Y., BEANE, A., VAN BENTUM-PUIJK, W., BERRY, L., BHIMANI, Z., BONTEN, M., BRADBURY, C., BRUNKHORST, F., BUXTON, M., BUZGAU, A., CHENG, A. C., DE JONG, M., DETRY, M., ESTCOURT, L., FITZGERALD, M., GOOSSENS, H., GREEN, C., HANIFFA, R., HIGGINS, A. M., HORVAT, C., HULLEGIE, S. J., KRUGER, P., LAMONTAGNE, F., LAWLER, P. R., LINSTRUM, K., LITTON, E., LORENZI, E., MARSHALL, J., MCAULEY, D., MCGLOTHIN, A., MCGUINNESS, S., MCVERRY, B., MONTGOMERY, S., MOUNCEY, P., MURTHY, S., NICHOL, A., PARKE, R., PARKER, J., ROWAN, K., SANIL, A., SANTOS, M., SAUNDERS, C., SEYMOUR, C., TURNER, A., VAN DE VEERDONK, F., VENKATESH, B., ZARYCHANSKI, R., BERRY, S., LEWIS, R. J., MCARTHUR, C., WEBB, S. A., GORDON, A. C., WRITING COMMITTEE FOR THE, R.-C. A. P. I., AL-BEIDH, F., ANGUS, D., ANNANE, D., ARABI, Y., VAN BENTUM-PUIJK, W., BERRY, S., BEANE, A., BHIMANI, Z., BONTEN, M., BRADBURY, C., BRUNKHORST, F., BUXTON, M., CHENG, A., DE JONG, M., DERDE, L., ESTCOURT, L., GOOSSENS, H., GORDON, A., GREEN, C., HANIFFA, R., LAMONTAGNE, F., LAWLER, P., LITTON, E., MARSHALL, J., MCARTHUR, C., MCAULEY, D., MCGUINNESS, S., MCVERRY, B., MONTGOMERY, S., MOUNCEY, P., MURTHY, S., NICHOL, A., PARKE, R., ROWAN, K., SEYMOUR, C., TURNER, A., VAN DE VEERDONK, F., WEBB, S., ZARYCHANSKI, R., CAMPBELL, L., FORBES, A., GATTAS, D., HERITIER, S., et al. 2020. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. *JAMA*, 324, 1317-1329.
- BAIN, W., YANG, H., SHAH, F. A., SUBER, T., DROHAN, C., AL-YOUSIF, N., DESENSI, R. S., BENSEN, N., SCHAEFER, C., ROSBOROUGH, B. R., SOMASUNDARAM, A., WORKMAN, C. J., LAMPENFELD, C., CILLO, A. R., CARDELLO, C., SHAN, F., BRUNO, T. C., VIGNALI, D. A. A., RAY, P., RAY, A., ZHANG, Y., LEE, J. S., METHE, B., MCVERRY, B. J., MORRIS, A. & KITSIOS, G. D. 2021. COVID-19 versus Non-COVID-19 Acute Respiratory Distress Syndrome: Comparison of Demographics, Physiologic Parameters, Inflammatory Biomarkers, and Clinical Outcomes. *Ann Am Thorac Soc*, 18, 1202-1210.
- BARNES, M., HEYWOOD, A. E., MAHIMBO, A., RAHMAN, B., NEWALL, A. T. & MACINTYRE, C. R. 2015. Acute myocardial infarction and influenza: a meta-analysis of case-control studies. *Heart*, 101, 1738-47.
- BERMEJO-MARTIN, J. F., ORTIZ DE LEJARAZU, R., PUMAROLA, T., RELLO, J., ALMANSA, R., RAMIREZ, P., MARTIN-LOECHES, I., VARILLAS, D., GALLEGOS, M. C., SERON, C., MICHELOUD, D., GOMEZ, J. M., TENORIO-ABREU, A., RAMOS, M. J., MOLINA, M. L., HUIDOBRO, S., SANCHEZ, E., GORDON, M., FERNANDEZ, V., DEL CASTILLO, A., MARCOS, M. A., VILLANUEVA, B., LOPEZ, C. J., RODRIGUEZ-DOMINGUEZ, M., GALAN, J. C., CANTON, R., LIETOR, A., ROJO, S., EIROS, J. M., HINOJOSA, C., GONZALEZ, I., TORNER, N., BANNER, D., LEON, A., CUESTA, P., ROWE, T. & KELVIN, D. J. 2009. Th1 and Th17 hypercytokinemia as early host response signature in severe pandemic influenza. *Crit Care*, 13, R201.
- BRUNNER, H. I., RUPERTO, N., ZUBER, Z., KEANE, C., HARARI, O., KENWRIGHT, A., LU, P., CUTTICA, R., KELTSEV, V., XAVIER, R. M., CALVO, I., NIKISHINA, I., RUBIO-PEREZ, N., ALEXEEVA, E., CHASNYK, V., HORNEFF, G., OPOKA-WINIARSKA, V., QUARTIER, P., SILVA, C. A., SILVERMAN,

- E., SPINDLER, A., BAILDAM, E., GAMIR, M. L., MARTIN, A., RIETSCHER, C., SIRI, D., SMOLEWSKA, E., LOVELL, D., MARTINI, A., DE BENEDETTI, F., PAEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION, P. & PEDIATRIC RHEUMATOLOGY COLLABORATIVE STUDY, G. 2015. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. *Ann Rheum Dis*, 74, 1110-7.
- CHERTOW, D. S. & MEMOLI, M. J. 2013. Bacterial coinfection in influenza: a grand rounds review. *JAMA*, 309, 275-82.
- CHIARETTI, A., PULITANO, S., BARONE, G., FERRARA, P., ROMANO, V., CAPOZZI, D. & RICCARDI, R. 2013. IL-1 beta and IL-6 upregulation in children with H1N1 influenza virus infection. *Mediators Inflamm*, 2013, 495848.
- CHINEN, Y., KINJO, Y., MEKARU, K., KINJO, T., HIGURE, Y., KINJO, T., MIYAGI, K., YAMADA, H., MASAMOTO, H., GOYA, H., YOSHIDA, T., MAESHIRO, S., NAKAMATSU, M., FUJITA, J. & AOKI, Y. 2021. Critical respiratory failure in pregnancy complicated with COVID-19: A case report. *Case Rep Womens Health*, 30, e00309.
- CRUZ-MACHADO, A. R., ANDRADE SILVA, L., BARREIRA, S. C., VEIGA, A., PONTE, C., PINTO, L., MACIEIRA, C. & CAPELA, S. 2021. Tocilizumab throughout pregnancy in two patients with severe Takayasu's arteritis. *Acta Reumatol Port*, 46, 193-195.
- DE BENEDETTI, F., BRUNNER, H. I., RUPERTO, N., KENWRIGHT, A., WRIGHT, S., CALVO, I., CUTTICA, R., RAVELLI, A., SCHNEIDER, R., WOO, P., WOUTERS, C., XAVIER, R., ZEMEL, L., BAILDAM, E., BURGOS-VARGAS, R., DOLEZALOVA, P., GARAY, S. M., MERINO, R., JOOS, R., GROM, A., WULFFRAAT, N., ZUBER, Z., ZULIAN, F., LOVELL, D., MARTINI, A., PRINTO & PRCSG 2012. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med*, 367, 2385-95.
- DERNONCOURT, A., LIABEUF, S., BENNIS, Y., MASMOUDI, K., BODEAU, S., LAVILLE, S., HURTEL-LEMAIRE, A. S., GRAS-CHAMPEL, V. & BATTEUX, B. 2023. Fetal and Neonatal Adverse Drug Reactions Associated with Biologics Taken During Pregnancy by Women with Autoimmune Diseases: Insights from an Analysis of the World Health Organization Pharmacovigilance Database (VigiBase((R))). *BioDrugs*, 37, 73-87.
- DIENZ, O., RUD, J. G., EATON, S. M., LANTHIER, P. A., BURG, E., DREW, A., BUNN, J., SURATT, B. T., HAYNES, L. & RINCON, M. 2012. Essential role of IL-6 in protection against H1N1 influenza virus by promoting neutrophil survival in the lung. *Mucosal Immunol*, 5, 258-66.
- DOYLE, J. D. & CAMPBELL, A. P. 2019. Pediatric influenza and illness severity: what is known and what questions remain? *Curr Opin Pediatr*, 31, 119-126.
- EASTERLIN, M. C., DE BERITTO, T., YEH, A. M., WERTHEIMER, F. B. & RAMANATHAN, R. 2020. Extremely Preterm Infant Born to a Mother With Severe COVID-19 Pneumonia. *J Investig Med High Impact Case Rep*, 8, 2324709620946621.
- EHRHARDT, C., WOLFF, T., PLESCHKA, S., PLANZ, O., BEERMANN, W., BODE, J. G., SCHMOLKE, M. & LUDWIG, S. 2007. Influenza A virus NS1 protein activates the PI3K/Akt pathway to mediate antiapoptotic signaling responses. *J Virol*, 81, 3058-67.
- ELY, E. W., RAMANAN, A. V., KARTMAN, C. E., DE BONO, S., LIAO, R., PIRUZELI, M. L. B., GOLDMAN, J. D., SARAIVA, J. F. K., CHAKLADAR, S., MARCONI, V. C. & GROUP, C.-B. S. 2022. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. *Lancet Respir Med*, 10, 327-336.

- FITZGERALD, J. C., WEISS, S. L., MAUDE, S. L., BARRETT, D. M., LACEY, S. F., MELENHORST, J. J., SHAW, P., BERG, R. A., JUNE, C. H., PORTER, D. L., FREY, N. V., GRUPP, S. A. & TEACHEY, D. T. 2017. Cytokine Release Syndrome After Chimeric Antigen Receptor T Cell Therapy for Acute Lymphoblastic Leukemia. *Crit Care Med*, 45, e124-e131.
- FROBERT, O., GOTBERG, M., ERLINGE, D., AKHTAR, Z., CHRISTIANSEN, E. H., MACINTYRE, C. R., OLDROYD, K. G., MOTOVSKA, Z., ERLIS, A., MOER, R., HLINOMAZ, O., JAKOBSEN, L., ENGSTROM, T., JENSEN, L. O., FALLESEN, C. O., JENSEN, S. E., ANGERAS, O., CALAIS, F., KAREGREN, A., LAUERMAN, J., MOKHTARI, A., NILSSON, J., PERSSON, J., STALBY, P., ISLAM, A., RAHMAN, A., MALIK, F., CHOUDHURY, S., COLLIER, T., POCOCK, S. J. & PERNOW, J. 2021. Influenza Vaccination After Myocardial Infarction: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. *Circulation*, 144, 1476-1484.
- GENOVESE, M. C., SMOLEN, J. S., TAKEUCHI, T., BURMESTER, G., BRINKER, D., ROONEY, T. P., ZHONG, J., DAOJUN, M., SAIFAN, C. G., CARDOSO, A., ISSA, M., WU, W. & WINTHROP, K. L. 2020. Safety profile of baricitinib for the treatment of rheumatoid arthritis over a median of 3 years of treatment: an updated integrated safety analysis. *The Lancet Rheumatology*, 2, e347 - e357.
- GENTILE, D., DOYLE, W., WHITESIDE, T., FIREMAN, P., HAYDEN, F. G. & SKONER, D. 1998. Increased interleukin-6 levels in nasal lavage samples following experimental influenza A virus infection. *Clin Diagn Lab Immunol*, 5, 604-8.
- GHALANDARI, N., CRIJNS, H., BERGMAN, J. E. H., DOLHAIN, R., VAN PUIJENBROEK, E. P. & HAZES, J. M. W. 2022. Reported congenital malformations after exposure to non-tumour necrosis factor inhibitor biologics: A retrospective comparative study in EudraVigilance. *Br J Clin Pharmacol*, 88, 5378-5388.
- GOTESTAM SKORPEN, C., HOELTZENBEIN, M., TINCANI, A., FISCHER-BETZ, R., ELEFANT, E., CHAMBERS, C., DA SILVA, J., NELSON-PIERCY, C., CETIN, I., COSTEDOAT-CHALUMEAU, N., DOLHAIN, R., FORGER, F., KHAMASHTA, M., RUIZ-IRASTORZA, G., ZINK, A., VENCOSKY, J., CUTOLO, M., CAEYERS, N., ZUMBUHL, C. & OSTENSEN, M. 2016. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis*, 75, 795-810.
- GROUP, R. C. 2021. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*, 397, 1637-1645.
- GROUP, R. C. 2022. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. *Lancet*, 400, 359-368.
- GUAN, X., YANG, W., SUN, X., WANG, L., MA, B., LI, H. & ZHOU, J. 2012. Association of influenza virus infection and inflammatory cytokines with acute myocardial infarction. *Inflamm Res*, 61, 591-8.
- GUIRITAN, A. T. & CATALUNA, J. G. 2023. A Case Report of Bowel Perforation in a Gravid COVID-19 Patient. *Case Rep Med*, 2023, 7737433.
- HAGAU, N., SLAVCOVICI, A., GONGANAU, D. N., OLTEAN, S., DIRZU, D. S., BREZOSZKI, E. S., MAXIM, M., CIUCE, C., MLESNITE, M., GAVRUS, R. L., LASLO, C., HAGAU, R., PETRESCU, M. & STUDNICKA, D. M. 2010. Clinical aspects and cytokine response in severe H1N1 influenza A virus infection. *Crit Care*, 14, R203.
- HAMILTON, C. E. & CRAIGLOW, B. G. 2020. JAK Inhibitors for the Treatment of Pediatric Alopecia Areata. *J Invest Dermatol Symp Proc*, 20, S31-S36.

- HOELTZENBEIN, M., BECK, E., RAJWANSHI, R., GOTESTAM SKORPEN, C., BERBER, E., SCHAEFER, C. & OSTENSEN, M. 2016. Tocilizumab use in pregnancy: Analysis of a global safety database including data from clinical trials and post-marketing data. *Semin Arthritis Rheum*, 46, 238-245.
- IMAIZUMI, C., SAITO, M., ABE, F., KAGA, H., SAITO, A., NARA, M., KAMEYAMA, S., MIURA, H., OGASAWARA, H., HIRAKAWA, T., MIZUNUMA, M., SATOH, M., KOMATSUDA, A., TERADA, Y. & TAKAHASHI, N. 2022. Adult-onset Still's Disease during Pregnancy Treated with Tocilizumab. *Intern Med*, 61, 3137-3140.
- ISAAC, B., HAZARI, K., HARB, D. K., MALLICK, A. K., ABDELKAREEM, W., AMMAR, A., GERGAWI, T., SAEED AL ZAHMI, E. & KHAMIS, A. H. 2023. Maternal and Fetal Outcome in Pregnant Women With Critical COVID-19 Treated With Tocilizumab in a Tertiary Care Hospital in Dubai. *Cureus*, 15, e34395.
- ISHIKAWA, I., HIRANO, Y., KANEKO, A., KIDA, D., SATO, T., KOJIMA, T. & AL., E. 2012. Pregnancy in patients with rheumatoid arthritis treated with biological agents: results of the 8-year of Japanese TBC registry. *Ann Rheum Dis*, 71.
- IULIANO, A. D., ROGUSKI, K. M., CHANG, H. H., MUSCATELLO, D. J., PALEKAR, R., TEMPIA, S., COHEN, C., GRAN, J. M., SCHANZER, D., COWLING, B. J., WU, P., KYNCL, J., ANG, L. W., PARK, M., REDLBERGER-FRITZ, M., YU, H., ESPENHAIN, L., KRISHNAN, A., EMUKULE, G., VAN ASTEN, L., PEREIRA DA SILVA, S., AUNGKULANON, S., BUCHHOLZ, U., WIDDOWSON, M. A., BRESEE, J. S. & GLOBAL SEASONAL INFLUENZA-ASSOCIATED MORTALITY COLLABORATOR, N. 2018. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet*, 391, 1285-1300.
- JIMENEZ-LOZANO, I., CARO-TELLER, J. M., FERNANDEZ-HIDALGO, N., MIARONS, M., FRICK, M. A., BATLLORI BADIA, E., SERRANO, B., PARRAMON-TEIXIDO, C. J., CAMBA-LONGUEIRA, F., MORAL-PUMAREGA, M. T., SAN JUAN-GARRIDO, R., CABANAS POY, M. J., SUY, A. & GORGAS TORNER, M. Q. 2021. Safety of tocilizumab in COVID-19 pregnant women and their newborn: A retrospective study. *J Clin Pharm Ther*, 46, 1062-1070.
- KALIL, A. C., PATTERSON, T. F., MEHTA, A. K., TOMASHEK, K. M., WOLFE, C. R., GHAZARYAN, V., MARCONI, V. C., RUIZ-PALACIOS, G. M., HSIEH, L., KLINE, S., TAPSON, V., IOVINE, N. M., JAIN, M. K., SWEENEY, D. A., EL SAHLY, H. M., BRANCHE, A. R., REGALADO PINEDA, J., LYE, D. C., SANDKOVSKY, U., LUETKEMEYER, A. F., COHEN, S. H., FINBERG, R. W., JACKSON, P. E. H., TAIWO, B., PAULES, C. I., ARGUINCHONA, H., ERDMANN, N., AHUJA, N., FRANK, M., OH, M. D., KIM, E. S., TAN, S. Y., MULARSKI, R. A., NIELSEN, H., PONCE, P. O., TAYLOR, B. S., LARSON, L., ROUPHAEL, N. G., SAKLAWI, Y., CANTOS, V. D., KO, E. R., ENGEMANN, J. J., AMIN, A. N., WATANABE, M., BILLINGS, J., ELIE, M. C., DAVEY, R. T., BURGESS, T. H., FERREIRA, J., GREEN, M., MAKOWSKI, M., CARDOSO, A., DE BONO, S., BONNETT, T., PROSCHAN, M., DEYE, G. A., DEMPSEY, W., NAYAK, S. U., DODD, L. E., BEIGEL, J. H. & MEMBERS, A.-S. G. 2021. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med*, 384, 795-807.
- KANEKO, K., SUGITANI, M., GOTO, M. & MURASHIMA, A. 2016. Tocilizumab and pregnancy: Four cases of pregnancy in young women with rheumatoid arthritis refractory to anti-TNF biologics with exposure to tocilizumab. *Mod Rheumatol*, 26, 672-5.
- KAWADA, J., KITAGAWA, Y., IWATA, N. & ITO, Y. 2013. Clinical characteristics of influenza virus infection in juvenile idiopathic arthritis patients treated with tocilizumab. *Mod Rheumatol*, 23, 972-6.
- KITSIOS, G. D., BAIN, W., AL-YOUSIF, N., DUTTAGUPTA, R., AHMED, A. A., MCVERRY, B. J. & MORRIS, A. 2021. Plasma microbial cell-free DNA load is associated with mortality in patients with COVID-19. *Respir Res*, 22, 24.

- KLEIN, E. Y., MONTEFORTE, B., GUPTA, A., JIANG, W., MAY, L., HSIEH, Y. H. & DUGAS, A. 2016. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. *Influenza Other Respir Viruses*, 10, 394-403.
- KONAGAI, N., KAMIYA, C. A., NAKANISHI, A., IWANAGA, N., SAWADA, M., KAKIGANO, A., KANAGAWA, T., ETO, S., NISHIDA, Y., NAKAOKA, Y. & YOSHIMATSU, J. 2023. Safe use of tocilizumab in pregnant women with Takayasu arteritis: three case studies. *RMD Open*, 9.
- KULICK, E. R., ALVORD, T., CANNING, M., ELKIND, M. S. V., CHANG, B. P. & BOEHME, A. K. 2021. Risk of stroke and myocardial infarction after influenza-like illness in New York State. *BMC Public Health*, 21, 864.
- KWONG, J. C., SCHWARTZ, K. L., CAMPITELLI, M. A., CHUNG, H., CROWCROFT, N. S., KARNAUCHOW, T., KATZ, K., KO, D. T., MCGEER, A. J., MCNALLY, D., RICHARDSON, D. C., ROSELLA, L. C., SIMOR, A., SMIEJA, M., ZAHARIADIS, G. & GUBBAY, J. B. 2018. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. *N Engl J Med*, 378, 345-353.
- LE GOFFIC, R., BALLOY, V., LAGRANDERIE, M., ALEXOPOULOU, L., ESCRIOU, N., FLAVELL, R., CHIGNARD, M. & SI-TAHAR, M. 2006. Detrimental contribution of the Toll-like receptor (TLR)3 to influenza A virus-induced acute pneumonia. *PLoS Pathog*, 2, e53.
- LEE, D. W., SANTOMASSO, B. D., LOCKE, F. L., GHOBADI, A., TURTLE, C. J., BRUDNO, J. N., MAUS, M. V., PARK, J. H., MEAD, E., PAVLETIC, S., GO, W. Y., ELDJEROU, L., GARDNER, R. A., FREY, N., CURRAN, K. J., PEGGS, K., PASQUINI, M., DIPERSIO, J. F., VAN DEN BRINK, M. R. M., KOMANDURI, K. V., GRUPP, S. A. & NEELAPU, S. S. 2019. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant*, 25, 625-638.
- LIU, Q., ZHOU, Y. H. & YANG, Z. Q. 2016. The cytokine storm of severe influenza and development of immunomodulatory therapy. *Cell Mol Immunol*, 13, 3-10.
- MANOHAR, P., LOH, B., NACHIMUTHU, R., HUA, X., WELBURN, S. C. & LEPTIHN, S. 2020. Secondary Bacterial Infections in Patients With Viral Pneumonia. *Front Med (Lausanne)*, 7, 420.
- MARCONI, V. C., RAMANAN, A. V., DE BONO, S., KARTMAN, C. E., KRISHNAN, V., LIAO, R., PIRUZELI, M. L. B., GOLDMAN, J. D., ALATORRE-ALEXANDER, J., DE CASSIA PELLEGRINI, R., ESTRADA, V., SOM, M., CARDOSO, A., CHAKLADAR, S., CROWE, B., REIS, P., ZHANG, X., ADAMS, D. H., ELY, E. W. & GROUP, C.-B. S. 2021. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med*, 9, 1407-1418.
- MARTINEZ-PORTILLA, R. J., SOTIRIADIS, A., CHATZAKIS, C., TORRES-TORRES, J., ESPINO, Y. S. S., SANDOVAL-MANDUJANO, K., CASTRO-BERNABE, D. A., MEDINA-JIMENEZ, V., MONARREZ-MARTIN, J. C., FIGUERAS, F. & POON, L. C. 2021. Pregnant women with SARS-CoV-2 infection are at higher risk of death and pneumonia: propensity score matched analysis of a nationwide prospective cohort (COV19Mx). *Ultrasound Obstet Gynecol*, 57, 224-231.
- NAKAJIMA, K., WATANABE, O., MOCHIZUKI, M., NAKASONE, A., ISHIZUKA, N. & MURASHIMA, A. 2016. Pregnancy outcomes after exposure to tocilizumab: A retrospective analysis of 61 patients in Japan. *Mod Rheumatol*, 26, 667-71.
- NAQVI, M., ZAKOWSKI, P., GLUCKSMAN, L., SMITHSON, S. & BURWICK, R. M. 2020. Tocilizumab and Remdesivir in a Pregnant Patient With Coronavirus Disease 2019 (COVID-19). *Obstet Gynecol*, 136, 1025-1029.
- PAQUETTE, S. G., BANNER, D., ZHAO, Z., FANG, Y., HUANG, S. S., LEOMICRONN, A. J., NG, D. C., ALMANSA, R., MARTIN-LOECHES, I., RAMIREZ, P., SOCIAS, L., LOZA, A., BLANCO, J., SANSONETTI, P., RELLO, J., ANDALUZ, D., SHUM, B., RUBINO, S., DE LEJARAZU, R. O., TRAN,

- D., DELOGU, G., FADDA, G., KRAJDEN, S., RUBIN, B. B., BERMEJO-MARTIN, J. F., KELVIN, A. A. & KELVIN, D. J. 2012. Interleukin-6 is a potential biomarker for severe pandemic H1N1 influenza A infection. *PLoS One*, 7, e38214.
- RADIGAN, K. A., NICHOLSON, T. T., WELCH, L. C., CHI, M., AMARELLE, L., ANGULO, M., SHIGEMURA, M., SHIGEMURA, A., RUNYAN, C. E., MORALES-NEBRED, L., PERLMAN, H., CECO, E., LECUONA, E., DADA, L. A., MISHARIN, A. V., MUTLU, G. M., SZNAJDER, J. I. & BUDINGER, G. R. S. 2019. Influenza A Virus Infection Induces Muscle Wasting via IL-6 Regulation of the E3 Ubiquitin Ligase Atrogin-1. *J Immunol*, 202, 484-493.
- RAMANAN, A., QUARTIER, P., OKAMOTO, N., MESZAROS, G., ARAUJO, J., WANG, Z., LIAO, R., CROWE, B., ZHANG, X., DECKER, R., KELLER, S., BRUNNER, H. & RUPERTO, N. 2022. LB0002 BARICITINIB IN JUVENILE IDIOPATHIC ARTHRITIS: A PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED, WITHDRAWAL, EFFICACY AND SAFETY STUDY. *Annals of the Rheumatic Diseases*, 81, 207-208.
- RECOVERY COLLABORATIVE GROUP 2021. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*, 397, 1637-1645.
- RECOVERY COLLABORATIVE GROUP 2022. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. *Lancet*, 400, 359-368.
- RECOVERY COLLABORATIVE GROUP, HORBY, P., LIM, W. S., EMBERSON, J. R., MAFHAM, M., BELL, J. L., LINSELL, L., STAPLIN, N., BRIGHTLING, C., USTIANOWSKI, A., ELMAHI, E., PRUDON, B., GREEN, C., FELTON, T., CHADWICK, D., REGE, K., FEGAN, C., CHAPPELL, L. C., FAUST, S. N., JAKI, T., JEFFERY, K., MONTGOMERY, A., ROWAN, K., JUSZCZAK, E., BAILLIE, J. K., HAYNES, R. & LANDRAY, M. J. 2021. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*, 384, 693-704.
- REMAP-CAP INVESTIGATORS, GORDON, A. C., MOUNCEY, P. R., AL-BEIDH, F., ROWAN, K. M., NICHOL, A. D., ARABI, Y. M., ANNANE, D., BEANE, A., VAN BENTUM-PUIJK, W., BERRY, L. R., BHIMANI, Z., BONTEN, M. J. M., BRADBURY, C. A., BRUNKHORST, F. M., BUZGAU, A., CHENG, A. C., DETRY, M. A., DUFFY, E. J., ESTCOURT, L. J., FITZGERALD, M., GOOSSENS, H., HANIFFA, R., HIGGINS, A. M., HILLS, T. E., HORVAT, C. M., LAMONTAGNE, F., LAWLER, P. R., LEAVIS, H. L., LINSTRUM, K. M., LITTON, E., LORENZI, E., MARSHALL, J. C., MAYR, F. B., MCAULEY, D. F., MCGLOTHLIN, A., MCGUINNESS, S. P., MCVERRY, B. J., MONTGOMERY, S. K., MORPETH, S. C., MURTHY, S., ORR, K., PARKE, R. L., PARKER, J. C., PATANWALA, A. E., PETTILA, V., RADEMAKER, E., SANTOS, M. S., SAUNDERS, C. T., SEYMOUR, C. W., SHANKAR-HARI, M., SLIGL, W. I., TURGEON, A. F., TURNER, A. M., VAN DE VEERDONK, F. L., ZARYCHANSKI, R., GREEN, C., LEWIS, R. J., ANGUS, D. C., MCARTHUR, C. J., BERRY, S., WEBB, S. A. & DERDE, L. P. G. 2021. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *N Engl J Med*, 384, 1491-1502.
- REYNOLDS, D., VAZQUEZ GUILLAMET, C., DAY, A., BORCHERDING, N., VAZQUEZ GUILLAMET, R., CHORENO-PARRA, J. A., HOUSE, S. L., O'HALLORAN, J. A., ZUNIGA, J., ELLEBEDY, A. H., BYERS, D. E. & MUDD, P. A. 2021. Comprehensive Immunologic Evaluation of Bronchoalveolar Lavage Samples from Human Patients with Moderate and Severe Seasonal Influenza and Severe COVID-19. *J Immunol*, 207, 1229-1238.
- RUBBERT-ROTH, A., GOUPILLE, P., MOOSAVI, S. & HOU, A. 2010. First experiences with pregnancies in RA patients receiving trastuzumab therapy [Abstract]. *Arthritis Rheum*, 62.
- RUSSELL, C. D., FAIRFIELD, C. J., DRAKE, T. M., TURTLE, L., SEATON, R. A., WOOTTON, D. G., SIGFRID, L., HARRISON, E. M., DOCHERTY, A. B., DE SILVA, T. I., EGAN, C., PIUS, R., HARDWICK, H. E.,

- MERSON, L., GIRVAN, M., DUNNING, J., NGUYEN-VAN-TAM, J. S., OPENSHAW, P. J. M., BAILLIE, J. K., SEMPLE, M. G., HO, A. & INVESTIGATORS, I. C. 2021. Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study. *Lancet Microbe*, 2, e354-e365.
- SAITO, J., YAKUWA, N., KANEKO, K., GOTO, M., KAWASAKI, H., HAMAMACHI, Y., SUZUKI, T., SAGO, H., YAMATANI, A. & MURASHIMA, A. 2021. Tocilizumab drug levels during pregnancy and lactation: A woman who discontinued tocilizumab therapy until the end of the first trimester and resumed it after birth. *Obstet Med*, 14, 260-262.
- SAITO, J., YAKUWA, N., KANEKO, K., TAKAI, C., GOTO, M., NAKAJIMA, K., YAMATANI, A. & MURASHIMA, A. 2019. Tocilizumab during pregnancy and lactation: drug levels in maternal serum, cord blood, breast milk and infant serum. *Rheumatology (Oxford)*, 58, 1505-1507.
- SAMMARITANO, L. R., BERMAS, B. L., CHAKRAVARTY, E. E., CHAMBERS, C., CLOWSE, M. E. B., LOCKSHIN, M. D., MARDER, W., GUYATT, G., BRANCH, D. W., BUYON, J., CHRISTOPHER-STINE, L., CROW-HERCHER, R., CUSH, J., DRUZIN, M., KAVANAUGH, A., LASKIN, C. A., PLANTE, L., SALMON, J., SIMARD, J., SOMERS, E. C., STEEN, V., TEDESCHI, S. K., VINET, E., WHITE, C. W., YAZDANY, J., BARBHAIYA, M., BETTENDORF, B., EUDY, A., JAYATILLEKE, A., SHAH, A. A., SULLIVAN, N., TARTER, L. L., BIRRU TALABI, M., TURGUNBAEV, M., TURNER, A. & D'ANCI, K. E. 2020. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. *Arthritis Rheumatol*, 72, 529-556.
- SAN-JUAN, R., BARBERO, P., FERNANDEZ-RUIZ, M., LOPEZ-MEDRANO, F., LIZASOAIN, M., HERNANDEZ-JIMENEZ, P., SILVA, J. T., RUIZ-RUIGOMEZ, M., CORBELLA, L., RODRIGUEZ-GONCER, I., FOLGUEIRA, M. D., LALUEZA, A., BATLLORI, E., MEJIA, I., FORCEN, L., LUMBRERAS, C., GARCIA-BURGUILLO, A., GALINDO, A. & AGUADO, J. M. 2020. Incidence and clinical profiles of COVID-19 pneumonia in pregnant women: A single-centre cohort study from Spain. *EClinicalMedicine*, 23, 100407.
- SHAFRAN, N., SHAFRAN, I., BEN-ZVI, H., SOFER, S., SHEENA, L., KRAUSE, I., SHLOMAI, A., GOLDBERG, E. & SKLAN, E. H. 2021. Secondary bacterial infection in COVID-19 patients is a stronger predictor for death compared to influenza patients. *Sci Rep*, 11, 12703.
- SIMS, J. T., KRISHNAN, V., CHANG, C. Y., ENGLE, S. M., CASALINI, G., RODGERS, G. H., BIVI, N., NICKOLOFF, B. J., KONRAD, R. J., DE BONO, S., HIGGS, R. E., BENSCHOP, R. J., OTTAVIANI, S., CARDOSO, A., NIRULA, A., CORBELLINO, M. & STEBBING, J. 2021. Characterization of the cytokine storm reflects hyperinflammatory endothelial dysfunction in COVID-19. *J Allergy Clin Immunol*, 147, 107-111.
- SKONER, D. P., GENTILE, D. A., PATEL, A. & DOYLE, W. J. 1999. Evidence for cytokine mediation of disease expression in adults experimentally infected with influenza A virus. *J Infect Dis*, 180, 10-4.
- TADA, Y., SAKAI, M., NAKAO, Y., MARUYAMA, A., ONO, N. & KOARADA, S. 2019. Placental transfer of tocilizumab in a patient with rheumatoid arthritis. *Rheumatology (Oxford)*, 58, 1694-1695.
- UYEKI, T. M., BERNSTEIN, H. H., BRADLEY, J. S., ENGLUND, J. A., FILE, T. M., FRY, A. M., GRAVENSTEIN, S., HAYDEN, F. G., HARPER, S. A., HIRSHON, J. M., ISON, M. G., JOHNSTON, B. L., KNIGHT, S. L., MCGEER, A., RILEY, L. E., WOLFE, C. R., ALEXANDER, P. E. & PAVIA, A. T. 2019. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza. *Clin Infect Dis*, 68, e1-e47.

- UYEKI, T. M., HUI, D. S., ZAMBON, M., WENTWORTH, D. E. & MONTO, A. S. 2022. Influenza. *Lancet*, 400, 693-706.
- WANG, J., PRINZ, R. A., LIU, X. & XU, X. 2020. In Vitro and In Vivo Antiviral Activity of Gingerenone A on Influenza A Virus Is Mediated by Targeting Janus Kinase 2. *Viruses*, 12.
- WANG, J., WANG, Q., HAN, T., LI, Y. K., ZHU, S. L., AO, F., FENG, J., JING, M. Z., WANG, L., YE, L. B. & ZHU, Y. 2015. Soluble interleukin-6 receptor is elevated during influenza A virus infection and mediates the IL-6 and IL-32 inflammatory cytokine burst. *Cell Mol Immunol*, 12, 633-44.
- WARREN-GASH, C., SMEETH, L. & HAYWARD, A. C. 2009. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. *Lancet Infect Dis*, 9, 601-10.
- WATANABE, T., KAWAKAMI, E., SHOEMAKER, J. E., LOPES, T. J., MATSUOKA, Y., TOMITA, Y., KOZUKA-HATA, H., GORAI, T., KUWAHARA, T., TAKEDA, E., NAGATA, A., TAKANO, R., KISO, M., YAMASHITA, M., SAKAI-TAGAWA, Y., KATSURA, H., NONAKA, N., FUJII, H., FUJII, K., SUGITA, Y., NODA, T., GOTO, H., FUKUYAMA, S., WATANABE, S., NEUMANN, G., OYAMA, M., KITANO, H. & KAWAOKA, Y. 2014. Influenza virus-host interactome screen as a platform for antiviral drug development. *Cell Host Microbe*, 16, 795-805.
- WEBER-SCHOENDORFER, C. & SCHAEFER, C. 2016. Pregnancy outcome after tocilizumab therapy in early pregnancy-a case series from the German Embryotox Pharmacovigilance Center. *Reprod Toxicol*, 60, 29-32.
- WHO RAPID EVIDENCE APPRAISAL FOR COVID-19 THERAPIES WORKING GROUP, SHANKAR-HARI, M., VALE, C. L., GODOLPHIN, P. J., FISHER, D., HIGGINS, J. P. T., SPIGA, F., SAVOVIC, J., TIERNEY, J., BARON, G., BENBENISHTY, J. S., BERRY, L. R., BROMAN, N., CAVALCANTI, A. B., COLMAN, R., DE BUYSER, S. L., DERDE, L. P. G., DOMINGO, P., OMAR, S. F., FERNANDEZ-CRUZ, A., FEUTH, T., GARCIA, F., GARCIA-VICUNA, R., GONZALEZ-ALVARO, I., GORDON, A. C., HAYNES, R., HERMINE, O., HORBY, P. W., HORICK, N. K., KUMAR, K., LAMBRECHT, B. N., LANDRAY, M. J., LEAL, L., LEDERER, D. J., LORENZI, E., MARIETTE, X., MERCHANTE, N., MISNAN, N. A., MOHAN, S. V., NIVENS, M. C., OKSI, J., PEREZ-MOLINA, J. A., PIZOV, R., PORCHER, R., POSTMA, S., RAJASURIAR, R., RAMANAN, A. V., RAVAUD, P., REID, P. D., RUTGERS, A., SANCHO-LOPEZ, A., SETO, T. B., SIVAPALASINGAM, S., SOIN, A. S., STAPLIN, N., STONE, J. H., STROHBEHN, G. W., SUNDEN-CULLBERG, J., TORRE-CISNEROS, J., TSAI, L. W., VAN HOOGSTRAATEN, H., VAN MEERTEN, T., VEIGA, V. C., WESTERWEEL, P. E., MURTHY, S., DIAZ, J. V., MARSHALL, J. C. & STERNE, J. A. C. 2021. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. *JAMA*, 326, 499-518.
- WINTHROP, K. L., HARIGAI, M., GENOVESE, M. C., LINDSEY, S., TAKEUCHI, T., FLEISCHMANN, R., BRADLEY, J. D., BYERS, N. L., HYSLOP, D. L., ISSA, M., NISHIKAWA, A., ROONEY, T. P., WITT, S., DICKSON, C. L., SMOLEN, J. S. & DOUGADOS, M. 2020. Infections in baricitinib clinical trials for patients with active rheumatoid arthritis. *Ann Rheum Dis*, 79, 1290-1297.
- YANG, M. L., WANG, C. T., YANG, S. J., LEU, C. H., CHEN, S. H., WU, C. L. & SHIAU, A. L. 2017. IL-6 ameliorates acute lung injury in influenza virus infection. *Sci Rep*, 7, 43829.
- ZAMBRANO, L. D., ELLINGTON, S., STRID, P., GALANG, R. R., ODUYEBO, T., TONG, V. T., WOODWORTH, K. R., NAHABEDIAN, J. F., 3RD, AZZIZ-BAUMGARTNER, E., GILBOA, S. M., MEANEY-DELMAN, D., PREGNANCY, C. C.-R. & INFANT LINKED OUTCOMES, T. 2020. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-October 3, 2020. *MMWR Morb Mortal Wkly Rep*, 69, 1641-1647.