


# Anti-Thrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC): Study design and methodology for an international, adaptive Bayesian randomized controlled trial

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## Abstract

**Background:** Mortality from COVID-19 is high among hospitalized patients and effective therapeutics are lacking. Hypercoagulability, thrombosis and hyperinflammation occur in COVID-19 and may contribute to severe complications. Therapeutic anticoagulation may improve clinical outcomes through anti-thrombotic, anti-inflammatory and anti-viral mechanisms. Our primary objective is to evaluate whether therapeutic-dose anticoagulation with low-molecular-weight heparin or unfractionated heparin prevents mechanical ventilation and/or death in patients hospitalized with COVID-19 compared to usual care.

**Methods:** An international, open-label, adaptive randomized controlled trial. Using a Bayesian framework, the trial will declare results as soon as pre-specified posterior probabilities for superiority, futility, or harm are reached. The trial uses response-adaptive randomization to maximize the probability that patients will receive the more beneficial treatment approach, as treatment effect information accumulates within the trial. By leveraging a common data safety monitoring board and pooling data with a second similar international Bayesian adaptive trial (REMAP-COVID anticoagulation domain), treatment efficacy and safety will be evaluated as efficiently as possible. The primary outcome is an ordinal endpoint with three possible outcomes based on the worst status of each patient through day 30: no requirement for invasive mechanical ventilation, invasive mechanical ventilation or death.

**Conclusion:** Using an adaptive trial design, the Anti-Thrombotic Therapy To Ameliorate Complications of COVID-19 trial will establish whether therapeutic anticoagulation can reduce mortality and/or avoid the need for mechanical ventilation in patients hospitalized with COVID-19. Leveraging existing networks to recruit sites will increase enrollment and mitigate enrollment risk in sites with declining COVID-19 cases.

## Keywords

Heparin, thrombosis, COVID-19, adaptive clinical trial, protocol

## Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a novel coronavirus that has rapidly spread across the globe causing severe respiratory infection.<sup>1,2</sup> With the possible exception of remdesivir, no therapies have proven efficacy.<sup>3,4</sup> Rapidly deployable, safe and effective therapeutic agents are urgently needed. Coronavirus disease 2019 (COVID-19) is associated with activation of coagulation and inflammatory pathways (Figure 1), suggesting that therapeutic-dose anticoagulation may improve clinical outcomes.

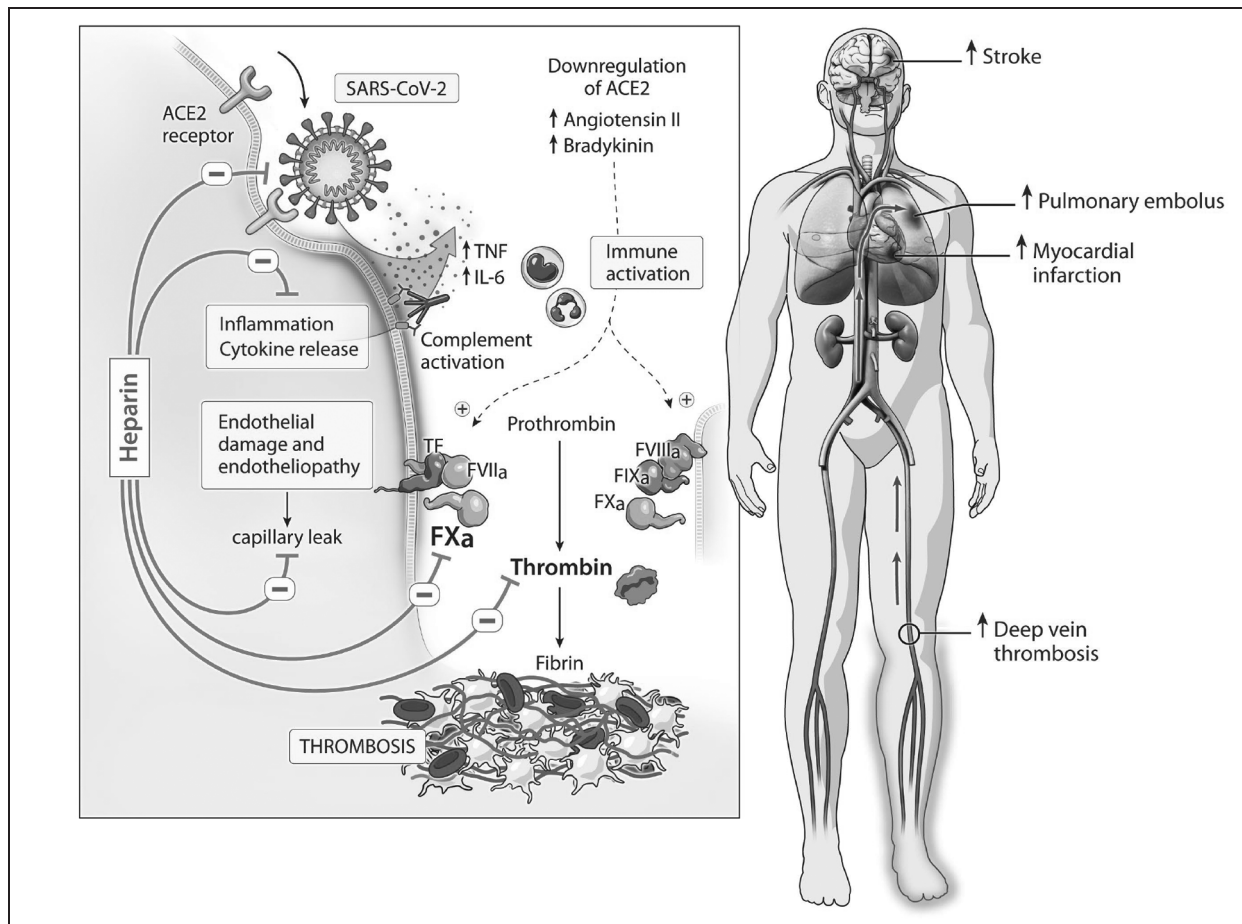
Early observational reports suggest that COVID-19 infection is associated with hypercoagulability and increased risk of thrombosis.<sup>5-7</sup> Thrombosis is closely linked to systematic vascular inflammation and, distinct from other respiratory viral syndromes, COVID-19 appears to be associated with a profound endotheliopathy.<sup>8</sup> D-dimer levels may signal this coagulopathy and predict poor prognosis.<sup>5,9,10</sup> D-dimers may also help identify patients most likely to benefit from anticoagulation.

Heparin is a commonly used anti-thrombotic agent that facilitates antithrombin-mediated inactivation of factors Xa and IIa. Heparin has diverse anti-inflammatory properties and is known to inhibit complement and adhesion molecule expression in the microvasculature<sup>11</sup> and downregulate interleukin 6.<sup>12</sup> Heparin may also exert direct anti-viral effects on

SARS-CoV-2.<sup>13</sup> Upon binding heparin, the SARS-CoV-2 spike protein undergoes conformational changes that interfere with binding to angiotensin converting enzyme-2. A similar anti-viral effect of heparin has also been observed with SARS-CoV-1.<sup>14,15</sup>

A significant body of evidence including laboratory data,<sup>11,12</sup> animal models,<sup>16</sup> observational studies,<sup>17</sup> randomized controlled trials in humans<sup>18,19</sup> and meta-analyses<sup>18,20</sup> support the potential for heparin to reduce mortality in sepsis. Data are limited in COVID-19, although an observational study from China suggested that the use of low-dose heparin may be associated with lower mortality in patients with elevated D-dimer levels.<sup>21,22</sup> A second observational cohort from New York observed that therapeutic anticoagulation was associated with longer survival among critically ill patients with COVID-19.<sup>23</sup> Both observational studies had important limitations and cited the need for randomized trials.

These data provide a compelling rationale to evaluate therapeutic anticoagulation with heparin in patients with COVID-19. The proposed Anti-Thrombotic Therapy To Ameliorate Complications of COVID-19 (ATTACC) trial will leverage an international network of over 30 sites across Canada, the United States, Brazil and Mexico to rapidly inform clinical practice. In this article, we describe and elaborate upon design considerations including our choices and rationale with an aim to provide helpful and generalizable guidance for the clinical trials community.



**Figure 1.** Proposed pathophysiologic mechanisms of thrombosis in COVID-19 infection.

ACE-2: angiotensin-converting enzyme II; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; TNF: tumor necrosis factor; IL-6: interleukin 6; TF: tissue factor.

## Methods

### Trial objective

To establish whether therapeutic-dose parenteral anticoagulation with heparin prevents the need for mechanical ventilation and/or death in patients hospitalized with COVID-19.

### Trial design

We will perform an international, open-label, pragmatic, adaptive randomized controlled trial enrolling adult patients hospitalized with confirmed COVID-19 infection.

ATTACC employs a Bayesian framework for statistical inference. We chose a Bayesian approach, as compared to frequentist approach, as it facilitates an adaptive trial design, which provides needed flexibility within a rapidly evolving pandemic where uncertainty exists surrounding event rates and potential treatment effect sizes. The incorporation of response-adaptive randomization according to baseline D-dimer facilitates allocation of a participant based on their observed

probability of benefit within a D-dimer-defined subgroup. In the context of emerging observational evidence suggesting potential benefit from therapeutic anticoagulation, response-adaptive randomization is useful to increase acceptance of the trial by both clinicians and patients given that patients have a higher probability of receiving therapeutic anticoagulation if there is early evidence of benefit in specific D-dimer subgroups. Frequent interim analyses with the ability to terminate based on clinically important conclusions will allow the trial to efficiently determine if heparin is efficacious, while monitoring safety. As an open trial, our operational procedures and statistical analyses have been detailed a priori to ensure scientific integrity and reduced bias.<sup>24</sup>

### Trial interventions

**Intervention group.** The active treatment arm will receive therapeutic-dose parenteral anticoagulation with either low-molecular-weight heparin or unfractionated heparin at doses for the treatment of venous

**Table 1.** Prophylactic and therapeutic dosing of commonly used heparin agents.

Heparin agent	Prophylactic dosing	Therapeutic dosing
Low-molecular-weight heparin <sup>a</sup>		
Dalteparin	5000 units once daily	200 units/kg once daily OR 100 units/kg twice daily
Enoxaparin	40 mg once daily	1 mg/kg twice daily OR 1.5 mg/kg once daily
Tinzaparin	4500 units daily	175 units/kg daily
Unfractionated heparin	5000 units subcutaneous twice daily	80 units/kg IV bolus followed by continuous infusion of 18 units/kg/h IV; adjust based on institutional protocol <sup>b</sup>

<sup>a</sup>All low-molecular-weight heparins are administered subcutaneously; kg: kilograms; IV: intravenous.

<sup>b</sup>Heparin dose adjusted for the treatment of venous thromboembolism according to the activated partial thromboplastin time (aPTT) or anti-Xa levels.

thromboembolism. Therapeutic anticoagulation will be continued for up to 14 days or until recovery, defined as hospital discharge or liberation from supplemental oxygen for >24 h if oxygen was initially required, whichever comes first. The intervention arm is designed to be accessible, flexible and pragmatic. Heparin is an inexpensive drug that is accessible to practitioners in health systems around the world. The specific heparin formulation, decisions pertaining to anticoagulation monitoring, dosing and dose adjustments will be conducted according to local practice. The choice of therapeutic (as opposed to intermediate) dose heparin is supported by observational studies of heparin in sepsis<sup>17</sup> and is associated with low bleeding rates.<sup>25</sup> Therapeutic dosing is required to provide separation between groups, especially given the heterogeneous thromboprophylactic strategies employed in the care of patients with COVID-19.<sup>23</sup>

**Control group.** The control arm will receive pharmacologic thromboprophylaxis (e.g. low-dose low-molecular-weight heparin or unfractionated heparin) according to local practice. Based on perceptions of thrombotic risk in some patients with COVID-19, intermediate doses of low-molecular-weight or unfractionated heparin for venous thromboprophylaxis may be used in some centers, but the doses administered in the control arm will remain below the therapeutic doses used in ATTACC; local practice may vary by center and over time, but will be recorded. Rather than protocolizing the thromboprophylactic strategy in the control group, to maximize acceptance of the trial protocol in the face of rapidly changing practice patterns, flexibility of dosing in the usual care group is required. Table 1 summarizes standard prophylactic and therapeutic doses of commonly used heparin drugs.

### Co-enrollment

As anticoagulation is anticipated to be an ancillary supportive care strategy in patients with COVID-19, co-enrollment is permitted provided the co-enrolling trials are not evaluating anticoagulants or anti-platelet medications. This is intended to encourage the efficient enrollment and conduct of alternative therapeutic trials in patients with COVID-19. Co-enrollment could conceivably influence point estimates in the presence of unexpected interactions; however, a priori interactions are not expected in the context of currently enrolling COVID-19 therapeutic trials. Interactions will be explored post hoc.

### Patient selection

**Inclusion criteria.** Patients  $\geq 18$  years of age admitted to hospital with laboratory-confirmed COVID-19. The anticipated duration of hospitalization must be >72 h from randomization, and patients must be enrolled within 72 h of hospital admission or confirmation of COVID-19. These criteria were chosen to exclude patients with a favorable clinical trajectory and imminent hospital discharge, as they would be less likely to benefit from ancillary supportive therapies.

**Exclusion criteria.** Major exclusions include invasive mechanical ventilation at the time of randomization, active bleeding or risk factors for bleeding. The complete list of exclusion criteria is presented in Table 2.

### Trial outcomes

**Primary outcome.** The primary outcome is an ordinal categorical endpoint with three possible outcomes based on the worst status of each patient through day



**Table 2.** Exclusion criteria.

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Mechanical ventilation (at time of randomization)
No intention to use pharmacologic thromboprophylaxis
Active bleeding
Risk factors for bleeding
Intracranial surgery or stroke within 3 months
History of intracranial arteriovenous malformation
Cerebral aneurysm or mass lesions of the central nervous system
Intracranial malignancy
History of bleeding diatheses (e.g. hemophilia)
Gastrointestinal bleeding within 3 months
Thrombolysis within 7 days
Presence of an epidural or spinal catheter
Major surgery within 14 days
Uncontrolled hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >120 mm Hg)
Other contraindications to therapeutic anticoagulation
Platelet count <50 × 10 <sup>9</sup> /L, international normalized ratio (INR) >2.0, or baseline activated partial thromboplastin time (aPTT) >50 s
Hemoglobin <8 g/dL (to minimize the likelihood of transfusion if bleeding were to occur)
Acute or subacute bacterial endocarditis
History of heparin-induced thrombocytopenia (HIT) or other heparin allergy or hypersensitivity
Current use of dual antiplatelet therapy (e.g. aspirin plus clopidogrel or ticagrelor or prasugrel)
Patients with an independent indication for therapeutic anticoagulation
Patients in whom imminent demise is anticipated and there is no commitment to active intervention
Anticipated transfer to a non-study site within 72 h
Pregnancy <sup>a</sup>
Enrollment in other trials related to anticoagulation or antiplatelet therapy
Refusal of the treating physician

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INR: international normalized ratio; HIT: heparin-induced thrombocytopenia.

<sup>a</sup>Applies only to sites in the United States.

30: no invasive mechanical ventilation, invasive mechanical ventilation or death. This endpoint was chosen because (a) invasive mechanical ventilation and death are clinically relevant outcomes with high importance to patients and healthcare systems; (b) the ordinal endpoint increases statistical power in comparison with a binary endpoint and is justified based on the clinical importance; and (c) the risk of ascertainment bias is low with this endpoint focused on objectively definable events. Venous thromboembolism was not included in the primary outcome due to concerns for ascertainment bias, as patients on therapeutic anticoagulation may be less likely to receive imaging, which would therefore favor the intervention arm. Similarly, myocardial infarction was not included in the primary outcome as cardiac injury in COVID-19 patients can result from a variety of mechanisms. The effect of heparin on myocardial injury is unclear. Both venous thromboembolism and myocardial infarction are captured as secondary outcomes.

**Secondary outcomes.** The following safety and efficacy outcomes will be assessed:

**Safety:** The two major safety concerns associated with heparin anticoagulation relate to major bleeding and heparin-induced thrombocytopenia (HIT).<sup>26</sup> As such,

our safety outcomes include laboratory confirmed heparin induced thrombocytopenia, and major bleeding defined according to the International Society on Thrombosis and Haemostasis.<sup>27</sup> This definition includes fatal bleeding, symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial or intramuscular with compartment syndrome), bleeding causing a fall in hemoglobin of  $\geq 2$  g/dL, or leading to the transfusion of 2 or more whole blood or red cell units. The presence of HIT and/or major bleeding will be assessed on days 1, 3, 7, 14 and 21.

**Efficacy.** (Assessed at 21 days): organ support-free days (days alive and without the need for invasive or non-invasive mechanical ventilation, high flow nasal cannula at  $\geq 30$  L/min flow, or vasopressor support); (Assessed at 30 days): use of non-invasive ventilation or high-flow nasal cannula, intubation, ventilator-free days, intensive care unit-free days, hospital-free days. For outcomes with “free-days” assessed at 21, 30 or 90 days, patients will be assigned a value of -1 if they die before 21, 30 or 90 days, respectively. (Assessed at 30 and 90 days): venous thromboembolism, myocardial infarction, ischemic stroke and all-cause mortality.

**Outcome adjudication.** The primary outcome will be independently verified by a centralized adjudication

committee. Given the importance of standardized definitions and reporting, major hemorrhage, laboratory confirmed HIT and venous and arterial thrombotic events will be adjudicated without knowledge of treatment assignment. A central adjudication committee is of importance given the trial is open-label, and there is both complexity and potential subjectivity associated with the reporting of bleeding and thrombotic events.

### **Recruitment and patient consent**

In response to pandemic-related infection control measures and policies that encourage the avoidance of unnecessary direct person-to-person contact, modifications to traditional written informed consent are required. Consent will be obtained as per Institutional Research Ethics Board/Institutional Review Board and Food and Drug Administration (FDA) recommendations, but is anticipated to include verbal consent and consent obtained by telephone from either the patient or their designated substitute decision maker/legally authorized representative.

### **Methods of data collection and the duration of follow-up**

To maximize the operational feasibility of the trial, following randomization, collected data include variables typically part of routine care. Laboratory investigations are not mandated, but will be ascertained using an electronic case report form as per the study schedule (Appendix 1). Electronic data collection using an online case report form has been prioritized to minimize infectious exposure. Subjects will be followed until hospital discharge or 90 days, whichever comes first. For those discharged before 90 days, telephone contact will be undertaken at days 30 and 90 to ascertain the secondary outcomes up to day 90.

**Concomitant medications.** Concomitant medications including proven or experimental COVID-19 treatments and anti-platelet agents will be collected from time of consent to 14 days or time of treatment discontinuation (whichever occurs first). Anticoagulant use up to the 30-day assessment will also be collected.

### **Risk and methods to protect against bias**

To meet the needs of the global pandemic, ATTACC has been intentionally designed as an open-label trial. This decision was made to substantively reduce resource burden on clinical and research staff at participating centers and minimize staff exposure to highly infectious patients. The components of our primary outcome (intubation and/or death) were felt to be minimally impacted by the lack of blinding and reflect

escalation of care due to deterioration of patients rather than knowledge of treatment assignment.

**Randomization and allocation concealment.** A secure, web-based randomization system will be used to allocate treatment assignments.

### **Analytic plan**

**Sample size and power calculations.** The trial design uses a Bayesian adaptive framework to reach a conclusion regarding superiority or futility in an efficient manner within three different baseline D-dimer-defined subgroups. D-dimer subgroups will be defined at the first interim analysis based on the 50th and 75th percentile values measured in the first 100 patients. The trial will enroll until the pre-specified stopping criterion for benefit ( $>99\%$  posterior probability of proportional odds ratio  $>1$ ) or futility ( $<10\%$  posterior probability of proportional odds ratio  $>1.2$ ) is reached within each D-dimer subgroup. An odds ratio of 1.2 is used as the minimum treatment effect threshold to declare futility given it is approximately equivalent to an absolute risk reduction in mortality of  $\leq 1\%$  assuming a baseline event rate of 25% for intubation and 12.5% for death. We will enroll up to a maximum of 3000 patients. Trial simulations indicate that the risk of Type I error remains below 5% at 3000 patients and that enrolling 2000 patients will give 90% power to detect an odds ratio  $\geq 1.5$  for avoiding intubation or death (equivalent to a  $\geq 5\%$  absolute risk reduction in mortality). If the treatment is harmful (odds ratio  $< 1$ ), there is a 60% chance that the trial will be halted after enrolling 200–300 patients based on the futility stopping criterion. Data will be analyzed based on the intention-to-treat principle.

**Analysis of primary and secondary outcomes.** The primary analysis of the ordered categorical endpoint is a Bayesian cumulative proportional odds model (odds ratio  $> 1$  suggests treatment benefit). The effect of therapeutic anticoagulation is modeled within prespecified patient subgroups based on the baseline D-dimer levels. Each patient is classified by their baseline D-dimer levels as highest (top quartile), median (3rd quartile) and lowest (less than median). An additional category will be added for patients in whom D-dimer is not available at the time of randomization. Treatment effects are modeled as potentially differential across D-dimer subgroups using a Bayesian hierarchical model. The Bayesian hierarchical model creates a statistical borrowing across the subgroups for improved estimates within each subgroup while allowing them to be differential. Each conclusion for therapeutic anticoagulation is determined using the posterior distribution of the subgroup-specific treatment effect. The baseline

risks for each group are modeled with independent weak prior distributions with the lowest D-dimer group serving as the reference population.

In addition to an overall adaptive sample size, the trial also employs an adaptive sample size and response-adaptive randomization within each of these three subgroups. Interim analyses will be conducted after every 100 patients enrolled. At each interim analysis, the trial may reach a conclusion of superiority (posterior probability of benefit  $> 99\%$ ) or futility (posterior probability of an odds ratio  $\geq 1.2$  is less than  $10\%$ ) within any of the subgroups, which would stop randomization in that subgroup. If no conclusion within a subgroup is reached and randomization continues, the randomization probabilities will be re-weighted based on posterior probabilities of benefit or harm within the subgroup to a maximum of  $90\%$  and a minimum of  $10\%$ . Post hoc analyses will be performed to investigate differential efficacy and safety by sex.

### *Risks to the safety of potential participants*

As an open-label trial of approved and commonly used drugs with well-established safety and side-effect profiles, adverse events and serious adverse events captured in this trial are events possibly related to the investigational agent, which includes major bleeding and laboratory confirmed HIT.

### *Study management and governance*

Given the time-sensitive nature of the pandemic, existing international expertise and capacity was leveraged to create a trial infrastructure with distributed roles among a number of academic institutions and organizations. The University of Manitoba (Winnipeg, Canada) is the study sponsor and will support site contracts and payments. The clinical coordinating center is Ozmosis Research Inc. (Toronto, Canada) who will be responsible for overall study management. The InCor Academic Research Organization will be responsible for monitoring and conducting all study activities in the Brazilian sites. The data coordinating center is SOCAR Research (Nyon, Switzerland), an academic clinical research organization in Switzerland. SOCAR will work closely with our trial statistical consultant, Scott Berry (Austin, USA) to prepare response-adaptive randomization algorithms and data for frequent interim analyses.

The Executive Committee will consist of the Principal Investigators, country leads and representatives from the clinical coordinating center. The Executive Committee is responsible for the execution of the trial according to the study protocol. A Steering Committee will be responsible for providing clinical

and methodological guidance, including overall study design, execution, analysis and publication of the main study results.

### *Data safety monitoring board*

An independent data safety monitoring board (DSMB) will regularly receive the results of interim analyses as well as adverse events and serious adverse events reports. Based on previously described trial conclusion parameters the DSMB may recommend stopping for superiority, futility or harm, of either the entire trial or the a priori defined D-dimer subgroups. The DSMB is empowered to report independently to health authorities at their discretion.

To minimize the time to trial completion, and to garner robust estimates of safety, the ATTACC investigators will combine data with patients enrolled in REMAP-COVID using a common external DSMB. REMAP-CAP is a randomized, embedded, multi-factorial, adaptive platform trial created to evaluate multiple interventions in community-acquired pneumonia. While the platform was designed to evaluate treatments for severe infectious community acquired pneumonia, the intent of the platform was to leverage trial infrastructure to be able to quickly respond to a respiratory pandemic. REMAP-COVID represents an appendix protocol to the REMAP-CAP (community-acquired pneumonia) core trial protocol. The REMAP-COVID protocol specifically addresses domains of interventions for hospitalized COVID-19 patients.<sup>28</sup> There are multiple COVID-19-specific domains including macrolide therapy, corticosteroids, antiviral therapy, immune modulation, antibody therapy, vitamin C and therapeutic anticoagulation. Similar to ATTACC, REMAP-COVID is a Bayesian adaptive platform trial that is currently activating up to 200 sites in the United States, United Kingdom and European Union sites. Although this trial is operationally separate from ATTACC, the three principal investigators from ATTACC serve on the working group for the Therapeutic Anticoagulation domain of REMAP-COVID (R.Z. (chair), E.G. (deputy chair) and P.L.). Trial procedures and endpoints have thus been harmonized between REMAP-COVID and ATTACC and the data will be combined to permit shared interim analyses in the context of a shared external DSMB. This innovative and highly collaborative data sharing structure permits evidence of efficacy and safety to be realized as quickly and as robustly as possible.

### *Estimated duration of the trial*

Based on projected enrolment rates (10 patients per month at, initially, 35 centers with expansion as

needed), we anticipate trial completion within 12 months. The inclusion of patients from high-volume sites in Canada, the United States, Brazil and Mexico may shorten this estimate. Given the Bayesian adaptive framework of ATTACC, the entire trial or specific subgroups of D-dimer patients may be stopped earlier based on the results of interim analyses. Although the maximum sample size is 3000 patients, trial simulations indicate a moderately high probability of stopping for superiority before this sample size is attained.

### **Dissemination strategy**

Results of the trial will be communicated rapidly to public health officials and policy makers as well as the general medical community in order to inform urgent pandemic management. We will work with our patient partners and knowledge users to prepare and disseminate trial results via traditional publications, society recommendations, policy statements, media and social media. Results will be published in open-access journals, with study data made available in an open-access repository.

### **Partnerships**

ATTACC has broad international support. In Canada, ATTACC has partnered with the Canadian Critical Care Trials Group, the Canadian venous thromboembolism research network and the Canadian trials for COVID trial network, a group of >50 hospitals participating in anti-viral therapeutic strategies for COVID-19 patients. Internationally, ATTACC has partnered with REMAP-COVID, an international adaptive platform trial that is currently expanding to potentially include over 200 sites in the United States, United Kingdom and European Union. ATTACC has also partnered with the Worldwide Network for Innovation in Clinical Education and Research network, which includes our centers in Brazil and Mexico, and is endorsed by both the International Network of Venous Thromboembolism Clinical Research Network and the International Forum of Acute Care Trialists. ATTACC has partnered with sites in Brazil and Mexico to increase the speed of recruitment and the generalizability of findings in low/middle-income countries. These international partnerships have been developed to permit efficient site recruitment and promote swift trial completion in the face of a rapidly evolving pandemic with changing and unpredictable case volumes.

### **Discussion**

ATTACC is a Bayesian adaptive trial that has been designed to urgently evaluate if therapeutic anticoagulation will benefit hospitalized patients with COVID-19

when compared with usual care. Multiple pandemic-specific design elements have been incorporated to promote the rapid recruitment of patients and terminate the trial as soon as a clinically relevant conclusion has been achieved. By leveraging existing networks, the ATTACC investigators have further created an international network of committed sites with the necessary expertise and infrastructure to advance our understanding of pathophysiologic mechanisms of thrombosis in COVID-19 and evaluate antithrombotic strategies to improve clinical outcomes.

A unique feature of ATTACC is the use of a common external DSMB shared with a second similar Bayesian adaptive international trial (REMAP-COVID).<sup>28</sup> By harmonizing the two trial procedures and outcomes, this innovative and highly collaborative data sharing structure permits evidence of efficacy and safety to be realized as quickly and as robustly as possible.

The scope of ATTACC and diverse international partnerships have facilitated early successes. Content experts from cardiology, hematology, thrombosis, intensive care, medication safety and trial methodology have collaborated to design a trial that meets the unique situational needs of the COVID-19 pandemic. Given the time-sensitive nature of the pandemic, roles were distributed internationally based on the immediate capacity and expertise. Existing trial networks were leveraged to recruit sites, which will increase enrollment and also mitigate enrollment risk in sites with declining COVID-19 cases. The trial team and infrastructure established create the opportunity to test future hypotheses such as the role of anti-platelet agents or other therapeutics.

ATTACC is planning an ancillary biomarker study and creation of a biobank that will advance our understanding of the pathophysiology of COVID-19 infection, the interplay between infection, inflammation and coagulation and the mechanistic role of heparin. The biobank will be leveraged for further research, extending beyond the duration of the trial.

In the context of an evolving global pandemic, the ATTACC trial has been designed to efficiently address a clinical question of global priority. To launch the trial as quickly as possible we chose to evaluate and repurpose an existing, widely accessible and inexpensive class of medications with strong biologic plausibility. If therapeutic anticoagulation is found to be superior to usual care, treatment can be rapidly instituted for patients hospitalized with COVID-19 around the world.

### **Declaration of conflicting interests**

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### Trial registration

Trial registration: NCT04372589: <https://clinicaltrials.gov/ct2/show/NCT04372589>

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### Supplemental material

Supplemental material for this article is available online.

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