**RESEARCH PROPOSAL SUBMISSION FORM**

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**STUDY SYNOPSIS (Maximum 1500 words)**

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| **TITLE** | AntiThrombotic Therapy to Ameliorate Clinical Complications in Community Acquired Pneumonia (ATTACC-CAP) |
| **PRINCIPAL INVESTIGATOR, AFFILIATIONS AND CONTACT DETAILS** | Prof Zoe McQuilten, Alfred Health and School of Public Health and Preventive Medicine, Monash University  553 St Kilda Rd, Melbourne, 3004 |
| **ASSOCIATE INVESTIGATORS AND AFFILIATIONS** | Prof Steven Tong, University of Melbourne and Doherty Institute of Infection and Immunity  Prof Steve Webb, Australian and New Zealand Intensive Care Research Centre, Monash University  A/Prof Huyen Tran, Alfred Health  A/Prof James McFadyen, Alfred Health  Dr Alisa Higgins, Australian and New Zealand Intensive Care Research Centre, Monash University  Dr Elizabeth Ryan, School of Public Health and Preventive Medicine, Monash University  Dr Ar Kar Aung, Alfred Health  Professor Bala Venkatesh, George Insitute for Global Health and Princess Alexandra Hospital, Brisbane  Professor Jason Roberts, University of Queensland |
| **IS THIS STUDY CURRENTLY A MULTICENTRE STUDY? (I.E. INVOLVEMENT OF MORE THAN ONE HEALTH SERVICES OR JURISDICTION)** | **YES** |
| **ARE YOU LOOKING FOR OPPORTUNITIES FOR MULTICENTRE COLLABORATION?** | **YES** |
| **IF ‘YES’ TO QUESTION ABOVE, CAN INTERESTED COLLABORATORS CONTACT YOU DIRECTLY?** | **YES** |
| **BACKGROUND** | Community acquired pneumonia (CAP) is a life-threatening lung infection and the most common cause of infection-related mortality globally.1, 2 **Poor clinical outcomes in CAP are driven by maladaptive inflammatory and thrombotic host responses** to infection, leading to micro- and macro-vascular thrombosis and organ dysfunction.3, 4 Antimicrobials and supportive therapy improves outcomes in CAP; however, effective therapies that modulate the host response are lacking. In CAP caused by SARS-CoV-2 (COVID-19), in our multiplatform RCT (mpRCT), we demonstrated that therapeutic-dose heparin, an antithrombotic with anti-inflammatory properties, **reduced the composite ordinal outcome of progression to intensive care unit (ICU)-level organ support (i.e., organ failure) and mortality in noncritically ill patients**.5 These findings have been incorporated into clinical practice guidelines internationally.6-9 Although both pneumonia caused by SARS-CoV-2 and CAP caused by other pathogens (referred to as ‘CAP’ for the remainder of the application) share converging pathways of inflammation and thrombosis, the **potential benefit of therapeutic-dose heparin in CAP is unknown**.  The risk of thrombosis is elevated in CAP and occurs in ~11% of patients at 30-days.10-12 Risk of venous thromboembolism (VTE) was highlighted in COVID-19,13-16 and the incidence of symptomatic VTE in COVID-19 and CAP is comparable (2.0% vs. 3.6%, respectively), and higher in mechanically ventilated patients.17 Cardiovascular (CV) thrombotic events, complicate CAP in up to 1/3 of hospitalizations.12, 18, 19 In our large, international mpRCT, we demonstrated that, compared to usual care thromboprophylaxis, therapeutic-dose heparin reduced the composite ordinal endpoint of progression to ICU-level organ support and death in hospitalized, noncritically ill patients (n=2219) with COVID-19 pneumonia.15 A meta-analysis of the mpRCT with other heparin trials demonstrated consistent reductions in mortality or invasive mechanical ventilation (OR 0.77, 95% CI 0.60-0.99) in moderate COVID-19.20 *Therapeutic-dose heparin is now recommended in multiple international clinical practice guidelines for noncritically ill COVID-19 pneumonia.*6-9  The clinical benefit of therapeutic-dose heparin in CAP specifically has never been studied in a RCT. Nonetheless, a significant body of evidence including laboratory data,21, 22 animal models,23 observational studies,24 and RCTs in humans support the potential for therapeutic-dose heparin to reduce mortality in sepsis and acute respiratory distress syndrome (ARDS).25-27 Taken together, these data provide a compelling rationale to evaluate therapeutic-dose anticoagulation in patients with CAP. |
| **RESEARCH QUESTION/HYPOTHESIS** | **Aim:** To determine, in noncritically ill adult patients hospitalized for CAP, whether therapeutic-dose heparin reduces the composite ordinal outcome of progression to ICU-level organ support and mortalitycompared to usual care thromboprophylaxis (i.e., low-dose heparins routinely given to prevent blood clots in hospitalized patients)?  **Hypothesis:** Administration of therapeutic-dose heparin early in CAP will result in improved outcomes and reduced burden of critical illness compared to usual care thromboprophylaxis. |
| **PRIMARY OUTCOME/PROCESS MEASURE** | The primary outcome is an ordinal endpoint reflecting survival to hospital discharge without ICU-level organ support. This ordinal outcome has three levels: (1) survival to hospital discharge without ICU-level organ support (the best outcome), (2) survival with organ support (an intermediate outcome), or (3) in-hospital death (the worst outcome). |
| **SECONDARY OUTCOME/PROCESS MEASURES** | Secondary safety outcomes: a) major bleeding defined according to the International Society on Thrombosis and Haemostasis (ISTH); b) the frequency and volume of red blood cell units transfused; and c) laboratory confirmed HIT; Secondary efficacy outcomes: a) composite endpoint of death, deep vein thrombosis, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke during hospitalization, at 30 days, and 90 days after randomization; b) ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 30 following randomization comprised of death, survival with invasive mechanical ventilation, or survival without invasive mechanical ventilation; c) ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 30 following randomization comprised of death, survival with noninvasive or invasive mechanical ventilation, or survival without noninvasive or invasive mechanical ventilation (i.e. survival without any respiratory support); d) all-cause mortality at 30 and 90 days; e) hospital-free days (days alive outside hospital) at day 30 and 90; f) health related quality of life using the EQ-5D-5L instrument at baseline, hospital discharge, and 90 days following randomization; g-i) symptomatic proximal venous thromboembolism (DVT or PE); myocardial infarction; and ischemic stroke, all assessed at 30 and 90 days following randomization. |
| **STUDY DESIGN**  **(IF THE STUDY IS A CLINICAL TRIAL, PLEASE INCLUDE INFORMATION ON SAMPLE SIZE CALCULATION, RANDOMISATION, AND BLINDING)** | We will perform an international, open-label, stratified RCT with Bayesian stopping rules enrolling adult patients hospitalized with CAP.  The ATTACC-CAP trial design uses a Bayesian adaptive framework to reach conclusions regarding superiority or futility. The trial uses Bayesian stopping rules to evaluate the treatment effects in two distinct patient groups (a *high-risk group* and a *low-risk group*). *High risk* is defined as the presenceof ≥1 of the following risk factors at enrollment: CRP ≥ 50 mg/L, D-dimer ≥ 2x upper limit of normal, or CURB-65 score ≥ 3.  Based on pre-trial simulations, with event rates and estimates of treatment efficacy for mortality and organ support informed by the literature and our mpRCT, enrolling 2,000 patients will give 80% power to detect an OR ≥ 1.5 for avoiding organ support or death in either risk group. With combined control event rates of 11% and 19.5% in the low and high-risk groups, respectively, this magnitude of treatment effect is equivalent to a 3.4% and 5.6% absolute risk reduction in the combined endpoint of requiring organ support or in-hospital mortality. The control event rates were directly informed by our mpRCT and the published literature.  A web-based randomization system will be used to allocate treatment assignments. The allocation sequence will be computer-generated using a randomly permuted block design with randomly varying lengths, stratified by sex and center and will be concealed from all investigators and research staff. The clinical outcome is robust and is not anticipated to be prone to bias. Clinical outcomes will be independently adjudicated by a central committee blinded to treatment allocation. |
| **INCLUSION CRITERIA** | Patients ≥18 years of age admitted to hospital for a suspected or confirmed diagnosis of CAP defined by the following criteria:   1. Radiographic evidence of new or worsening infiltrate 2. One of the following signs and/or symptoms of lower respiratory tract infection    1. New or increased cough or sputum production    2. Fever of > 37.8oC or temperature <36.0oC    3. WBC > 11 x109/L or < 4 x109/L 3. Requires supplemental oxygen to prevent hypoxemia (or requires an increased level of supplemental oxygen if on chronic oxygen therapy) 4. The primary diagnosis is believed to be CAP as per the attending physician 5. Hospital admission anticipated to last ≥72 hours from randomization |
| **EXCLUSION CRITERIA** | Patients with active COVID-19 infection; a clinical indication for therapeutic anticoagulation; high risk of bleeding or clinical indication for dual antiplatelet therapy; or a known heparin allergy, including heparin-induced thrombocytopenia (HIT). |
| **EXPECTED NUMBER OF PARTICIPANTS** | As this is an adaptive trial, there is no fixed sample size. Simulations for ATTACC-CAP indicate that 3,500 patients will provide 80% power to detect superiority if odds ratio (OR) = 1.35. Under varying assumptions, including beneficial treatment effects restricted to the high-risk group, or beneficial but different treatment effects are observed across groups, robust conclusions of efficacy will likely be achieved in a maximum 4000 patients enrolled and, in many simulations, with substantially fewer patients. The final sample size will be determined by the observed control event rate and treatment effect.  In Australia, we plan to open 20 sites for ATTACC-CAP and will also be the central organizing country for recruitment in other regions as in our previous study, pending funding for patient payments. In the ASCOT anticoagulation trial, we enrolled 1574 patients across 32 sties in 14 months (approx. 3.5 patients/site/month). We conservatively estimate we will enroll up to 720 patients over 3 years (1.0 patients/site/month) in ATTACC-CAP. |
| **STUDY DURATION** | 4 years |
| **ANALYSIS** | The primary analysis of the ordinal endpoint is intention-to-treat using a cumulative proportional odds model. The effect of therapeutic-dose heparin is modeled within two risk-stratified patient groups. The treatment effect of therapeutic-dose heparin for the two risk groups is nested in a hierarchical prior distribution centered on an overall intervention effect estimated with a neutral prior distribution, but distinct effects are estimated in each risk group. When consistent effects are observed between the risk groups, the posterior distribution for each patient subgroup effect is shrunk toward the overall estimate (dynamic borrowing). Dynamic borrowing accelerates trial conclusions, should relative treatment effects be similar between the risk groups, and mitigates outlying treatment estimates. The primary analysis model will additionally adjust for site, enrollment time period, sex, and age. Adaptive analyses will be conducted with every 250 patients enrolled. At each adaptive analysis, the trial could reach a conclusion of **superiority** or **futility** in either risk group, which would stop randomization into that group. We have successfully employed a similar adaptive sequential stopping design in COVID-19.5, 28, 29 |
| **IMPORTANCE TO GENERAL MEDICINE** | CAP is a leading cause of hospitalization and mortality globally.1 An Australian study estimated CAP incidence in all age groups as 161.3/10,000, rising to 319.3/10,000 and 659.9/10,000 person-years in patients 65 to 74 years and > 75 years, respectively. Morbidity and mortality for patients hospitalized with CAP are high; overall mortality at 30-days is 12-13%,19, 30 and at 6 months is 23%.19 Between 6 to 21% require ICU admission,31, 32 with a mortality risk of 37% among ICU patients.33 In Australia, CAP accounted for 147,984 hospitalizations and 3,329 deaths in 2019.  ATTACC-CAP will provide the first and highest-quality evidence on the clinical and economic effectiveness to inform decision-making on whether therapeutic anticoagulation should be administered to all hospitalised patients with CAP in Australia and internationally. If shown to be effective, this low cost and simple intervention has the potential to reduce mortality, need for intensive care support and reduce healthcare costs for one of the most common indications for hospitalisation in Australia. |
| **FUNDING** | Application to MRFF is being submitted. |
| **HAS CONSIDERATION BEEN GIVEN TO HOW THIS PROJECT MIGHT IMPROVE EQUITY IN INDIGENOUS OR VULNERABLE POPULATIONS? PLEASE PROVIDE EXPLANATION** | Nothing specific is planned within this trial, however we are testing a low-cost, easy to administer intervention that can be implemented broadly and by recruiting across 20 sites in Australia, our results will be widely applicable to Australian hospitalised patients with CAP. |
| **CURRENT PROGRESS** | Design and protocol development [x]  Ethics application [overseas, not in Australia]  Study in progress [x]  Manuscript write-up in progress or under review []  Accepted or published []  Aborted |
| **IMSANZ-RN OFFICE USE ONLY** | **ENDORSED** |

**REFERENCES:**

1. Ferreira-Coimbra J, et al. *Adv Ther*. 2020;37:1302-1318.

2. *Lancet*. 2018;392:1736-1788.

3. Engelmann B, et al. *Nat Rev Immunol*. 2013;13:34-45.

4. Cangemi R, et al. *Thromb Haemost*. 2022;122:257-266.

5. Lawler PR, et al. *N Engl J Med*. 2021;385:790-802.

6. American Society of Hematology. ASH Guidelines on Use of Anticoagulation in Patients with COVID-19. 2021.

7. Moores LK, et al. *Chest*. 2022.

8. National Institute of Health. Antithrombotic Therapy in Patients With COVID-19. *COVID-19 treatment guidelines*. 2021.

10. Stals M, et al. *Res Pract Thromb Haemost*. 2021;5:412-20.

11. Wunderink RG, et al. *Am J Respir Crit Care Med*. 2011;183:1561-8.

12. Violi F, et al. *Clin Infect Dis*. 2017;64:1486-1493.

13. Klok FA, et al. *Thromb Res*. 2020;191:145-147.

14. Tang N, et al. *J Thromb Haemost*. 2020;18:844-847.

15. Investigators A, et al. *The New England journal of medicine*. 2021;385:790-802.

16. Spyropoulos AC, et al. *JAMA Intern Med*. 2021.

17. Mei F, et al. *Arterioscler Thromb Vasc Biol*. 2020;40:2332-2337.

18. Musher DM, et al. *N Engl J Med*. 2019;380:171-176.

19. Ramirez JA, et al. *Clin Infect Dis*. 2017;65:1806-1812.

20. Sholzberg M, et al. *medRxiv*. 2021:2021.07.08.21259351.

21. Mummery RS, et al. *J Immunol*. 2000;165:5671-9.

22. Lever R, et al. *Br J Pharmacol*. 2000;129:533-40.

23. Cornet AD, et al. *Thromb Haemost*. 2007;98:579-86.

24. Zarychanski R, et al. *Crit Care Med*. 2008;36:2973-9.

25. Mouncey PR, et al. *N Engl J Med*. 2015;372:1301-11.

26. Venkatesh B, et al. *N Engl J Med*. 2018;378:797-808.

27. Brower RG, et al. *N Engl J Med*. 2000;342:1301-8.

28. Goligher EC, et al. *N Engl J Med*. 2021;385:777-789.

29. Lawler PR, et al. *Circulation*. 2022;145:629-632.

30. Johnstone J, et al. *Medicine (Baltimore)*. 2008;87:329-334.

31. Jain S, et al. *N Engl J Med*. 2015;373:415-27.

32. Storms AD, et al. *BMC Pulm Med*. 2017;17:208.

33. Fine MJ, et al. *Jama*. 1996;275:134-41.