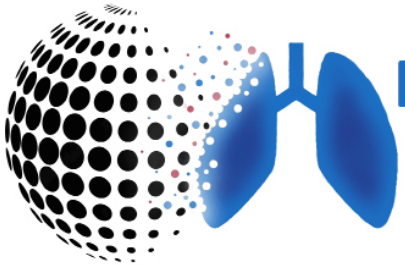

REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

# Domain-Specific Appendix: COVID-19 Antiplatelet

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

Antiplatelet Domain-Specific Appendix Version 1.0 dated 24 August 2020

**Summary**

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

- No Antiplatelet
- Aspirin
- P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor)

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

☐ No Antiplatelet

☐ Aspirin

☐ P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor)

- ☐ Clopidogrel
- ☐ Prasugrel
- ☐ Ticagrelor

This DSA applies to the following states and stratum:

| Stratum | Pandemic infection suspected or proven (PISOP) | | | Pandemic infection neither suspected nor proven (PINSNP) |
|---|---|---|---|---|
| Core protocol documents | REMAP-CAP Core Protocol + Pandemic Appendix, or REMAP-COVID Core Protocol | | | REMAP-CAP Core Protocol |
| Illness Severity State | Moderate State | | Severe State | Severe State |
| Interventions specified in this DSA | No Antiplatelet<br>Aspirin<br>P2Y12 inhibitor | | No Antiplatelet<br>Aspirin<br>P2Y12 inhibitor | Not available |
| Interventions submitted for approval in this jurisdiction | ☐ No Antiplatelet<br>☐ Aspirin<br>☐ P2Y12 inhibitor | | ☐ No Antiplatelet<br>☐ Aspirin<br>☐ P2Y12 inhibitor | Not available |
| Interventions offered at this site | Ward | ICU | ICU | ICU |
| | ☐ No Antiplatelet<br>☐ Aspirin<br>☐ P2Y12 inhibitor | ☐ No Antiplatelet<br>☐ Aspirin<br>☐ P2Y12 inhibitor | ☐ No antiplatelet<br>☐ Aspirin<br>☐ P2Y12 inhibitor | Not available |

| **REMAP-CAP: COVID-19 Therapeutic Anticoagulation Domain Summary** | |
|---|---|
| Interventions | • No Antiplatelet therapy<br>• Aspirin<br>• P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor)<br><br>Note: Gastric protection with proton pump inhibition or H2 antagonist is recommended for patients receiving antiplatelet therapy. |
| Unit of Analysis, Strata, and State | This domain is analyzed only in the pandemic statistical model.<br><br>The pandemic statistical model includes only patients who are in the Pandemic Infection Suspected or Proven (PISOP) stratum. 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 or d-dimer strata or both. 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 illness severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum. Response Adaptive Randomization may also be applied according to D-dimer strata status. |
| Evaluable treatment-by-treatment Interactions | Interaction will be evaluated with the Therapeutic Anticoagulation domain. The Antiplatelet domain and the Therapeutic Anticoagulation domain will be analyzed as a factorial, with the available interventions in the Antiplatelet domain and the available interventions in the Therapeutic Anticoagulation domain. |
| Nesting | There is one nest comprising all active antiplatelet interventions. |
| 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:<br>• COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing<br>• 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:<br>• More than 48 hours has elapsed since ICU admission (noting that this may be operationalized as more than 48 hours has elapsed since commencement of sustained organ failure support)<br>• Clinical or laboratory bleeding risk or both that is sufficient to contraindicate antiplatelet therapy<br>• Patient is already receiving antiplatelet therapy or NSAID (non-steroidal anti-inflammatory drug) or a clinical decision has been made to commence antiplatelet or NSAID therapy<br>• Enrolment in a trial evaluating anticoagulation or antiplatelet therapy for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial<br>• Patients otherwise eligible for the Therapeutic Anticoagulation Domain will be excluded from the Antiplatelet Domain if age is more than 75 years<br>• Creatinine Clearance <30 ml/min, or receiving renal replacement therapy or ECMO<br>• The treating clinician believes that participation in the domain would not be in the best interests of the patient |
| Intervention-Specific Exclusions | Criteria that exclude a patient from one or more interventions are:<br>• Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent<br>• Known or suspected pregnancy will result in exclusion from the P2Y12 inhibitor intervention |

| | |
|---|---|
| | • Administration or intention to administer lopinavir/ritonavir will result in exclusion from the P2Y12 inhibitor intervention at sites that are using clopidogrel and ticagrelor as the P2Y12 inhibitor |
| Outcome measures | Primary REMAP endpoint: refer to REMAP-CAP Core Protocol + Pandemic Appendix and REMAP-COVID Core Protocol<br><br>Secondary REMAP endpoints: refer to REMAP-CAP Core Protocol + Pandemic Appendix and REMAP-COVID Core Protocol<br><br>Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment):<br>• Confirmed deep venous thrombosis<br>• Confirmed pulmonary embolism<br>• Confirmed ischemic cerebrovascular event<br>• Total red cell blood cell units transfused between randomization and the end of study day 15<br>• Acute myocardial infarction<br>• Peak troponin<br>• Major bleeding<br>• Other thrombotic event including mesenteric ischemia and limb ischemia<br>• Serious Adverse Events (SAE) as defined in relevant core protocol documents and this DSA |

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# 1. ABBREVIATIONS

| | |
|---|---|
| ACE2 | Angiotensin-Converting Enzyme 2 |
| aPTT | Activated partial thromboplastin time |
| ARDS | Acute Respiratory Distress Syndrome |
| CCP | Clinical Characterization Protocol |
| DSA | Domain-Specific Appendix |
| DIC | Disseminated Intravascular Coagulation |
| DSMB | Data Safety and Monitoring Board |
| DSWG | Domain-Specific Working Group |
| HIT | Heparin Induced Thrombocytopenia |
| ICU | Intensive Care Unit |
| ISIG | International Statistics Interest Group |
| ITSC | International Trial Steering Committee |
| LMWH | Low Molecular Weight Heparin |
| MERS-CoV | Middle East respiratory syndrome coronavirus |
| PAtC | Pandemic Appendix to the Core Protocol |
| PE | Pulmonary Embolus |
| PISOP | Pandemic infection is suspected or proven |
| 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 | Serious Acute Respiratory Syndrome |
| UFH | Unfractionated heparin |

| | |
|---|---|
| VTE | Venous Thromboembolism |
| 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. It is planned that, 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 ANTIPLATELET DOMAIN-SPECIFIC APPENDIX VERSION

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

## *3.1. Version history*

Version 1: Approved by the Antiplatelet Domain-Specific Working Group (DSWG) on 24th August 2020

# 4. COVID-19 ANTIPLATELET DOMAIN GOVERNANCE

## *4.1. Domain members*

**Chair:** Dr. Charlotte Bradbury

**Deputy Chair:** Dr. Patrick Lawler

**Members:**

Prof. Derek Angus
Dr. Scott Berry
Dr. Shailesh Bihari
Prof. Marc Carrier
A/Prof. Timothy Girard
Dr. Ewan Goligher
Prof. Anthony Gordon
A/Prof. Ghady Haidar
A/Prof. Christopher Horvat

Prof. David Huang

Prof. Beverley Hunt

Prof. Anand Kumar

Dr. Patrick Lawless

Dr. Colin McArthur

A/Prof. Bryan McVerry

Prof. John Marshall

Dr. Zoe McQuilten

A/Prof. Matthew Neal

Prof. Alistair Nichol

A/Prof. Christopher Seymour

Prof. Simon Stanworth

Prof. Steve Webb

A/Prof. Alexandra Weissman

Dr. Ryan Zarychanski

### *4.2. Contact Details*

**Chair:** Dr. Charlotte Bradbury

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## 5. COVID-19 ANTIPLATELET DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

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

**Chair** Date 24th August 2020

Dr. Charlotte Bradbury

# 6. BACKGROUND AND RATIONALE

## 6.1. Domain definition

This is a domain within the REMAP-CAP platform to test the effectiveness of antiplatelet therapy for patients with acute illness due to suspected or proven COVID-19.

## 6.2. Domain-specific background

### 6.2.1. COVID-19 infection

The first report of infection with COVID-19 occurred in Wuhan, China, in late 2019. Since that time, and as of the time of writing of this DSA, there have been over 10 million reported cases across the world with a range of severity, approximately 500,000 deaths and sustained human-human transmission. On January 30th 2020, the World Health Organization (WHO) declared this outbreak a Public Health Emergency of International Concern (https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)). Given past history with novel coronaviruses, such as Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS-CoV), public health agencies have responded aggressively to the urgent need to acquire knowledge regarding this emerging infection. An important component of this urgently needed knowledge includes understanding the effectiveness of alternative treatment strategies in patients with suspected or proven infection. It should also be noted that clinical guidance issued by the WHO indicates that unproven therapies should be administered preferably only as part of a clinical trial (https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf).

Estimates of the burden of critical illness among patients infected with COVID-19 vary, with estimates of case-fatality and proportion of patients who become critically ill being unstable. Several factors contribute to this uncertainty including differential timing between diagnosis and development of critical illness or death, the true incidence of infection being uncertain because of possible under-reporting of asymptomatic or mild cases driven largely by limitations in the number of diagnostic tests that can be performed.

The first case descriptions of COVID-19 disease were communicated by Chinese investigators. These reports describe a progressive severe pneumonia, with a significant proportion of patients requiring mechanical ventilation and some reports of multi-organ dysfunction. In a study of 41 hospitalized patients with laboratory-confirmed COVID-19 infection, 13 (32%) patients were admitted to an ICU and six (15%) died. Invasive mechanical ventilation was required in four (10%) patients, with two patients (5%) receiving extracorporeal membrane oxygenation as salvage therapy (Huang et al.). In another study of 99 hospitalized patients with COVID-19 pneumonia, 23 (23%) were admitted to ICU, 17 (17%) developed acute respiratory distress syndrome (ARDS), three (3%) acute renal failure and four (4%) septic shock. In a study of 138 patients with COVID-19 infection, 36/138 (26%) required ICU care. Patients admitted to ICU were older and were more likely to have underlying comorbidities. In the ICU, four patients (11% of those admitted to ICU) received high-flow oxygen and 15 (44.4%) received noninvasive ventilation. Invasive mechanical ventilation was required in 17 patients (47.2%), four of whom received extracorporeal membrane oxygenation as rescue therapy. A total of 13 patients received vasopressors and two patients received kidney replacement therapy (Wang et al., 2020). In a study from the Chinese Centers for Disease Control that reported on 72,314 patients, 49% of patients defined as critically ill died before hospital discharge (1,023 of 2,087) (Wu and McGoogan, 2020).

As with the other major coronaviruses that have circulated in outbreaks in recent decades, SARS and MERS-CoV, no specific therapy, or an element of supportive care, has been formally evaluated in randomized controlled trials with sufficient statistical power to identify changes in patient-centered outcomes.

Interim recommendations from the WHO for clinical care of infected patients focus upon supportive care, including organ support as needed, prevention of complications, with any specific therapy to only be provided as part of a research protocol (https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf).

### 6.2.2. Intervention strategy for this domain

This domain will test the potential benefits of antiplatelet therapy compared to no antiplatelet therapy.

If at any stage, 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. Thrombotic complications in COVID-19

Severe COVID-19 infection is associated with a profound systemic inflammatory response that drives hypercoagulability. There is also direct viral infection of the vascular endothelium with resulting injury, activation and local vascular inflammation. These factors combine with the prothrombic effects of hospitalization and immobility to result in a high risk of thrombotic complications in patients with COVID-19 admitted to hospital (Spyropoulos et al., 2020, Bikdeli et al., 2020, Helms et al., 2020, Klok et al., 2020). By contrast, significant bleeding is uncommon, even for patients on therapeutic anticoagulation (Helms et al., 2020, Paranjpe et al., 2020). COVID-19 related thrombotic complications are diverse and have been reported within the venous circulation (VTE, e.g. Pulmonary Embolism, PE), arterial circulation (e.g. ischemic cardiac events or strokes or mesenteric ischemia, peripheral vascular ischemia), microvascular circulation (contributing to organ dysfunction) and extracorporeal circuits (e.g. clotting within hemofiltration circuits). Microvascular injury, activation, inflammation and thrombosis are also central to the pathogenesis of the viral pneumonitis and development of acute respiratory distress syndrome (ARDS) seen in severe COVID-19 infection (Perlman and Dandekar, 2005, Blondonnet et al., 2016). Autopsies and histology from those who have died from COVID-19, have revealed widespread thrombosis in large and small blood vessels of the pulmonary vasculature (Buja et al., 2020).

Multiple studies have looked at thrombotic rates in hospitalized patients with COVID-19 infection. For example, a multicenter, retrospective study in the US described the rate and severity of hemostatic and thrombotic complications in 400 hospital-admitted COVID-19 patients, including 144 critically ill patients (Al-Samkari et al., 2020). These patients primarily received standard-dose prophylactic heparin anticoagulation, yet the overall thrombotic complication rate was reported at 9.5% (6.8-12.8%). The overall bleeding and major bleeding rates were 4.8% (2.9-7.3%) and 2.3% (1.0-4.2%) respectively. Patients at highest risk of thrombotic complications are those with severe COVID admitted to intensive care units. In spite of standard thromboprophylaxis, in this cohort, reported VTE events occur in approximately 30% (most commonly PE) and arterial events in 4% (Klok et al., 2020, Helms et al., 2020). Similar rates of thrombosis (25%) in ITU patients have also been reported in China where patients do not receive thromboprophylaxis routinely (Cui et al., 2020). Patients with COVID-19 related ARDS have been shown to have a higher risk of thrombotic complications than similar cohorts of patients with non-COVID-19 ARDS (Helms et al., 2020). As very few centers

perform routine scans and post mortems are rarely performed, the actual incidence of thrombosis is likely higher than the proportion of patients who receive a diagnosis. Therefore, pulmonary emboli and other thrombotic complications may contribute to morbidity and mortality in those who never receive a diagnosis before death.

Comorbid cardiovascular disease, diabetes and hypertension are distinct risk factors for COVID-19 associated mortality (Zhou et al., 2020). Patients with COVID-19 are also at increased risk of arterial events including reports of stroke in young patients. Stroke occurred in 2.8% (6 out of 214 patients, 41% male, mean age 53 years) in a cohort from Wuhan, China (Mao et al., 2020). From New York City, over a 2-week period from March 23 to April 7, 2020, a total of five patients <50 years old presented with new-onset symptoms of large-vessel ischemic stroke. All five patients tested positive for Covid-19. By comparison, every 2 weeks over the previous 12 months, the same service treats on average, 0.73 patients <50 years with large-vessel stroke (Oxley et al., 2020). Ischemic injury of the fingers and toes has also been reported in patients with severe COVID-19 (Li et al., 2020). Acute cardiac injury (troponin >99th percentile of upper limit of normal) is a common feature of COVID-19 infection and associated with a poor prognosis (Shi et al., 2020b, Shi et al., 2020a). The underlying mechanism of cardiac injury includes direct infection via ACE2 of cardiac myocytes and coronary endothelium resulting in coronary and microvascular thrombosis as well as myocarditis. Elevated Troponin-I and arrhythmia are both associated with poor outcome (Guo et al., 2020). Of 416 hospitalized patients with COVID-19, approximately 20% had cardiac injury and cardiac injury was associated with an increased risk of complications including renal failure, as well as a 3.4-fold increase in mortality (Shi et al., 2020b). Reports of acute cardiovascular collapse with echocardiographic evidence of right heart strain has also been reported. In a consecutive case series of 184 COVID-19 positive patients admitted to a Dutch teaching hospital routinely receiving pharmacological thromboprophylaxis, the incidence of a composite outcome (symptomatic PE, deep-vein thrombosis, ischemic stroke, myocardial infarction, or systemic arterial embolism) occurred in 31% of patients (Klok et al., 2020).

The pathogenesis of thrombosis in COVID-19 involves a combination of hypercoagulability, endothelial injury and inflammation. Patients with severe COVID-19 infection demonstrate hypercoagulability including high levels of fibrinogen, factor VIII, Von Willibrand factor, D-dimers, platelet activation, impaired fibrinolysis and low antithrombin (Helms et al., 2020). The hypercoagulability in patients with severe COVID-19 infection is driven by the profound inflammatory response to COVID-19 and is an exaggerated version of the acute phase response commonly seen in patients unwell with infection, cancer or inflammatory disorders. Laboratory

analysis of COVID-19 patients' blood demonstrates overt prothrombotic changes beyond the normal range and also beyond what is considered "normal" for non-COVID hospitalized patients with markedly hypercoagulable thromboelastography traces (Panigada et al., 2020). Derangements in coagulation laboratory parameters are strongly associated with worse outcomes and various lines of evidence suggest that the prothrombotic state is causally related to poor outcomes. In a series of 183 patients, patients who died (11%) exhibited markedly elevated D-dimers and elevated fibrin degradation products; 15 of the patients who died met criteria for disseminated intravascular coagulation (DIC), whereas only 1 survivor developed DIC (Tang et al., 2020). Similar derangements in hemostasis were documented in a separate case series of 94 patients (Lippi and Plebani, 2020). Development of DIC correlated with clinical deterioration. In multiple large case series, elevated D-dimer is consistently associated with a higher risk of developing ARDS and death (Wu and McGoogan, 2020, Zhou et al., 2020). However, in the majority of patients with COVID-19, raised D-dimers are not associated low fibrinogen levels or thrombocytopenia or prolonged prothrombin times. Therefore, although there is microvascular thrombosis, the COVID-19 coagulopathy is very rarely associated with disseminated intravascular coagulation (DIC).

Given that thrombotic complications maybe a potentially preventable cause of significant number of COVID-19 related deaths and of morbidity in survivors, as well as a significant burden to health care resource, we hypothesize that more intensive thrombotic prevention strategies may have the potential to improve clinical outcomes.

#### 6.2.4. Rationale for antithrombotic strategies in COVID-19

The two predominant clinical strategies for thrombosis prevention are anticoagulation and antiplatelet therapy. Anticoagulation is generally used for prevention of VTE and antiplatelet agents for prevention of arterial events. In addition, there are some clinical indications, such as acute coronary syndrome, where a combination has shown synergistic efficacy, albeit with an increased bleeding risk.

Non-randomized observational data suggest that thrombosis prevention with therapeutic anticoagulation may be associated with improved survival for hospitalized patients with COVID-19, with an acceptable, low risk of bleeding complications (Paranjpe et al., 2020, Tang et al., 2020). Among 2,773 hospitalized COVID-19 patients in New York, 786 (28%) received systemic anticoagulation during hospitalization. In-hospital mortality for anticoagulated patients was 22.5% with a median survival of 21 days, compared to 22.8% and median survival of 14 days in patients

who did not receive anticoagulation. Patients treated with anticoagulation had poorer prognostic indicators, including significantly higher D-dimers and requirement for invasive mechanical ventilation (29.8% vs 8.1%, p<0.001). In patients who required mechanical ventilation (n=395), in-hospital mortality was 29.1% with a median survival of 21 days for those treated with anticoagulation as compared to in-hospital mortality of 62.7% with a median survival of 9 days in patients who did not receive anticoagulation. In a multivariate proportional hazards model, longer duration of anticoagulation was associated with a reduced mortality risk (adjusted HR of 0.86 per day, 95% confidence interval 0.82-0.89, p<0.001). This important study also showed among those who did not receive anticoagulation, 38 (1.9%) individuals had bleeding events, compared to 24 (3%) among those anticoagulated (p=0.2). Of the 24 patients who had bleeding events on anticoagulation, 15 (63%) had bleeding events after starting AC and 9 (37%) had bleeding events before starting AC. Bleeding events were more common among patients intubated (30/395; 7.5%) than among non-intubated patients (32/2378; 1.35%) (Paranjpe et al., 2020). Although this data is limited, it gives support to properly evaluate antithrombotic strategies in COVID-19 within randomized controlled clinical trials with anticoagulation, antiplatelet therapy or both.

The anticoagulation domain in REMAP-CAP compares therapeutic anticoagulation with unfractionated or low molecular weight heparin to standard of care thromboprophylaxis. There is potential synergy for combination therapy with antiplatelet and anticoagulant treatments to target separate complimentary pathways. However, as there is also potential for increased bleeding complications, it's essential that any combination strategies are formally assessed for efficacy and safety within a randomized controlled trial. The separate anticoagulation and antiplatelet domains within REMAP will allow these interventions to be tested separately but also in combination. As the profound hypercoagulability in COVID-19 is driven by the hosts immune response which in turn is driven by the virus itself, treatment strategies to tackle the exaggerated immune response (such as IL6 inhibition) or the virus may ameliorate the risk thrombotic complications. For this reason, this thrombosis prevention research question is well placed to be implemented within the adaptive REMAP-CAP COVID-19 with other domains assessing immune modulation and antiviral treatments.

### 6.2.5. Rationale for antiplatelet therapies

Arterial thrombotic events are common in hospitalized patients with COVID-19 and pre-existing cardiovascular comorbidity is associated with increased mortality risk in patients with COVID-19. Therefore, as antiplatelet therapy is the cornerstone of management for arterial thrombosis, it is logical to test whether antiplatelet therapies have potential to improve outcomes in patients with COVID-19 by reducing platelet reactivity and thereby thrombotic complications.

Recently, published data has shown that platelets may be important in the pathogenesis of COVID-19 morbidity and mortality. Platelets are activated and hyper-aggregable (aggregating after stimulation with very low thrombin concentrations) (https://doi.org/10.1101/2020.06.23.20137596). Resting platelets from COVID-19 patients had increased P-selectin expression basally and upon activation. Circulating platelet-neutrophil, -monocyte, and -T-cell aggregates were all significantly elevated in COVID-19 patients compared to healthy donors. Furthermore, platelets from COVID-19 patients aggregated faster and showed increased spreading on both fibrinogen and collagen. The increase in platelet activation and aggregation could partially be attributed to increased MAPK pathway activation and thromboxane generation (Manne et al., 2020). Platelets can also carry SARS-CoV-2, and thus potentially disseminate it through the body.

In addition, as platelets are intimately involved in the inflammatory response to infection, their inhibition may also have beneficial effects in COVID-19 patients beyond their antithrombotic properties. For example, the extravasation of neutrophils and their invasion of inflamed tissues require their interaction with activated platelets. Indeed, the liberation of neutrophil-extracellular trap (NETosis), a process by which neutrophils release extracellular DNA, requires platelets and is observed in COVID-19 (Zuo et al., 2020, Barnes and Somerville, 2020). Platelets also express immune and inflammatory molecules such as interleukin-1 (IL1), and a set of immune receptors including CD40L, Toll-like receptors (TLR) and the Fc receptor for IgG FcγRIIA. Platelets from patients with COVID-19 were more potent at producing IL-1β and soluble CD40L upon exposure to 0.05 U/mL of thrombin in comparison with healthy subjects (https://doi.org/10.1101/2020.06.23.20137596).

Aspirin inhibits cyclo-oxygenase (COX) and not only inhibits platelet reactivity but also has direct anti-inflammatory properties, by inhibiting the formation of prostaglandins (PGs) that cause inflammation, swelling, pain and fever (Vane and Botting, 2003). In addition, Aspirin and P2Y12 antagonists (clopidogrel, prasugrel, ticagrelor) inhibit platelet-neutrophil interactions and abrogate the inflammatory response to sepsis (Mansour et al., 2020, Schrottmaier et al., 2015, Akinosoglou and Alexopoulos, 2014, Russwurm et al., 2002). High rates of on-treatment platelet reactivity (biological resistance) occur with the second-generation thienopyridine clopidogrel (approximately 30%), and its clinical implications led to the development of the more effective platelet P2Y12 inhibitors prasugrel (a third-generation thienopyridine) and ticagrelor (a cyclopentyl-triazolo-pyrimidine). The pharmacokinetics and pharmacodynamics of prasugrel and ticagrelor indicate that they provide more consistent, rapid, and potent platelet inhibition than clopidogrel, which translates into improved ischemic outcomes although with associated increased bleeding (Siller-Matula et al., 2013). Unlike clopidogrel and ticagrelor, prasugrel does not significantly interact with

lopinavir/ritonavir being assessed in the antiviral domain. An advantage of clopidogrel include widespread familiarity of use, ease of dosing and lower risk of bleeding than prasugrel or ticagrelor. Aspirin is an effective antiplatelet agent with widespread availability, low cost, anti-inflammatory properties, safety in pregnancy and lack of interaction with antiviral agents. Therefore, aspirin is also included in the antiplatelet domain.

Clinical data in patients hospitalized for non-COVID19 pneumonia, at risk for acute lung injury, and/or critically ill, revealed an association between antiplatelet therapy and reduction in short-term mortality, acute lung injury and the need for intensive care, without a concomitant increased bleeding risk (Akinosoglou and Alexopoulos, 2014). Overall, therefore antiplatelet therapy would be expected to reduce the thrombotic consequences of COVID-19 and also ameliorate the exaggerated innate inflammatory response to COVID-19, both processes contributing to the clinical deterioration and death in patients with COVID-19.

#### 6.2.6. Safety

Gastrointestinal (GI) bleeding is the commonest adverse event associated with any antiplatelet agent and peptic ulcers are the commonest cause. The main risk factors for this complication include older age, renal dysfunction, underlying pre-existing pathology, concurrent use of NSAIDs or anticoagulants (Pipilis et al., 2014). Lanas et al showed that the relative risk for upper GI bleeding was 3.7 for low-dose aspirin, 2.8 for clopidogrel and 16.4 for combination of aspirin with clopidogrel (Lanas et al., 2006). In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, aspirin plus clopidogrel combination prevented 23 new cardiovascular events in the place of 10 major bleeding episodes for every 1,000 patients; while in the case of ticagrelor they were 22 and 6 and for prasugrel, the figures were 19 and 7 (Wiviott et al., 2007, Wallentin et al., 2009, Pipilis et al., 2014, Yusuf et al., 2001).

No data exists to estimate the risk of major bleeding with single agent antiplatelet therapy used for a short course of 14 days in COVID-19 hospitalized patients. However, by extrapolation from other data, the increase in absolute risk would be expected to be acceptably low (<1%). The hypercoagulability in patients with COVID-19 may reduce bleeding risk and this protocol recommends additional gastric protection with proton pump inhibition to reduce this risk further.

## 7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of antiplatelet therapy for patients with acute illness due to suspected or proven pandemic 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 antiplatelet therapy. The following interventions will be available:

- No Antiplatelet
- Aspirin
- P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor)

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

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

We hypothesize that the treatment effect of antiplatelet therapy is different depending on allocation status in the Therapeutic Anticoagulation Domain. This is a treatment-by-treatment interaction between interventions in the Therapeutic Anticoagulation Domain and the Antiplatelet Domain.

We hypothesize that the treatment effect of Antiplatelet therapy is different depending on D-dimer strata status.

# 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 the core protocol documents.

## *8.1. Population*

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

## *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 this specific COVID-19 Antiplatelet Domain.

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

### *8.2.1.* Domain inclusion criteria

Patients are eligible for this domain if:

- COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing (i.e. PISOP stratum)
- Microbiological testing for SARS-CoV-2 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:

- More than 48 hours has elapsed since ICU admission (noting that this may be operationalized as more than 48 hours has elapsed since commencement of sustained organ failure support)
- Clinical or laboratory bleeding risk or both that is sufficient to contraindicate antiplatelet therapy
- Patient is already receiving antiplatelet therapy or NSAID (non-steroidal anti-inflammatory drug) or a clinical decision has been made to commence antiplatelet or NSAID therapy
- Enrolment in a trial evaluating anticoagulation or antiplatelet therapy for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial
- Patients otherwise eligible for the Therapeutic Anticoagulation Domain will be excluded from the Antiplatelet Domain if their age is more than 75 years
- Creatinine Clearance <30 ml/min, or receiving renal replacement therapy or ECMO
- 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 P2Y12 inhibitor intervention
- Administration or intention to administer lopinavir/ritonavir will result in exclusion from the P2Y12 inhibitor intervention at sites that are using clopidogrel and ticagrelor as the P2Y12 inhibitor

Co-administration of clopidogrel and ticagrelor with lopinavir/ritonavir is contraindicated. At REMAP-CAP sites that are not participating in the COVID-19 Antiviral Domain treatment with, or intention to commence, lopinavir/ritonavir will be operationalized as an exclusion criteria to this domain. Any site that is participating in the COVID-19 Antiviral Domain and the site has selected to participate in any intervention that includes assignment to lopinavir/ritonavir is precluded from participating in the P2Y12 inhibitor intervention if either clopidogrel or ticagrelor is chosen as the P2Y12 inhibitor at that site. At sites participating in the COVID-19 Antiviral Domain and the site has not selected to participate in any intervention that includes lopinavir/ritonavir participation in the Antiplatelet Domain is permitted using any of the three available P2Y12 inhibitors. Sites that choose prasugrel as the P2Y12 inhibitor can select to also include lopinavir/ritonavir as an intervention, if the site is participating in the COVID-19 Antiviral Domain.

## *8.3. Interventions*

### 8.3.1. Antiplatelet 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 Antiplatelet therapy

☐ Aspirin

☐ P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor)

Sites participating in the P2Y12 inhibitor intervention must choose one agent, either clopidogrel, prasugrel, or ticagrelor according to availability and local preference.

Note: Gastric protection with proton pump inhibition or H2 antagonist is recommended for patients receiving antiplatelet therapy.

#### 8.3.2. No Antiplatelet therapy

Patients assigned to this intervention are not to receive any antiplatelet agent or NSAID for 14 days after randomization. Commencement of any agent that inhibits platelet function is not permitted unless there is an accepted clinical indication such as an acute coronary syndrome, ischemic stroke or transient ischemic event. Commencement of such an agent in the absence of an accepted clinical indication is a protocol deviation. After 14 days, decisions regarding antiplatelet therapy are at the discretion of the treating clinician.

#### 8.3.3. Aspirin

Aspirin will be administered daily by the enteral route at a dose of either 75 or 100 mg per day.

#### 8.3.4. P2Y12 inhibitor

Each site will choose one P2Y12 inhibitor based on local availability and preference and administer as follows.

##### 8.3.4.1. *Clopidogrel*

Clopidogrel will be administered daily via the enteral route at a dose of 75mg per day. No loading dose will be administered.

##### 8.3.4.2. *Prasugrel*

Prasugrel will be administered daily by the enteral route as follows: If the patient's age is less than 75 years and measured or estimated weight is 60 kg or more, an initial loading dose of 60 mg will be administered followed by 10 mg per day. If the patient's age is more than 75 years or measured or estimated weight is less than 60 kg an initial loading dose of 60 mg will be administered followed by 5 mg per day.

#### 8.3.4.3. *Ticagrelor*

Ticagrelor will be administered by the enteral route at a dose of 60 mg twice daily. No loading dose will be administered.

### 8.3.5. Duration of antiplatelet therapy

Patients assigned to aspirin or P2Y12 interventions are to receive the allocated antiplatelet agent until the end of study day 14 or hospital discharge, whichever occurs first. After 14 days decisions regarding antiplatelet therapy are at the discretion of the treating clinician.

### 8.3.6. Discontinuation of study intervention

Antiplatelet therapy may be discontinued if there is clinical bleeding or other complication sufficient to warrant cessation in the opinion of the treating clinician. Major bleeding, including death due to bleeding, is an SAE. Antiplatelet therapy may be recommenced if deemed appropriate by the treating clinician. It is permitted to discontinue antiplatelet therapy if patients develop renal failure requiring renal replacement therapy and this is not a protocol deviation.

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. Temporary cessation, for the shortest period of time possible, to allow surgical or other procedures is not a protocol deviation.

Temporary or permanent cessation of the study interventions for bleeding is not a protocol deviation.

### 8.3.7. COVID-19 antiplatelet strategy in patients negative for COVID-19 infection

In patients with suspected COVID-19 infection who receive an allocation status to receive active antiplatelet but who subsequently test negative for COVID-19 infection 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 infection among hospitalized patients and sensitivity of testing for COVID-19 infection.

## *8.4. Concomitant care*

Additional agents, other than those specified in the platform, that are intended to modify the patient's coagulation function as a treatment for COVID-19 infection should not be administered. Commencement of any additional agent that inhibits platelet function is not permitted unless there

is an accepted clinical indication such as an acute coronary syndrome, ischemic stroke or transient ischemic event. Commencement of such an agent in the absence of an accepted clinical indication is a protocol deviation. Commencement of NSAIDs is also not permitted. After 14 days, decisions regarding antiplatelet therapy are at the discretion of 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 + Pandemic Appendix or REMAP-COVID Core Protocol.

### 8.5.2. Secondary endpoints

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

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

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

- Confirmed deep venous thrombosis
- Confirmed pulmonary embolism
- Confirmed ischemic cerebrovascular event
- Total red cell blood cell units transfused between randomization and the end of study day 15
- Acute myocardial infarction
- Peak troponin
- Major bleeding defined as one or more of the following:
    - Fatal bleeding
    - Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome

  - Blood loss above 300mls, or bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or a requirement for transfusion of two or more units of whole blood or red cells because of bleeding
- Other thrombotic event including mesenteric ischemia and limb ischemia
- Serious Adverse Events (SAE) as defined in relevant core protocol documents and 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.

Sites that are participating in this domain are encouraged to also participate in the Clinical Characterization Protocol (CCP) for patients with COVID-19 that has been established by the International Severe Acute Respiratory and Emerging Infectious Consortium (https://isaric.tghn.org/CCP/). This protocol specifies the collection of biological samples from patients with COVID-19. Samples collected in patients who are enrolled in the CCP may be made available to REMAP-CAP investigators to evaluate aspects of host or pathogen biology associated with assignment in this domain. Ethical approval at such sites and agreement from patients to undertake the CCP will be obtained separately.

## *9.2. Domain-specific data collection*

Additional domain-specific data will be collected.

- Baseline measures of coagulation including d-dimer
- Administration of anticoagulant agents
- Administration of agents that inhibit platelet function
- Transfusion of red cells
- Peak troponin
- Acute Myocardial Infarction (using fourth international definition)
- Major bleeding (using the International Society on Thrombosis and Hemostasis definition)
- Mesenteric ischemia, limb ischemia, and other thrombotic events

### *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 following Platform Conclusions are possible in this domain and in combination with the Therapeutic Anticoagulation Domain:

- Inferiority for all interventions in the domain
- Superiority for an active antiplatelet intervention compared with all other interventions in the domain
- Effectiveness for one or more active antiplatelet intervention(s) compared with no antiplatelet intervention
- Futility for one or more active antiplatelet intervention(s) compared with no antiplatelet intervention
- Equivalence among a pair of active antiplatelet interventions
- Superiority for an active antiplatelet intervention in combination with therapeutic anticoagulation compared with all other combinations in both domains
- Effectiveness for one or more active antiplatelet intervention(s) in combination with therapeutic anticoagulation compared with the combination of no antiplatelet and thromboprophylaxis
- Harm for an active antiplatelet intervention in combination with therapeutic anticoagulation compared with the combination of no antiplatelet and thromboprophylaxis

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 or d-dimer strata or both. The D-dimer strata will contain up to 3 stratum, the breakpoints of which will be determined not later than the first interim analysis using data derived from patients enrolled in REMAP-CAP as well as any other trials that may utilize the same statistical model. The D-dimer strata may be applied to one or both States. 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 illness severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum. Response Adaptive Randomization may also be applied according to D-dimer strata status. The decision to apply the SARS-CoV-2 and D-dimer strata will be operational.

At the time of a Platform Conclusion, results will be reported for all randomized patients, patients in whom COVID-19 infection is confirmed by microbiological testing, microbiological tests do not detect or isolate COVID-19 infection, and testing is 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*

An a priori interaction with the Therapeutic Anticoagulant Domain is considered possible and will be incorporated into the statistical models used to analyze this domain. The Antiplatelet Domain and the Therapeutic Anticoagulation Domain will be analyzed as a factorial.

An *a priori* interaction with the Antibiotic Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the Macrolide Duration Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Influenza Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the Corticosteroid Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the COVID-19 Immune Modulation Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Antiviral Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Statin Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Vitamin C Domain is not considered possible and will not be incorporated into the statistical model used to evaluate this domain in the pandemic statistical model or is not able to be evaluated for PINSNP patients as analysis occurs in different statistical models.

No interaction is evaluable between the Ventilation Domain and this domain.

## *10.5. Nesting of interventions*

There is one nest comprising all active antiplatelet interventions.

### *10.6. Threshold probability for superiority, effectiveness, harm and inferiority*

The threshold probability for statistical triggers for superiority, effectiveness, harm, and inferiority are those specified in the relevant core protocol documents.

### *10.7. Threshold odds ratio delta for equivalence and futility*

The threshold odds ration delta for equivalence in this domain is that specified in the relevant core protocol documents. 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 of antiplatelet therapy.

### *10.8. Informative priors*

This domain will launch with priors that are not informative for main effects.

### *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:

- Proven concomitant bacterial co-infection, defined as having isolation or detection of a known pathogen that causes CAP from blood, pleural fluid, or lower respiratory tract specimen
- Whether therapeutic anticoagulation is initiated with UFH or LMWH
- Shock strata
- Receiving invasive mechanical ventilation at baseline
- Baseline troponin
- 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, efficacy, inferiority, or futility of different interventions with respect to the primary endpoints 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*

For patients assigned to any intervention, occurrence of any of the following should be reported as an SAE

- Major bleeding, including death due to bleeding

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-specific consent issues*

As noted in the background, and endorsed by the WHO, in the absence of evidence of effectiveness of anticoagulation for COVID-19, the use of a usual care control is both appropriate and ethical.

Antiplatelet therapies are being used, off-trial, and typically without consent, for patients with proven or suspected COVID-19 infection. 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.

Where all interventions that are available at a participating site and 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.

### *11.4. Relationship to anticoagulation domain*

The antiplatelet domain and the anticoagulation domain will be analyzed as a 2 x N factorial, with N interventions being available within the antiplatelet domain.

## 12.GOVERNANCE ISSUES

### *12.1. Funding of domain*

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. 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*

All antiplatelet agents will be provided by participating hospitals. The cost of all agents specified in this domain are known to be inexpensive.

### *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.

# 13.REFERENCES

AKINOSOGLOU, K. & ALEXOPOULOS, D. 2014. Use of antiplatelet agents in sepsis: a glimpse into the future. *Thromb Res,* 133**,** 131-8.

AL-SAMKARI, H., KARP LEAF, R. S., DZIK, W. H., CARLSON, J. C., FOGERTY, A. E., WAHEED, A., GOODARZI, K., BENDAPUDI, P., BORNIKOVA, L., GUPTA, S., LEAF, D., KUTER, D. J. & ROSOVSKY, R. P. 2020. COVID and Coagulation: Bleeding and Thrombotic Manifestations of SARS-CoV2 Infection. *Blood*.

BARNES, B. J. & SOMERVILLE, C. C. 2020. Modulating Cytokine Production via Select Packaging and Secretion From Extracellular Vesicles. *Front Immunol,* 11**,** 1040.

BIKDELI, B., MADHAVAN, M. V., JIMENEZ, D., CHUICH, T., DREYFUS, I., DRIGGIN, E., NIGOGHOSSIAN, C., AGENO, W., MADJID, M., GUO, Y., TANG, L. V., HU, Y., GIRI, J., CUSHMAN, M., QUERE, I., DIMAKAKOS, E. P., GIBSON, C. M., LIPPI, G., FAVALORO, E. J., FAREED, J., CAPRINI, J. A., TAFUR, A. J., BURTON, J. R., FRANCESE, D. P., WANG, E. Y., FALANGA, A., MCLINTOCK, C., HUNT, B. J., SPYROPOULOS, A. C., BARNES, G. D., EIKELBOOM, J. W., WEINBERG, I., SCHULMAN, S., CARRIER, M., PIAZZA, G., BECKMAN, J. A., STEG, P. G., STONE, G. W., ROSENKRANZ, S., GOLDHABER, S. Z., PARIKH, S. A., MONREAL, M., KRUMHOLZ, H. M., KONSTANTINIDES, S. V., WEITZ, J. I., LIP, G. Y. H., GLOBAL COVID-19 THROMBOSIS COLLABORATIVE GROUP, E. B. T. I. N. E., THE IUA, S. B. T. E. S. C. W. G. O. P. C. & RIGHT VENTRICULAR, F. 2020. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. *J Am Coll Cardiol,* 75**,** 2950-2973.

BLONDONNET, R., CONSTANTIN, J. M., SAPIN, V. & JABAUDON, M. 2016. A Pathophysiologic Approach to Biomarkers in Acute Respiratory Distress Syndrome. *Dis Markers,* 2016**,** 3501373.

BUJA, L. M., WOLF, D. A., ZHAO, B., AKKANTI, B., MCDONALD, M., LELENWA, L., REILLY, N., OTTAVIANI, G., ELGHETANY, M. T., TRUJILLO, D. O., AISENBERG, G. M., MADJID, M. & KAR, B. 2020. The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): Report of 3 autopsies from Houston, Texas, and review of autopsy findings from other United States cities. *Cardiovasc Pathol,* 48**,** 107233.

CUI, S., CHEN, S., LI, X., LIU, S. & WANG, F. 2020. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost,* 18**,** 1421-1424.

GUO, T., FAN, Y., CHEN, M., WU, X., ZHANG, L., HE, T., WANG, H., WAN, J., WANG, X. & LU, Z. 2020. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*.

HELMS, J., TACQUARD, C., SEVERAC, F., LEONARD-LORANT, I., OHANA, M., DELABRANCHE, X., MERDJI, H., CLERE-JEHL, R., SCHENCK, M., FAGOT GANDET, F., FAFI-KREMER, S., CASTELAIN, V., SCHNEIDER, F., GRUNEBAUM, L., ANGLES-CANO, E., SATTLER, L., MERTES, P. M., MEZIANI, F. & GROUP, C. T. 2020. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med,* 46**,** 1089-1098.

HUANG, C., WANG, Y., LI, X., REN, L., ZHAO, J., HU, Y., ZHANG, L., FAN, G., XU, J., GU, X., CHENG, Z., YU, T., XIA, J., WEI, Y., WU, W., XIE, X., YIN, W., LI, H., LIU, M., XIAO, Y., GAO, H., GUO, L., XIE, J., WANG, G., JIANG, R., GAO, Z., JIN, Q., WANG, J. & CAO, B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*.

KLOK, F. A., KRUIP, M., VAN DER MEER, N. J. M., ARBOUS, M. S., GOMMERS, D., KANT, K. M., KAPTEIN, F. H. J., VAN PAASSEN, J., STALS, M. A. M., HUISMAN, M. V. & ENDEMAN, H. 2020.

Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res,* 191**,** 145-147.

LANAS, A., GARCIA-RODRIGUEZ, L. A., ARROYO, M. T., GOMOLLON, F., FEU, F., GONZALEZ-PEREZ, A., ZAPATA, E., BASTIDA, G., RODRIGO, L., SANTOLARIA, S., GUELL, M., DE ARGILA, C. M., QUINTERO, E., BORDA, F., PIQUE, J. M. & ASOCIACION ESPANOLA DE, G. 2006. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. *Gut,* 55**,** 1731-8.

LI, T., LU, H. & ZHANG, W. 2020. Clinical observation and management of COVID-19 patients. *Emerg Microbes Infect,* 9**,** 687-690.

LIPPI, G. & PLEBANI, M. 2020. Laboratory abnormalities in patients with COVID-2019 infection. *Clin Chem Lab Med,* 58**,** 1131-1134.

MANNE, B. K., DENORME, F., MIDDLETON, E. A., PORTIER, I., ROWLEY, J. W., STUBBEN, C. J., PETREY, A. C., TOLLEY, N. D., GUO, L., CODY, M. J., WEYRICH, A. S., YOST, C. C., RONDINA, M. T. & CAMPBELL, R. A. 2020. Platelet Gene Expression and Function in COVID-19 Patients. *Blood*.

MANSOUR, A., BACHELOT-LOZA, C., NESSELER, N., GAUSSEM, P. & GOUIN-THIBAULT, I. 2020. P2Y12 Inhibition beyond Thrombosis: Effects on Inflammation. *Int J Mol Sci,* 21.

MAO, L., JIN, H., WANG, M., HU, Y., CHEN, S., HE, Q., CHANG, J., HONG, C., ZHOU, Y., WANG, D., MIAO, X., LI, Y. & HU, B. 2020. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*.

OXLEY, T. J., MOCCO, J., MAJIDI, S., KELLNER, C. P., SHOIRAH, H., SINGH, I. P., DE LEACY, R. A., SHIGEMATSU, T., LADNER, T. R., YAEGER, K. A., SKLIUT, M., WEINBERGER, J., DANGAYACH, N. S., BEDERSON, J. B., TUHRIM, S. & FIFI, J. T. 2020. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med,* 382**,** e60.

PANIGADA, M., BOTTINO, N., TAGLIABUE, P., GRASSELLI, G., NOVEMBRINO, C., CHANTARANGKUL, V., PESENTI, A., PEYVANDI, F. & TRIPODI, A. 2020. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost,* 18**,** 1738-1742.

PARANJPE, I., FUSTER, V., LALA, A., RUSSAK, A. J., GLICKSBERG, B. S., LEVIN, M. A., CHARNEY, A. W., NARULA, J., FAYAD, Z. A., BAGIELLA, E., ZHAO, S. & NADKARNI, G. N. 2020. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. *J Am Coll Cardiol,* 76**,** 122-124.

PERLMAN, S. & DANDEKAR, A. A. 2005. Immunopathogenesis of coronavirus infections: implications for SARS. *Nat Rev Immunol,* 5**,** 917-27.

PIPILIS, A., MAKRYGIANNIS, S., CHRISANTHOPOULOU, E., SOURLAS, N., KALIAMBAKOS, S. & NTAILIANAS, P. 2014. Gastrointestinal bleeding in patients receiving antiplatelet and anticoagulant therapy: practical guidance for restarting therapy and avoiding recurrences. *Hellenic J Cardiol,* 55**,** 499-509.

RUSSWURM, S., VICKERS, J., MEIER-HELLMANN, A., SPANGENBERG, P., BREDLE, D., REINHART, K. & LOSCHE, W. 2002. Platelet and leukocyte activation correlate with the severity of septic organ dysfunction. *Shock,* 17**,** 263-8.

SCHROTTMAIER, W. C., KRAL, J. B., BADRNYA, S. & ASSINGER, A. 2015. Aspirin and P2Y12 Inhibitors in platelet-mediated activation of neutrophils and monocytes. *Thromb Haemost,* 114**,** 478-89.

SHI, S., QIN, M., CAI, Y., LIU, T., SHEN, B., YANG, F., CAO, S., LIU, X., XIANG, Y., ZHAO, Q., HUANG, H., YANG, B. & HUANG, C. 2020a. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J,* 41**,** 2070-2079.

SHI, S., QIN, M., SHEN, B., CAI, Y., LIU, T., YANG, F., GONG, W., LIU, X., LIANG, J., ZHAO, Q., HUANG, H., YANG, B. & HUANG, C. 2020b. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol*.

SILLER-MATULA, J. M., TRENK, D., SCHROR, K., GAWAZ, M., KRISTENSEN, S. D., STOREY, R. F., HUBER, K. & EPA 2013. Response variability to P2Y12 receptor inhibitors: expectations and reality. *JACC Cardiovasc Interv,* 6**,** 1111-28.

SPYROPOULOS, A. C., LEVY, J. H., AGENO, W., CONNORS, J. M., HUNT, B. J., IBA, T., LEVI, M., SAMAMA, C. M., THACHIL, J., GIANNIS, D., DOUKETIS, J. D. & SUBCOMMITTEE ON PERIOPERATIVE, C. C. T. H. O. T. S. S. C. O. T. I. S. O. T. H. 2020. Scientific and Standardization Committee Communication: Clinical Guidance on the Diagnosis, Prevention and Treatment of Venous Thromboembolism in Hospitalized Patients with COVID-19. *J Thromb Haemost*.

TANG, N., LI, D., WANG, X. & SUN, Z. 2020. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost,* 18**,** 844-847.

VANE, J. R. & BOTTING, R. M. 2003. The mechanism of action of aspirin. *Thromb Res,* 110**,** 255-8.

WALLENTIN, L., BECKER, R. C., BUDAJ, A., CANNON, C. P., EMANUELSSON, H., HELD, C., HORROW, J., HUSTED, S., JAMES, S., KATUS, H., MAHAFFEY, K. W., SCIRICA, B. M., SKENE, A., STEG, P. G., STOREY, R. F., HARRINGTON, R. A., INVESTIGATORS, P., FREIJ, A. & THORSEN, M. 2009. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med,* 361**,** 1045-57.

WANG, D., HU, B., HU, C., ZHU, F., LIU, X., ZHANG, J., WANG, B., XIANG, H., CHENG, Z., XIONG, Y., ZHAO, Y., LI, Y., WANG, X. & PENG, Z. 2020. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA*.

WIVIOTT, S. D., BRAUNWALD, E., MCCABE, C. H., MONTALESCOT, G., RUZYLLO, W., GOTTLIEB, S., NEUMANN, F. J., ARDISSINO, D., DE SERVI, S., MURPHY, S. A., RIESMEYER, J., WEERAKKODY, G., GIBSON, C. M., ANTMAN, E. M. & INVESTIGATORS, T.-T. 2007. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med,* 357**,** 2001-15.

WU, Z. & MCGOOGAN, J. M. 2020. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*.

YUSUF, S., ZHAO, F., MEHTA, S. R., CHROLAVICIUS, S., TOGNONI, G., FOX, K. K. & CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS TRIAL, I. 2001. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med,* 345**,** 494-502.

ZHOU, F., YU, T., DU, R., FAN, G., LIU, Y., LIU, Z., XIANG, J., WANG, Y., SONG, B., GU, X., GUAN, L., WEI, Y., LI, H., WU, X., XU, J., TU, S., ZHANG, Y., CHEN, H. & CAO, B. 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet,* 395**,** 1054-1062.

ZUO, Y., YALAVARTHI, S., SHI, H., GOCKMAN, K., ZUO, M., MADISON, J. A., BLAIR, C., WEBER, A., BARNES, B. J., EGEBLAD, M., WOODS, R. J., KANTHI, Y. & KNIGHT, J. S. 2020. Neutrophil extracellular traps (NETs) as markers of disease severity in COVID-19. *medRxiv*.

# 14.APPENDIX 1. OVERVIEW OF DESIGN AND INITIAL RESULTS FOR THE ANTIPLATELET DOMAIN

## *14.1. Introduction*

This document describes the statistical design and analysis of the testing of antiplatelet therapy versus no antiplatelet therapy in the COVID-19 appendix as part of the REMAP-CAP trial. Our goal is to investigate whether this is independently beneficial in increasing the number of ICU- free days for patients with COVID-19.

### 14.1.1. Treatment Arms

The main effect for antiplatelet therapy in this domain will be modeled as specified in the PAtC.

### 14.1.2. Primary Endpoint

The primary efficacy endpoint is as specified in the PAtC, the ordinal endpoint, organ support-free days through 21 days with the classification of in hospital death as the worst outcome.

## *14.2. Primary Analysis Model*

The primary analysis is based on a Bayesian cumulative logistic regression assuming proportional odds for intervention effects as outlined in the PAtC.

### 14.2.1. Domain Platform Conclusions.

The Platform Conclusions of Superiority and Inferiority are as specified in the PAtC and are unchanged.

This domain substitutes a Platform Conclusion of Futility in place of Equivalence to the no antiplatelet intervention for this domain as demonstration of equivalence in not relevant but a conclusion of Futility of antiplatelet therapy is relevant. If the probability of at least a 20% odds ratio improvement for antiplatelet therapy is less than 5% then the Statistical Trigger for Futility will have been met. This Futility trigger is the one-sided extension of the equivalence rule in PAtC. That is, Futility of antiplatelet therapy will be declared if $Pr(OR_1 > 1.2) < 0.05$, where $OR_1$ refers to the odd ratio for therapeutic anticoagulation compared to SOC for this domain.

## 14.3. Simulation Details

In this section, we outline the simulations conducted for understanding the performance of this domain. Simulations were conducted separately assuming only this domain.

### 14.3.1. Standard-of-Care Rates and antiplatelet effect assumptions

We created possible standard-of-care rates across the 23 levels of the outcome. We worked within a few clinically guided expected parameters: 20% mortality rate, 10% of patients are receiving organ support in the ICU for 21 days, and median number of days receiving organ support in the ICU is 7 amongst those that did not die. Figure 1 shows the assumed rates for the organ support-free day endpoint in the left panel.

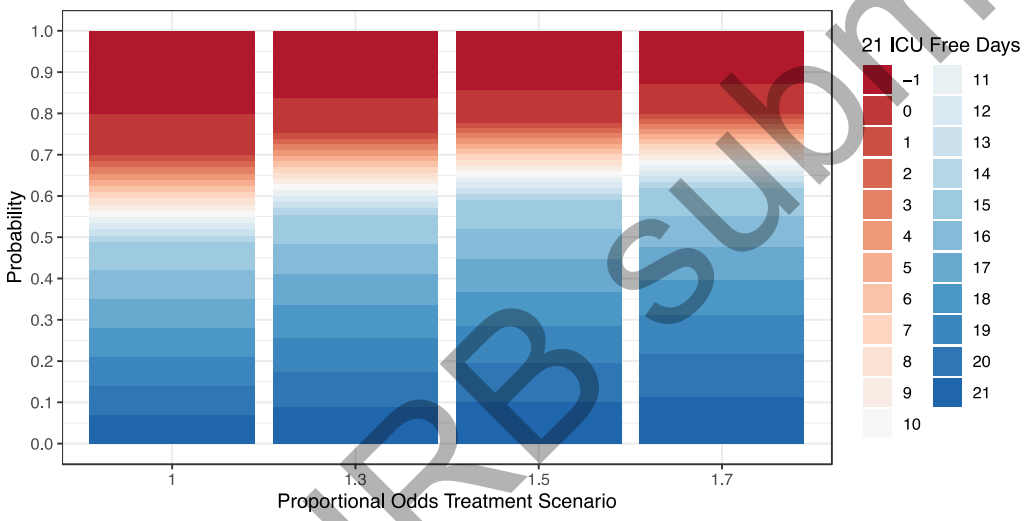


*Figure 1. Control outcome probabilities for the organ support-free day end point (left panel) and then the probabilities for treatment effects of odds ratios of 1.3, 1.5, and 1.7.*

For the simulations in this section interim analyses are assumed to occur at 200, 400, 600, 800, 1000, 1500, 2000, 2500, and 3000 patients enrolled in this domain.

## 14.4. Operating Characteristics

Figure 2 presents the cumulative probability to determine that an antiplatelet therapy is superior to no antiplatelet therapy as a function of the total number of patients enrolled (x-axis) and the assumed effect sizes (1.3, 1.5, and 1.7). The left panel assumes both arms are effective and have equal efficacy. The right panel provides the probability for the one effective arm assuming it is the only antiplatelet arm that is effective. These power calculations ignore the interaction with any anticoagulation domain.

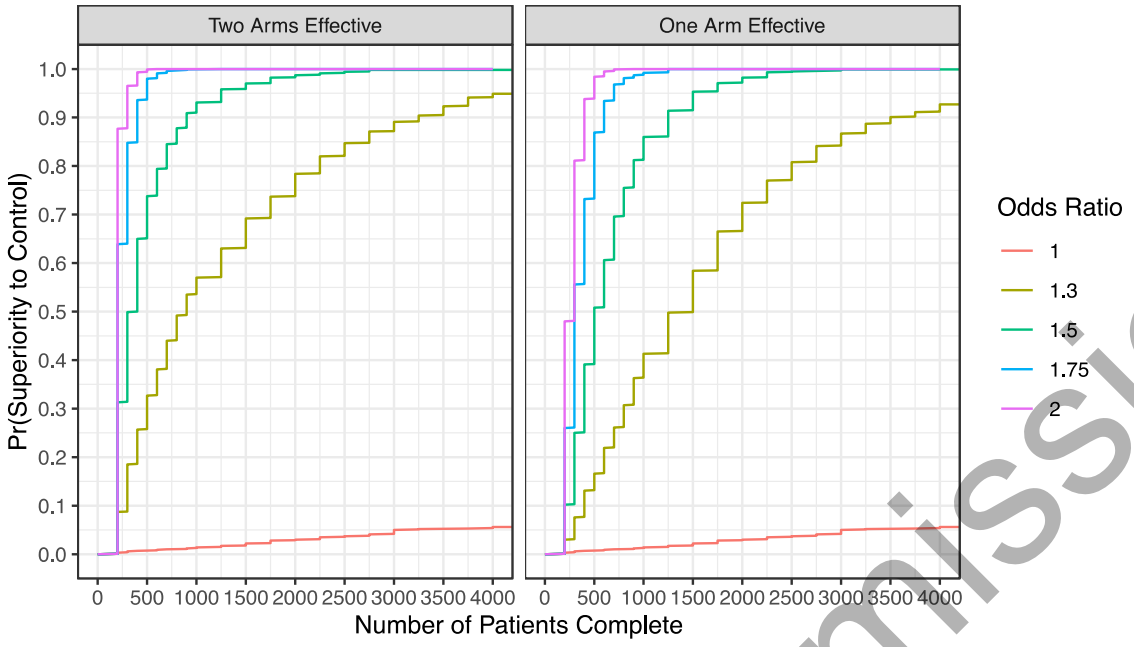


*Figure 2: The cumulative power for each of the explored treatment effects (odds ratios of 1.3, 1.5, and 1.7). The cumulative type I error for each intervention is shown as the red line (effect size of 1).*

### *14.5. Summary*

The domain is designed to provide high-level evidence. The domain has at least 80% power to demonstrate superiority of an antiplatelet therapy to no antiplatelet therapy by 400 patients enrolled assuming an odds ratio effect size of 1.7. For an effect size of 1.5 the power is 80% for 800 patients enrolled. The cumulative type I error through 3000 patients is less than 5%.