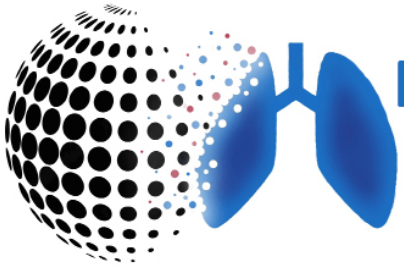

REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Domain-Specific Appendix: COVID-19 Antiviral Therapy

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

COVID-19 Antiviral Therapy Domain-Specific Appendix Version 3.0 dated 24 March 2021

Summary

In this domain of the REMAP-CAP trial, participants meeting the platform-entry criteria with suspected or microbiological testing-confirmed COVID-19 will be randomized to receive one of two interventions:

- No ivermectin for COVID-19 (no placebo)
- Ivermectin

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

☐ No ivermectin for COVID-19 (no placebo)

☐ Ivermectin

This DSA applies to the following states and stratum:

<table>
<tr><td>Stratum</td><td colspan="3">Pandemic infection suspected or proven (PISOP)</td><td>Pandemic infection neither suspected nor proven (PINSNP)</td></tr>
<tr><td>Core protocol documents</td><td colspan="3">REMAP-CAP Core Protocol + Pandemic Appendix, or REMAP-COVID Core Protocol</td><td>REMAP-CAP Core Protocol</td></tr>
<tr><td>Illness Severity State</td><td colspan="2">Moderate State</td><td>Severe State</td><td>Severe State</td></tr>
<tr><td>Interventions specified in this DSA</td><td colspan="2">No ivermectin for COVID-19
Ivermectin</td><td>No ivermectin for COVID-19
Ivermectin</td><td>N/A</td></tr>
<tr><td>Interventions submitted for approval in this jurisdiction</td><td colspan="2">☐ No ivermectin for COVID-19
☐ Ivermectin</td><td>☐ No ivermectin for COVID-19
☐ Ivermectin</td><td>N/A</td></tr>
<tr><td rowspan="2">Interventions offered at this site</td><td>Ward</td><td>ICU</td><td>ICU</td><td>ICU</td></tr>
<tr><td>☐ No ivermectin for COVID-19
☐ Ivermectin</td><td>☐ No ivermectin for COVID-19
☐ Ivermectin</td><td>☐ No ivermectin for COVID-19
☐ Ivermectin</td><td>N/A</td></tr>
</table>

REMAP-CAP: COVID-19 Antiviral Therapy Domain Summary	
Interventions	• No ivermectin for COVID-19 (no placebo) • Ivermectin
Unit of Analysis, Strata, and State	This domain is analyzed only in the pandemic statistical model. The pandemic statistical model includes patients who are in the pandemic infection suspected or confirmed (PISOP) stratum. Within the stratum the unit-or-analysis is defined by illness severity state at the time of enrollment, defined as either Moderate State or Severe State. Unit-of-analysis may also be defined by SARS-CoV-2 infection strata. Borrowing is permitted between states and strata. If the SARS-CoV-2 infection strata is applied in analysis, Response Adaptive Randomization will be applied to patients in the PISOP stratum using probabilities derived from the SARS-CoV-2 confirmed stratum.
Evaluable treatment-by-treatment Interactions	No interactions will be evaluated with any other domain.
Nesting	None.
Timing of Reveal	Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal if prospective agreement to participate is required.
Inclusions	Patients will be eligible for this domain if: • COVID-19 is suspected by the treating clinician or has been confirmed by microbiological testing • Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • If in the Moderate State, more than 96 hours has elapsed since hospital admission • If in the Severe State, more than 48 hours has elapsed since ICU admission, unless the patient has already been assigned to an intervention in another domain in the Moderate State, in which case exclusion will occur if more than 48 hours has elapsed since commencement of sustained organ failure support in an ICU. • There is intention to commence or continue an antiviral agent that is not licensed for the treatment of COVID-19. Antiviral agents licensed for the treatment of COVID-19 such as remdesivir do not meet this exclusion criteria. • Patient has been randomized in a trial evaluating an antiviral intended to be active against COVID-19, where the protocol of that trial requires ongoing administration of study drug • In areas where MERS-CoV infection is endemic, the patient has laboratory confirmed MERS-CoV infection • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	• Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent • Intention to commence or continue ivermectin will result in exclusion from any intervention that includes ivermectin • Patients who are known or suspected to be pregnant or breastfeeding will be excluded from any intervention that includes ivermectin • Known severe liver disease or an alanine aminotransferase or an aspartate aminotransferase that is more than 5 times the upper limit of normal will result in exclusion from any intervention that includes ivermectin

	• Patients with renal impairment with creatinine clearance < 30ml/min who are not receiving renal replacement therapy will be excluded from any intervention that includes ivermectin
Outcome measures	Primary REMAP endpoint: refer to REMAP-CAP Core Protocol + PAtC or REMAP-COVID Core Protocol. Secondary REMAP endpoints: refer to REMAP-CAP Core Protocol + PAtC or REMAP-COVID Core Protocol. Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment): • Serious Adverse Events (SAE) as defined in Core Protocol

CONTENTS

1. ABBREVIATIONS

ARDS	Acute Respiratory Distress Syndrome
CCP	Clinical Characterization Protocol
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
MERS-CoV	Middle East respiratory syndrome coronavirus
MMF	Mycophenolate mofetil
PAtC	Pandemic Appendix to the Core Protocol
PISOP	Pandemic infection is suspected or proven
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS	Serious Acute Respiratory Syndrome
WHO	World Health Organization

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, Section 1.2 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 (details of the current statistical analysis plan and models); Simulations Appendix (details of the current simulations of the REMAP); 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 a 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 and Simulations Appendices. These Appendices 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 International Statistics Interest Group (ISIG) and the 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 (either REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol), DSAs, RSAs and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).

3. COVID-19 ANTIVIRAL THERAPY DOMAIN-SPECIFIC APPENDIX VERSION

The version of the COVID-19 Antiviral Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the COVID-19 Domain Specific Working Group (DSWG) on 11 March, 2020

Version 2: Approved by the COVID-19 DSWG on 1 April, 2020

Version 2.1: Approved by the COVID-19 DSWG on 9 June, 2020

Version 3: Approved by the COVID-19 Antiviral DSWG on 24 March, 2021

4. COVID-19 ANTIVIRAL DOMAIN GOVERNANCE

4.1. Domain members

Chair: Prof. Yaseen Arabi

Deputy Chair Prof. Alistair Nichol (Version 3 adaptation lead)

Members:

Prof. Derek Angus

Dr. Diptesh Aryal

Dr. Kenneth Baillie

Prof. Richard Beasley

A/Prof. Scott Berry

Prof. Marc Bonten

Prof. Frank Brunkhorst

Prof. Allen Cheng

Prof. Menno de Jong

Dr. Lennie Derde

Dr. Rob Fowler

Prof. Herman Goossens

Prof. Anthony Gordon

Mr. Cameron Green

A/Prof. Rashan Haniffa

A/Prof. Madiha Hashmi

Dr. Thomas Hills

Prof. David Huang

Dr. Sabin Koirala

Dr. Ed Litton

Prof. John Marshall

Dr. Colin McArthur

Dr. Susan Morpeth

Dr. Srinivas Murthy

Dr. Mihai Netea

A/Prof. Rachael Parke

Ms. Jane Parker

Prof. Sid Patanwala

Prof. Kathy Rowan

Dr. Steve Tong

Dr. Tim Uyeki

Dr. Frank van de Veerdonk

Prof. Steve Webb

4.2. Contact Details

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5. COVID-19 ANTIVIRAL DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The COVID-19 Antiviral Domain-Specific Working Group have read this appendix and authorize it as the official COVID-19 Antiviral Therapy Domain-Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair Yaseen Arabi _____ Date 24 March, 2021

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP trial to test the effectiveness of different strategies for antiviral therapy in patients with acute illness due to suspected or proven COVID-19.

6.2. Domain-specific background

6.2.1. COVID-19 infection

6.2.1.1. *Introduction*

COVID-19 is caused by a novel coronavirus designated SARS-CoV-2. In December 2019, COVID-19 was first reported when a cluster of patients with severe pneumonia of unknown cause was identified in Wuhan, China. SARS-CoV-2 quickly spread across the globe and the WHO declared

COVID-19 a pandemic in March 2020 (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf). The spectrum of illness due to SARS-CoV-2 ranges from asymptomatic infection through to severe pneumonia, respiratory distress, multiorgan dysfunction, and death. A substantial proportion of patients admitted to hospital because of COVID-19 require provision of organ failure support in an Intensive Care Unit (ICU) and in-hospital mortality within this group is high (Tan et al., 2021). Early clinical management recommendations focus on supportive care, including organ support as needed and the prevention of complications. Effective treatments are urgently needed. The WHO have recommended that "investigational anti-COVID-19 therapeutics should be used only in approved, randomized, controlled trials" (https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf).

6.2.1.2. *Clinical trials for COVID-19 infection*

Observational data cannot determine treatment effects reliably due to the risk of systematic bias (Califf et al., 2020). Clinical trials to identify effective COVID-19 treatments are needed and a large number of trials are underway. Early in the pandemic, the WHO provided guidance regarding both trial design and prioritization of candidate therapies. With regards to trial design, the WHO noted that initially there were no treatments with proven efficacy in patients with COVID-19. Therefore, the recommended 'standard of care' comparator was a control group that did not receive an agent intended to be active against COVID-19, its associated immune response, or other complications (https://apps.who.int/iris/bitstream/handle/10665/330694/WHO-HEO-RDBlueprintnCoV-2020.4-eng.pdf?ua=1). As effective COVID-19 treatments are identified, it is anticipated that 'standard of care', both inside and outside of a clinical trial, will continue to change to incorporate the use of agents with proven efficacy. REMAP-CAP randomizes COVID-19 patients to a range of therapeutic interventions across different domains. Up to date information regarding active and inactive interventions and domains is available at www.remapcap.org.

It is recognized that in patients with COVID-19 the effect of treatments can be different depending on stage or progression and severity of illness (Recovery Collaborative Group et al., 2020). As such, therapies should be evaluated independently in pre-defined patient groups e.g. those who are critically ill, those who are admitted to hospital but are not critically ill, and those who have COVID-19 but have not been admitted to hospital. Among trials that evaluate interventions in patients who are critically ill, it is common for the results of the trial to be different to that which was predicted based on a prior understanding of mechanism of action combined with known mechanism of disease (Landoni et al., 2015, Webb, 2015). This observation reinforces the importance of not necessarily

relying on extrapolation of results (both positive and negative) from patients who are not critically ill. It is also possible different disease mechanisms apply at different levels of illness severity and that this may influence the balance between beneficial and adverse effects of a particular intervention, reinforcing the importance of obtaining estimates of treatment effect dependent on the level of illness severity.

6.2.2. Antiviral therapy for COVID-19

Early in the pandemic it was thought likely that antiviral treatments would be effective treatments for SARS-CoV-2 infection. However, to date, trials have not been successful with regards to identifying antiviral agents that prevent death.

Remdesivir is licensed and in widespread use but has not been demonstrated to be highly effective at reducing mortality when administered to patients who are admitted to hospital. There is high quality evidence that administration of remdesivir to patients admitted to hospital results in more rapid recovery (Beigel et al., 2020). However, the SOLIDARITY trial reported no beneficial effect on 28-day mortality (rate ratio 0.95, 95% CI 0.81 to 1.11) (WHO Solidarity Trial Consortium et al., 2021). For patients who were receiving invasive mechanical ventilation at the time of enrollment the point estimate for mortality was higher in patients receiving remdesivir (rate ratio 1.2 but with wide confidence limits (95% CI 0.8 to 1.8). Remdesivir is currently the only antiviral that has been licensed and is in clinical practice. Nevertheless, many clinicians, including clinicians at sites that are participating in REMAP-CAP do not prescribe remdesivir due to it high costs and uncertain benefit on mortality. For example, among patients reported by REMAP-CAP in relation to the treatment effect of IL-6 receptor antagonists, 32.8% of patients received concomitant treatment with remdesivir (REMAP-CAP Investigators et al., 2021).

Hydroxychloroquine, chloroquine, and lopinavir/ritonavir were reported to be ineffective in patients who were admitted to hospital with suspected or proven COVID-19 in the RECOVERY and SOLIDARITY trials (WHO Solidarity Trial Consortium et al., 2021, Recovery Collaborative Group, 2020). The previous version of the REMAP-CAP Antiviral Domain compared hydroxychloroquine, lopinavir/ritonavir, and a combination of both of these agents against a Standard of Care control. The interventions containing hydroxychloroquine were removed from the platform on 13th of July, 2020 as a consequence of external information. Evaluation of lopinavir/ritonavir continued in REMAP-CAP, which in this domain enrolled only patients who were critically ill, because the results of both RECOVERY and SOLIDARITY were not directly applicable to critically ill patients as neither of these trials enrolled sufficient numbers of such patients to provide precise estimates of treatment

effect. The lopinavir/ritonavir intervention in the antiviral domain was ceased on 19th of November, 2020 following a statistical trigger for futility. From that time forward the antiviral domain of REMAP-CAP has been dormant.

It is noteworthy that large numbers of patients with COVID-19 received these agents outside of clinical trials and it was only publication of results from the RECOVERY and SOLIDARITY trials that led to change in practice.

Another agent which is being widely promoted as effective against SARS-CoV-2 and being used widely without adequate clinical evidence to support its use, is ivermectin. Version 2 of the REMAP-CAP anti-viral DSA will examine whether ivermectin is superior to no ivermectin.

6.2.3. Intervention strategy for this domain

This domain has evolved taking into account external information, as well as results derived from the previous version of the Antiviral Domain of REMAP-CAP. This amendment specifies the comparison of two interventions: a standard of care control, which prohibits ivermectin but allows for the use of antiviral agents such as remdesivir that are licensed for COVID-19 and are local standard of care; and ivermectin.

The revision of this domain will include a control group (i.e., some patients will not receive ivermectin or any other unlicensed antiviral agent that is intended to be active against COVID-19 infection). However, as discussed above some sites use remdesivir as a licensed antiviral agent for COVID-19 for all critically ill patients. In sites where remdesivir is licensed for the treatment of COVID-19 and regarded as a component of standard of care remdesivir may be prescribed, at the discretion of the treating clinician, to patients assigned to either intervention in this domain. This is appropriate for two reasons. Firstly, the trial will not alter the standard of care in administering licensed antiviral agents in participating sites. In these sites, patients will receive remdesivir, or ivermectin plus remdesivir. Secondly, we will specify baseline administration of an antiviral licensed for use in COVID-19 as a sub-group that will be evaluated after a platform conclusion to determine if the treatment effect of ivermectin is influenced by concomitant treatment with a licensed antiviral for COVID-19.

Earlier versions of this DSA evaluated hydroxychloroquine, lopinavir/ritonavir, and the combination of these agents. All of these agents have been removed from this domain and this version (version 3) specifies ivermectin as the only agent that is being evaluated, at this time. It is noted that additional antiviral agents could be added (allowing evaluation of several agents against a common control

intervention) as well as allowing introduction of combinations of agents (to evaluate potential synergy). However, any such changes to the intervention structure of the domain will be specified using one or more amendments to this DSA with implementation of additional agents occurring only after all necessary ethical and regulatory approvals have been obtained.

As in the previous version of this DSA, if at any stage evidence of harm or definitive evidence of absence of effectiveness in critically ill patients emerges for any intervention specified in this domain, the ITSC, as advised by the DSWG, may remove an intervention prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to that intervention will occur, so as to contribute additional weight of evidence available in the public domain.

6.2.4. Ivermectin

6.2.4.1. *Introduction*

Ivermectin is an anti-parasitic medicine on the WHO 'List of Essential Medicines'. There are almost 50 years of in-vitro and in-vivo work that show ivermectin has antiviral activity against several RNA viruses such as Avian Influenza A, Zika, and Dengue. It has been used in human clinical trials since the early 1980s. Since the emergence of the COVID-19 pandemic, ivermectin has been administered to treat COVID-19, both as an intervention in clinical trials as well as routine clinical practice.

Multiple media reports proclaim ivermectin as a 'miracle cure' for COVID, including patients who are critically ill as a consequence of COVID-19 infection (https://covid19criticalcare.com/videos-and-press/). We are aware of many locations, including REMAP-CAP participating sites in high-, as well as low- and middle-income countries in which use of ivermectin is occurring. Advocates of ivermectin have written opinion pieces, published clinical guidelines and formed consortia to promote the clinical use of ivermectin in routine clinical practice (https://covid19criticalcare.com/). These advocates assert that ivermectin is effective and there is no need for further clinical evidence to support the efficacy and safety of ivermectin in the critically ill. As an example, the United States Senate Committee on Homeland Security and Governmental Affairs—which held a hearing on "Early Outpatient Treatment: An Essential Part of a COVID-19 Solution"— heard testimony strongly advocating the clinical use of ivermectin (https://covid19criticalcare.com/videos-and-press/). The video was watched 5 million times in 10 days but was subsequently deleted by YouTube. Celebrities have attributed their survival from COVID due to this drug (https://covid19criticalcare.com/videos-and-press/). Advocates have lobbied regulators to have ivermectin added to formularies (https://ewn.co.za/2021/02/03/sahpra-we-ensured-controlled-access-to-ivermectin-to-treat-covid-

19). In some regions ivermectin is being smuggled due to high demand from the community (https://www.sabcnews.com/sabcnews/ivermectin-drug-busts-increase-after-it-was-cleared-to-treat-covid-19-symptoms/). These campaigns have had an impact and ivermectin is being used by clinicians outside of clinical trials.

It is the view of the REMAP-CAP Investigators that the enthusiasm associated with this agent for the treatment of COVID-19 is not currently supported either by the pre-clinical rationale or the available clinical evidence. Nevertheless, because of clinical use that is occurring in the absence of evidence, as well as the possibility that ivermectin represents a widely available and low-cost treatment with an established safety profile that could be effective, there is an imperative that the agent is evaluated in high-quality randomized trials.

The following sections outline a summary of the status of research investigating ivermectin for the treatment of COVID-19.

6.2.4.2. *Pre-clinical evidence for ivermectin and COVID-19*

In-vitro and animal model studies report that ivermectin has anti-viral activity against SARS-CoV-2 and anti-inflammatory activity in COVID-19. Caly et al. (2020) reported that ivermectin inhibits SARS-CoV-2 replication and postulated that the mechanism of action relates to inhibition of nuclear import of host and viral proteins. Additionally, ivermectin's competitive binding with the host-receptor binding region of SARS-CoV-2 spike protein has been observed in several studies (Hussien and Abdelaziz, 2020, Lehrer and Rheinstein, 2020, Dayer, 2020, Maurya, 2020, Nallusamy et al., 2020, Suravajhala et al., 2020). This may be an alternate mechanism through which effects are mediated, with some of these studies showing that ivermectin displayed one of the highest binding affinities to spike protein S1 binding domains of SARS-CoV-2 (Scheim, 2020). In several animal models investigating SARS-CoV-2 and coronaviruses, ivermectin diminished viral load significantly and was reported to be protective against organ damage (Arevalo et al., 2020, de Melo et al., 2020). However, the ivermectin levels required to achieve some of these effects are not easily achievable clinically. There are also several studies demonstrating that ivermectin inhibits cytokine production and transcription of nuclear factor-kB (Zhang et al., 2008, Zhang et al., 2009) indicating possible anti-inflammatory effects. Other agents with anti-inflammatory properties have been shown to be beneficial in COVID-19 (Writing Committee for the REMAP-CAP Investigators et al., 2020, REMAP-CAP Investigators et al., 2021).

It should be note that, Merck the manufacturer of ivermectin, announced that its internal review of the literature indicated that there is no scientific basis for a therapeutic effect of ivermectin in

COVID-19 from preclinical studies (https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/). In summary, while there are a number of postulated mechanisms which ivermectin could be of benefit in patients with COVID-19, there is no single mechanism of action that is highly likely to confer therapeutic effect and the levels required to achieve some of these effects are not easily achieved in the clinical environment.

6.2.4.3. *Clinical trials of ivermectin for COVID-19*

There has been intense interest in ivermectin as a therapeutic agent from early in the COVID-19 SARS-CoV-2 pandemic.

At time of writing, there has been only one high-quality RCT regarding the use of ivermectin for the treatment of COVID-19 (Lopez-Medina et al., 2021). This trial did not support the clinical effectiveness of ivermectin but is of limited relevance to REMAP-CAP as the trial recruited only ambulatory patients from a community setting. This trial was double-blind and conducted at a single site in Columbia. The trial evaluated the effect of 0.3mg/kg ivermectin daily for 5 days in adult COVID19 patients (n=476) with mild symptoms who received treatment in the community. This dose of ivermectin did not significantly improve the time to resolution of symptoms. Ivermectin did not result in an increase in serious adverse events nor adverse events. The authors called for larger trials on other clinically important outcomes. Other studies conducted in out-patient settings include RCTs (Hashim et al., 2020, Cadegiani et al., 2020, Mahmud, 2020) and case series (Khan et al., 2020, Carvallo et al., 2020, Gorial et al., 2020, Morgenstern et al., 2020). These studies suggested ivermectin reduces time to recovery and prevents progression to more severe illness states if patients are treated early after symptom onset. However, all of these studies have potential methodologic flaws including small sample size, conducted at single sites, and inadequate blinding.

Several studies that recruited patient admitted to hospital have been reported, but all are of low quality and subject to multiple potential sources of bias. Single center randomized controlled trials with relatively small sample sizes (Shoumann et al., 2021, Elgazzar et al., 2020) have reported benefit. However, these studies included comparator groups that were randomized to alternative treatments that may have induced harm, such as HCQ. Both studies reported that patients receiving ivermectin treatment recovered quicker, avoided admission to ICU and had a higher chance of surviving hospitalization (Elgazzar et al., 2020, Hashim et al., 2020, Niaee et al., 2020, Spoorthi and Sasank, 2020). However, these trials were conducted at single centers and the use of an active comparator limits valid interpretation.

The largest RCT to date (n=400) Elgazzar et al. (2020) randomized patients among 4 treatment groups, each with equal patient numbers (n=100). Group 1 (mild/moderately ill patients) and Group 3 (severely ill patients) received 0.5mg/kg of ivermectin daily for 4 days plus Egyptian standard of care protocol for COVID-19. Group 2 (mild/moderately ill patients) and Group 4 received severely ill patients) received hydroxychloroquine (400 mg every 12 hours for one day followed by 200 mg every 12 hours for 5 days) plus Egyptian standard of care protocol for COVID-19. In the critically ill subgroup receiving ivermectin (Group 3), greater effects were seen from treatment with ivermectin; with reduced mortality (2% versus 20%, p<0.001) and rates of disease progression (4% versus 30%, p<0.001).

Preliminary results of a WHO-sponsored systematic review and meta-analysis conducted by Dr Andrew Hill at the University of Liverpool (Hill et al., 2021) suggest the current evidence supports the investigation of ivermectin for COVID-19 prevention and treatment. In this meta-analysis of randomized trials to date (11 trials, n=1456 patients total) (Hill et al., 2021), sample sizes for these trials range from 24 to 400 patients, mostly with mild/moderate illness and some severe, with doses of ivermectin as an intervention from 0.2mg/kg up to 0.6mg/kg, and dose durations of 1-5 days, where the comparator is usually hydroxychloroquine or azithromycin. The individual trial data alone is insufficient to determine the efficacy and effectiveness of ivermectin in COVID-19, despite the preliminary results of the WHO-sponsored meta-analysis (Hill et al., 2021) that combines data from the RCTs yielding an 83% reduction in mortality rate (95% CI 65-92%, p<0.001). Additionally, rates of clinical recovery (reported in various ways) was improved by 43% (95% CI 21-67%). Yet, the individual studies were mostly single centered and categorized as low-quality.

Interestingly, dose response effects were also observed with the strongest effects on outcomes seen in the trial by Elgazzar et al. (2020) where the dose was 0.4mg/kg (max daily dose 24mg) for 5 days. These effects were in mild/moderate and severe patients. Smaller yet significant effects were seen at 0.2mg/kg for 1-2 days (Niaee et al., 2020), and 0.2mg/kg for 5 days (Ahmed et al., 2020).

A recent review of the literature by an NIH guidelines committee highlighted the deficiencies in the current evidence base: i) the sample size of most of the trials was small; ii) various doses and schedules of ivermectin were used; iii) some of the randomized controlled trials were open-label studies in which neither the participants nor the investigators were blinded to the treatment arms; iv) patients received various concomitant medications (e.g., doxycycline, hydroxychloroquine, azithromycin, zinc, corticosteroids) in addition to ivermectin or the comparator, which confounded the assessment of the efficacy or safety of ivermectin; v) the severity of COVID-19 in the study participants was not always well described; and vi) the study outcome measures were not always

clearly defined (https://www.covid19treatmentguidelines.nih.gov/statement-on-ivermectin/). The NIH guidance was updated from "not to use" to "insufficient evidence to guide practice" (https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/ivermectin/).

In summary, the trial data to date is of low quality but it raises the possibility of benefit. However, despite these reservations, many have interpreted these findings as sufficient to support the use of ivermectin in routine clinical practice.

6.2.4.4. *Safety profile of ivermectin*

Ivermectin was discovered in 1975 (resulting in the awarding of a Nobel prize in 2015) and used to treat onchocerciasis, lymphatic filariasis and scabies. Over 33 countries have provided over 570 million doses in the first 20 years of the Meztican Donation program. Low rates of adverse effects are reported, and these are likely related to the death of the parasites, and include itch, rash, swollen lymph glands and joint pain (Kircik et al., 2016). Currently the only medication contraindicated with the use of ivermectin are anti-tuberculosis medications and cholera vaccines. It is noted that concomitant use of warfarin requires close monitoring of the therapeutic effect of warfarin. The NIH treatment guidelines (https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/ivermectin/), noted that ivermectin is generally well tolerated. Adverse effects may include dizziness, pruritis, nausea, or diarrhea. Neurological adverse effects have been reported with the use of ivermectin for the treatment of onchocerciasis and other parasitic diseases, but it is not clear whether these adverse effects were caused by ivermectin or the underlying conditions (Chandler, 2018). Clinical trials in COVID-19, to date, have reported a low occurrence of adverse effects.

Drugs.com (as of 8th of January 2021) list no severe interactions, 73 moderate reactions (mostly related to changes in ivermectin levels) and 2 mild interactions with ivermectin. Ivermectin is primarily metabolized by CYP3A4. Studies of *in vitro* human liver microsomes suggest that at clinically relevant concentrations, ivermectin does not affect the metabolizing ability of CYP3A4 (https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf). It is considered to be a minor substrate of CPY3A4 (https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/ivermectin/) and thus it is not expected to have clinically relevant drug interaction potential. There is one known drug interaction between ivermectin and warfarin, which may be due to an anti-vitamin K effect. This was described in a report of 28 patients who had elevated prothrombin times, with two patients developing complications (Homeida et al., 1988). No other studies have reported clinically relevant complications due to this interaction. Thus, current recommendations are to monitor INR in patients who are on concurrent warfarin therapy. In this domain, concomitant

therapy with warfarin has not been listed as an exclusion criteria, as use of this agent in the critically is rare (because of interactions) and, if used, it is entirely reasonable to presume that close monitoring of INR will occur as this is universal standard practice.

There are no recommendations for dose adjustment of ivermectin in patients with renal or hepatic failure. Less than 1% of ivermectin is eliminated unchanged in the urine (https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf) and therefore renal failure is not a contraindication to ivermectin use. However, as it is metabolized by the liver, severe liver failure could result in drug accumulation (https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf) and experience in patients with severe acute kidney injury, including patients receiving continuous renal replacement therapy is limited. In this domain, both severe hepatic and renal impairment are listed as exclusion criteria. Ivermectin is generally given on an empty stomach with water; however, administering ivermectin with food increases its bioavailability.

A systematic review and meta-analysis (Navarro et al., 2020) examined the safety of high-dose (>0.4mg/kg) ivermectin in humans across a range of indications. Six studies were included in the meta-analysis (5 in Africa, 1 in Europe). Descriptive statistics indicated no difference in the severity of the adverse events between standard (less than 0.4mg/kg) and higher doses of ivermectin (higher than 0.4mg/kg). In one trial investigating treatments for onchocerciasis, there was a number of transient, ocular events but overall, the review indicates no clear differences in the safety of high-dose ivermectin versus standard doses.

6.2.4.5. *Summary of background*

There is a strong rationale for evaluation of ivermectin in a well-designed RCT. Although the pre-clinical rationale for effectiveness is weak, the limited, albeit low quality, clinical evidence supports the possibility of benefit. Moreover, the treatment is in widespread use and, as such, there is a time-critical imperative to establish if the treatment is effective, ineffective, or harmful in critically ill patients. The design of REMAP-CAP facilitates rapid evaluation of candidate interventions for COVID-19 and the use of Response Adaptive Randomization facilitates the welfare and safety of trial participants. The domain has been designed to compare no ivermectin (in combination with antiviral agents that are licensed and in standard care) compared with ivermectin (also permitting the use of antivirals licensed for COVID-19).

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of different antiviral agents for patients with acute illness due to suspected or proven COVID-19.

We hypothesize that the probability of occurrence of the primary end-point specified in the relevant core protocol documents will differ based on the allocated antiviral strategy. The following interventions will be available:

- No ivermectin for COVID-19 (no placebo)
- Ivermectin

We hypothesize that the treatment effect of different antiviral strategies is different depending on whether SARS-CoV-2 infection is confirmed to be present or absent.

We hypothesize that the treatment effect of different antiviral strategies is different depending on the illness severity state at the time of enrollment.

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial. Treatment allocation will be adaptive, as described in the core protocol documents.

8.1. Population

The REMAP enrolls patients admitted to hospital with acute illness due to suspected or proven COVID-19, including patients admitted to ICU.

8.1.1. State

This domain is available for patients who have acute illness due to suspected or proven pandemic infection in the Moderate State and the Severe State.

8.1.2. Domain-specific Strata

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

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 either the REMAP-CAP Core Protocol + Pandemic Appendix or the REMAP-COVID Core Protocol. Patients eligible for the REMAP may have conditions that exclude them from the COVID-19 Antiviral Therapy Domain.

8.2.1. Domain inclusion criteria

Patients are eligible for this domain if:

- COVID-19 is suspected by the treating clinician or has been confirmed by microbiological testing (i.e. PISOP stratum)
- Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur

8.2.2. Domain exclusion criteria

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

- If in the Moderate State, more than 96 hours has elapsed since hospital admission
- If in the Severe State, more than 48 hours has elapsed since ICU admission, unless the patient has already been assigned to an intervention in another domain in the Moderate State, in which case exclusion will occur if more than 48 hours has elapsed since commencement of sustained organ failure support in an ICU
- There is intention to commence or continue any antiviral agent that is not licensed for the treatment of COVID-19. Antiviral agents licensed for the treatment of COVID-19 such as remdesivir do not meet this exclusion criteria.
- Patient has been randomized in a trial evaluating an antiviral intended to be active against COVID-19, where the protocol of that trial requires ongoing administration of study drug or ongoing activity of study drug is anticipated.
- In areas where MERS-CoV infection is endemic, the patient has laboratory confirmed MERS-CoV infection
- 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.

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 who are not eligible for this domain 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
- Intention to commence or continue ivermectin will result in exclusion from any intervention that includes ivermectin
- Patients who are known or suspected to be pregnant or breastfeeding will be excluded from any intervention that includes ivermectin
- Known severe liver disease or an alanine aminotransferase or an aspartate aminotransferase that is more than 5 times the upper limit of normal will result in exclusion from any intervention that includes ivermectin
- Patients with renal impairment with creatinine clearance < 30ml/min who are not receiving renal replacement therapy will be excluded from any intervention that includes ivermectin

8.3. Interventions

8.3.1. Antiviral interventions

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

☐ No ivermectin for COVID-19 (no placebo)

☐ Ivermectin

8.3.2. No Ivermectin for COVID-19

Patients assigned to this intervention are not to receive any ivermectin or any antiviral that is not licensed for the treatment of confirmed or suspected COVID-19. Administration of any antiviral agent that is licensed for the treatment of COVID-19 in the country of the participating site between randomization and the end of Study Day 28 is not a protocol deviation. This applies to any antiviral agent that is licensed at the commencement of this domain, or becomes licensed while this domain is active.

8.3.3. Ivermectin

8.3.3.1. *Dosing of Ivermectin*

Ivermectin will be administered via the enteral route at a dose of 0.2 mg/kg once daily, with a maximum daily dose of 24 mg. For patients who are unable to swallow whole tablets, ivermectin may be dispersed in water and delivered via an enteral feeding tube.

Administration of any antiviral agent that is licensed for the treatment of COVID-19 in the country of the participating site is permitted. Treatment with any antiviral that is not licensed for COVID-19 and is intended to be active against SARS-Cov-2, other than ivermectin, is a protocol deviation.

8.3.3.2. *Duration of administration of ivermectin*

Ivermectin will be administered once daily for up to five days, or until hospital discharge, whichever occurs first. Omission of two or more consecutive doses of ivermectin will be considered a protocol deviation, except where discontinuation of ivermectin is considered by the treating clinician to be in the best interests of the patient.

8.3.4. Discontinuation of study drug

An antiviral agent for COVID-19 should be discontinued if there is development of a serious adverse event (SAE) (see section 8.13.2). Study drug can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

8.3.5. COVID-19 antiviral strategy in patients negative for SARS-CoV-2 infection

Patients with suspected COVID-19 who receive an allocation status to receive an active intervention but who subsequently test negative for SARS-CoV-2 infection after allocation may have treatment ceased unless the treating clinician believes that doing so is not clinically appropriate. This decision

should take into account the known or suspected local population incidence of COVID-19 among hospitalized patients and sensitivity of testing for SARS-CoV-2 infection.

8.4. Concomitant care

Additional drugs, other than those specified in the platform, intended to be active against SARS-CoV-2 infection, should not be administered. All 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 + Pandemic Appendix or REMAP-COVID Core Protocol.

8.5.2. Secondary endpoints

All secondary endpoints as specified in the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol.

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

- SAE as defined in Core Protocol and qualified in this DSA

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 testing is specified in this protocol.

9.2. Domain-specific data collection

9.2.1. Clinical data collection

Additional domain-specific data will be collected.

- Administration of systemic corticosteroids
- Administration of antiviral agents intended to be active against COVID-19
- Administration of immune modulatory agents intended to influence host response to COVID-19

9.3. Criteria for discontinuation

Refer to relevant core protocol documents for criteria for discontinuation of participation in the REMAP-CAP 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 domain has adapted as a consequence of application of external information (cessation of interventions that included hydroxychloroquine) and occurrence of a statistical trigger (cessation of lopinavir/ritonavir for futility). This amendment (Version 3.0) specifies one new active intervention (ivermectin) and a standard-of-care control intervention that is modified as a consequence of permitting the use of antivirals that are licensed for the treatment of COVID-19.

Whether the standard-of-care control intervention is analyzed as a continuation of the control intervention in the previous version of this domain or whether it is analyzed as a new separate (contemporaneous only) control intervention will be an operational decision. If the current standard-of-care control intervention is analyzed as a continuation of the earlier control intervention a sensitivity analysis will be conducted that compares patients assigned to ivermectin with control patients who are contemporaneous with the ivermectin intervention.

The following Platform Conclusions are possible in this domain:

- Superiority of ivermectin compared to no ivermectin
- Futility of ivermectin compared to no ivermectin

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

This domain is analyzed only in the pandemic statistical model and includes only patients who are in the pandemic suspected or proven stratum, as specified in the REMAP-CAP Pandemic Appendix and corresponding to the eligibility criteria specified in the REMAP-COVID Core Protocol. Within this stratum, the unit-of-analysis is defined by illness severity state at time of enrollment, defined as either Moderate State or Severe State. Unit of analysis may also be defined by SARS-CoV-2 infection. Borrowing is permitted between states and strata. If the SARS-CoV-2 strata is applied in analysis, Response Adaptive Randomization will be applied to all PISOP patients, in each severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum. If RAR is applied, the cap on the maximum proportion of patients assigned to an intervention that is specified in core protocol documents may be reduced by the Statistical Analysis Committee (SAC) if needed to reduce the likelihood of sites being unblinded during a period of rapid recruitment. If a reduced cap is applied this will be an operational decision of the SAC, who will inform the DSMB, but blinded trial personnel will not be informed. The decision to apply strata will be an operational decision.

At the time of a Platform Conclusion, results will be reported for all randomized patients, patients in whom SARS-CoV-2 infection is confirmed by microbiological testing, microbiological tests do not detect or isolate SARS-CoV-2 infection, and testing was not performed.

The shock strata will not contribute to unit-of-analysis for this domain, as this strata is not applied in the Pandemic Statistical Model.

The influenza strata will not contribute to unit-of-analysis for this domain.

10.3. 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 if prospective agreement to participate is required for this domain (see relevant core protocol documents).

10.4. Interactions with interventions in other domains

Interactions with other domains are either not evaluable or not considered possible and will not be incorporated into the statistical model 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. Nesting of interventions

Nesting is not applicable to this domain.

10.6. Threshold probability for superiority and inferiority

The threshold odds ratio delta for superiority and inferiority in this domain are those specified as the default thresholds in the relevant core protocol documents.

10.7. Threshold odds ratio delta for futility and equivalence

The platform conclusion of equivalence will not be evaluated in this domain. The same odds ratio delta as specified in the relevant core protocol documents for equivalence will be used for futility. This will be applied in a one-sided analysis for futility for active interventions specified in this domain.

10.8. Informative priors

This domain will not include priors that are informative. If new antiviral agents are added to the domain, consideration will be given to the use of informative priors at the time of amendment of the DSA.

10.9. 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:

- Baseline administration of any antiviral licensed for the treatment of COVID-19 and baseline administration of remdesivir
- Shock strata
- Receiving invasive mechanical ventilation at baseline

- All remaining potentially evaluable treatment-by-treatment interactions with other domains

11.ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority or futility of ivermectin with respect to the primary endpoint are possible.

The DSMB should take into account the public health, as well as clinical significance, of the analyses of this domain and are empowered to discuss results with relevant international and national public health authorities, with rapid dissemination of results to the larger community being the goal.

Safety secondary outcomes will be reported to the DSMB who are empowered to require additional analyses regarding these outcomes as required.

11.2. Potential domain-specific adverse events

11.2.1. Reporting of SAEs

There are no pre-specified domain-specific adverse events.

11.3. Domain-specific consent issues

As noted in the background, and endorsed by the WHO, in the absence of evidence of effectiveness of at least one antiviral agent for COVID-19, the use of a no treatment control is both appropriate and ethical.

Interventions in this domain are in “off-label” clinical use, and typically without consent, for patients who meet the entry criteria for this domain. Clinicians may choose not to enroll individual patients if they feel that participation is not in the patient’s best interests, and safety criteria are used to exclude patients from this domain for appropriate clinical reasons.

Where all interventions that are available at a participating site are regarded as being part of the acceptable spectrum of standard care and given the time imperative necessary to evaluate these interventions, entry to the study, for participants who are not competent to consent, is preferred to be via waiver-of-consent or some form of delayed consent.

During a 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 are specified in the 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

Ivermectin will be provided by participating hospitals on the basis that it is a generic drug that is unlikely to be of significant cost burden.

12.3. Domain-specific declarations of interest

All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAP website. These are updated periodically and publicly accessible on the study website.

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