**RESEARCH PROPOSAL SUBMISSION FORM**

 **STUDY SYNOPSIS (Maximum 1500 words)**

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| **TITLE** | **Antivirals and steroids for hospitalised patients with influenza – an extension of the Australasian COVID-19 Trial (ASCOT)** |
| **PRINCIPAL INVESTIGATOR, AFFILIATIONS AND CONTACT DETAILS** | Professor Steven TongUniversity of MelbourneSteven.tong@unimelb.edu.au |
| **ASSOCIATE INVESTIGATORS AND AFFILIATIONS** | Steven Tong, Ar Kar Aung, Asha Bowen, Joshua Davis, Justin Denholm, Steve Webb, Allen Cheng, Susan Morpeth, Thomas Hills, Srin Murthy, Anna McGlothlin, James Totterdell |
| **I AM SEEKING FOR MY STUDY TO BE CONSIDERED AS A (PLEASE CHOOSE ONE):** | **IMSANZ-RN PARTNERED STUDY** |
| **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?** | **NO** |
| **BACKGROUND** | The Australasian COVID-19 Trial (ASCOT) intends to join a global collaborative platform trial in testing treatments for hospitalised patients with influenza. We present this trial on behalf of the Australasian Society for Infectious Diseases Clinical Research Network, and in collaboration with the Australian and New Zealand REMAP-CAP (Randomised Embedded Multicentre Adaptive Platform for Community Acquired Pneumonia) consortium.Originally designed as a COVID-19 trial platform, ASCOT is joining with REMAP-CAP and broadening to include acute respiratory infections beyond COVID-19. ASCOT focuses on non-critically ill patients. REMAP-CAP focuses on the critically ill (although has had limited enrolment of non-critically ill). Current guidelines vary in their recommendations for the use of antivirals for patients hospitalised with influenza due to the lack clear evidence in this population. Similarly, the role of corticosteroids in patients with influenza pneumonia has been a longstanding controversy. |
| **RESEARCH QUESTION/HYPOTHESIS** | In this project, we will randomise patients hospitalised with influenza to different antiviral strategies (different durations and combinations of oseltamivir and baloxavir) and the use of steroids (or no steroids).The antiviral domain interventions comprise:* No antiviral
* Oseltamivir for 5 days
* Oseltamivir for 10 days
* Baloxavir on days 1 and 4
* Combination of Oseltamivir for 5 days and Baloxavir on days 1 and 4
* Combination of Oseltamivir for 10 days and Baloxavir on days 1 and 4

The corticosteroid domain interventions comprise:* No corticosteroids
* Dexamethasone 6mg (0.15mg/kg for children) oral or intravenous for 10 days while in hospital
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| **PRIMARY OUTCOME/PROCESS MEASURE** |  28-day organ support-free days, incorporating mortality |
| **SECONDARY OUTCOME/PROCESS MEASURES** | * Symptom severity – vital signs, degree of respiratory distress
* WHO ordinal scale
* Incidence of ICU admission
* Incidence of invasive mechanical ventilation
* Duration of all organ support, including invasive mechanical ventilation and non-invasive respiratory support
* Duration of ICU and hospital stay
* 90-and 180-day mortality
* Longer term follow-up at 6 months including survival, Health Related Quality of Life (HRQoL) using EQ-5D-5L and disability using WHODAS 2.0 score.
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| **STUDY DESIGN****(IF THE STUDY IS A CLINICAL TRIAL, PLEASE INCLUDE INFORMATION ON SAMPLE SIZE CALCULATION, RANDOMISATION, AND BLINDING)**  | The primary analysis will be generated using a Bayesian Hierarchical cumulative logistic model, which will calculate posterior probability distributions of the primary outcome (organ support-free days, including mortality) based on data accumulated in the trial. Prior distributions for individual treatment effects will be neutral. The primary model adjusts for location (site, nested within country), age, sex, disease severity (moderate and severe) and time-period to account for changes in clinical care and potential changes in virus patterns over time. It includes pre-specified treatment-by-treatment interactions across domains.At each adaptive analysis if a statistical trigger is reached then effectiveness (compared to control) and superiority (compared to other interventions) are concluded if there is a greater than 99% probability that the odds ratio for an improvement in the primary outcome is greater than 1.0. Futility (compared to control) is concluded if there is a greater than 95% probability that the odds ratio for an improvement in the primary outcome is less than 1.2. Equivalence (between two active interventions) is concluded if there is a greater than 90% probability that the odds ratio is between 1.2 and 0.83 (1 divided by 1.2). These thresholds have been accepted by major medical journals, the WHO, RAPID C-19 and other worldwide groups for developing clinical practice guidelines during the COVID-19 pandemic.Extensive pre-trial modelling using Monte Carlo simulation ensures adequate control of Type I error with these multiple adaptive analyses. For the six-arm antiviral domain, with simulations incorporating nesting the 5- and 10-day oseltamivir arms, we will have 80% power to detect superiority with 4000 patients at an odds ratio of 1.4 and with 1300 patients at an odds ratio of 1.7. For the steroid domain we will have 90% power at 1800 patients to detect superiority at an odds ratio of 1.7. Through all of these, type I error is kept below 10%. The treatment effect for each intervention is directly estimated, so there are no issues with respect to multiplicity of testing. These simulations incorporate the pre-planned interactions across domains.Interventions will be open label. This is a pragmatic trial, with clinically objective endpoints. The requirement to blind allocation status would substantially increase complexity and cost. The investigators believe that in a trade-off between sample size and blinding that the goal of generating evidence to inform patient care is best achieved by conduct as an open-label study.Participants can be concurrently eligible for both domains depending on domain specific exclusion criteria. Randomisation allocations will be revealed immediately on platform entry for the antiviral domain; and for the steroid domain if and when the participant requires supplemental O2.Randomisation occurs through a web-based data capture system (Spiral, NZ), which establishes eligibility and intervention-specific exclusions. Data collection will meet CONSORT guidelines. |
| **INCLUSION and EXCLUSION CRITERIA** | Core Inclusion criteria: 1) Admitted to hospital; 2) Confirmed influenza by PCR.Core Exclusion criteria: 1) Currently receiving non-invasive or invasive mechanical ventilation or inotropic support; 2) >14 days since admission with symptoms of influenza; 3) Patient expected to be discharged from hospital today or tomorrow; 4) Previous participation in trial; 5) Treating team deems enrolment is not in patient’s best interests; 6) Death deemed imminent & inevitable AND treating team not committed to active treatment.Antiviral domain. *Exclusion criteria*: 1) Already received ≥2 doses of oseltamivir or ≥1 dose of baloxavir for this illness. 2) <12 years of age for baloxavir (safety data currently under review).Corticosteroid domain. *Inclusion criteria*: Receiving supplemental O2. *Exclusion criteria*: Receiving or planned to receive corticosteroids for alternate indication. |
| **EXPECTED NUMBER OF PARTICIPANTS** | 4000 globally; of which ASCOT will aim to recruit 400 in Australia / NZ |
| **STUDY DURATION** | 3 years, with final year for follow-up / study close out |
| **ANALYSIS** | See above section Study Design. |
| **IMPORTANCE TO GENERAL MEDICINE**  | Globally, influenza is estimated to cause 3 to 5 million cases of severe illness, and up to 650,000 deaths. In Australia, influenza is estimated to cause over 13,500 hospitalisations and over 3,000 deaths each year, with most severe cases occurring in people aged 50 years and older. There is a considerable burden on hospital capacity during the influenza season. In 2019 in Australia, the peak rate of admissions with influenza was 4.5 per 100 beds/week. With a mean hospital stay of 4.9 days, during such peaks, an estimated 3.2% of hospital beds were occupied by patents with influenza1. The majority of these beds will be under general medicine. |
| **FUNDING** | This is to support a grant application to MRFF. |
| **CURRENT PROGRESS** | Design and protocol development [Completed]Ethics application []Study in progress []Manuscript write-up in progress or under review []Accepted or published []Aborted |
| **IMSANZ-RN OFFICE USE ONLY** | **APPROVED****APPROVAL CATEGORY: PARTNERED STUDY** |