**RESEARCH PROPOSAL SUBMISSION FORM**

 **STUDY SYNOPSIS (Maximum 1500 words)**

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| **TITLE** | **A Multicentre Concealed-Allocation Parallel-Group Blinded Randomised Controlled Trial to ascertain the effect of intravenous followed by oral Vitamin C compared to Placebo on mortality at 30 days in hospitalised Community Acquired Pneumonia Patients** |
| **PRINCIPAL INVESTIGATOR, AFFILIATIONS AND CONTACT DETAILS** | A/Prof Yogesh SharmaDepartment of General MedicineDivision of Medicine, Cardiac & Critical CareFlinders Medical Centre, SA, 5042Tel 0431811421Email Yogesh.Sharma@sa.gov.auProf Campbell ThompsonDiscipline of MedicineUniversity of Adelaide, SA, 5000Email Campbell.Thompson@adelaide.edu.au |
| **ASSOCIATE INVESTIGATORS AND AFFILIATIONS** | Prof Richard WoodmanCollege of Medicine & Public HealthFlinders University, SA, 5042 |
| **I AM SEEKING FOR MY STUDY TO BE CONSIDERED AS A (PLEASE CHOOSE ONE):** | **IMSANZ-RN ENDORSED STUDY****IMSANZ-RN SUPPORTED STUDY****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?** | **YES** |
| **BACKGROUND** | Community Acquired Pneumonia (CAP) is an acute respiratory tract infection involving lung parenchyma and is a leading cause of morbidity and mortality, worldwide. CAP resulted in 2.6 million deaths in 2019 and was overall the fourth leading cause of death, globally1 In Australia, influenza and pneumonia were found to be associated with an 33.5% (42.6 per 100,000 people) increased risk of mortality in 2022 compared to previous years 2. This increase was driven by more deaths due to corona virus disease (COVID-19), which was the underlying cause for over a quarter (27%) of these deaths 2.In developed countries, 20-30% of patients with CAP require hospitalisation. Inhospital mortality from CAP ranges from 4-6%, while mortality in patients who require intensive care unit (ICU) admission can be as high as 12-36%. 3 4. Despite advancements in clinical care, recent years have not witnessed any major reduction in mortality associated with CAP. Therefore, further development of efficacious adjunctive therapies targeting a reduction in mortality and complications have important implications in the treatment of pneumonia. Inflammation and oxidative stress are the key mechanisms which leads to complications of pneumonia including development of respiratory failure, sepsis-induced organ injury and death 5. Vitamin C or Ascorbic acid is a key circulating antioxidant, however, cannot be synthesised in humans because of lack of an enzyme called gulonolactone synthase 6. Vitamin C levels decline rapidly during acute illness due to increased metabolic needs for antioxidative and anti-inflammatory processes 7. The decline in vitamin C levels may also be because of poor intake in these patients and inadequate supplementation in medical nutrition therapy 8. A systematic review9 which included 5 randomised controlled trials (RCTs) evaluating the benefits of vitamin C supplementation among patients with pneumonia have yielded varied results. This review found that the certainty of evidence was limited because the included studies had small sample sizes, flawed research designs, and administered relatively smaller doses of vitamin C for a short duration of time. A recent RCT10, which included only 75 patients found no mortality benefits but a trend towards reduction in time to clinical stabilisation in CAP patients with the use of vitamin C. However, this study was not sufficiently powered to determine the benefits of vitamin C supplementation in CAP. In the context of previous smaller studies9 10 and use of vitamin C in relatively smaller doses, the current trial will constitute a rigorous assessment of vitamin C supplementation on patient related outcomes in hospitalised patients with CAP. Moreover, we propose to conduct this trial at multiple centres in Australia and aim for an international collaboration to generate robust evidence, which could be widely generalisable. We aim to measure the effects of vitamin C on 30-day mortality, which has been identified as one of the most important clinical endpoints in CAP research in addition to determination of the health-related quality of life (HQoL)11.  |
| **RESEARCH QUESTION/HYPOTHESIS** | To determine whether intravenous followed by oral vitamin C supplementation when compared to placebo reduces mortality and morbidity in CAP, and compare biochemical measures of inflammation, and HQoL at 6 months. |
| **PRIMARY OUTCOME/PROCESS MEASURE** | To compare the effect of high dose intravenous followed by oral vitamin C compared to placebo on mortality assessed at 30 days from the day of hospital admission in CAP |
| **SECONDARY OUTCOME/PROCESS MEASURES** | To compare the effect of high dose intravenous followed by oral vitamin C compared to placebo in CAP on:1. Time to clinical stability
2. Improvement in CAP-related symptoms at 30 days from day of admission measured with the 18-item CAP symptom questionnaire12
3. Risk of admission to ICU
4. Requirement for invasive and non-invasive mechanical ventilation
5. Requirement for vasopressor support
6. 6 months mortality
7. 30-days readmission rate
8. Hospital length of stay
9. 6 months HQoL
10. Biomarkers of inflammation, infection and endothelial dysfunction measured on day 1 and 7
11. Assess baseline vitamin C levels
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| **STUDY DESIGN****(IF THE STUDY IS A CLINICAL TRIAL, PLEASE INCLUDE INFORMATION ON SAMPLE SIZE CALCULATION, RANDOMISATION, AND BLINDING)**  | This trial will be a multi-centre concealed allocation parallel group RCT. Patients will be randomly assigned to vitamin C supplementation (2.5g intravenous, 8 hourly) till the treating clinical team decides to change intravenous antibiotics to oral treatment. At that point, patient will be switched to oral vitamin C replacement (1g three times daily) which will be continued for a period of 7-days. The control group will receive a matching placebo. **Rationale for vitamin C regimen**In the absence of specific guidelines for parenteral vitamin C replacement, we have adopted our intervention from a clinical trial by Chambers et al13. The authors of the above-mentioned clinical trial have used this regimen safely in hospitalised patients with CAP. The preliminary signal of clinical benefits found in the above-mentioned trial forms a compelling argument to use the same dosing strategy. **Sample size** Previous studies suggest that 30-day mortality in CAP patients who require hospitalisation range from 6-13% 14. Assuming a 10% mortality in control arm and risk ratio of 0.5 at 80% power, the calculated sample size will be 879. Assuming that 5% patients will be lost to follow-up, a total sample size of 930 will be sufficient for this study.**Randomisation** Using web randomisation service (randomise.net) which is available 24/7, trial participants will be randomised in 1:1 ratio to vitamin C or matching placebo group. We will use permuted blocks of variable sizes and stratify randomisation by clinical site.**Blinding**The treating clinicians, research team members, nursing and allied health staff, participants, members of the Executive and Steering Committee and the statistician will be blinded to the treatment allocation. |
| **INCLUSION CRITERIA** | * + 1. **Inclusion criteria**
1. Patients ≥18 years of age
2. Admitted to hospital with CAP (clinical symptoms of cough, sputum production, dyspnoea, and fever along with imaging evidence of an infiltrate)
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| **EXCLUSION CRITERIA** | 1. Admitted >48 hours prior to screening
2. Unable to give informed consent
3. CURB6515 pneumonia severity score <2
4. Pneumonia was not the principal reason for admission
5. Bronchiectasis or suspected tuberculosis
6. Hospital admission in previous 2 weeks
7. Severe immunosuppression (e.g., neutropenia <350 cells/microL, haematological malignancy, HIV positive with CD4+ count <350 cells/microL, currently receiving cancer chemotherapy, receiving prednisolone >20mg/day or anti-rejection medications)
8. History of nephrolithiasis
9. Renal impairment (eGFR <30 ml/min)
10. G6PD deficiency
11. Haemochromatosis
12. Pregnancy or breast feeding
13. Previously enrolled in a clinical trial where co-enrolment is not allowed
14. Expected death or withdrawal of life-sustaining measures within 48 hours
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| **EXPECTED NUMBER OF PARTICIPANTS** | 930 |
| **STUDY DURATION** | 3 years |
| **ANALYSIS** | We will compare the proportion of patients meeting the endpoint of death at 30 days of hospital admission between groups using a logistic regression model with random centre effect to account for the stratification variable. Continuous variables such as (biomarkers of inflammation etc.) will be analysed by use of the analysis of covariance and adjusted for baseline biomarker levels to evaluate the change in biomarker concentration from day 1 to day 7. To study the impact of vitamin C supplementation on biomarker concentration, we will used linear mixed models adjusted for baseline biomarker concentration and day of study drug therapy.**Trial Monitoring**The outcomes and adverse events will be adjudicated by a Data Safety Monitoring Committee which will comprise of 3 members who will be completely independent of study investigators. This Committee will advise the Executive and Steering Committees on any concerns relating to participant safety and conduct of the trial and will make recommendations for continuation for study, for study termination, for continuation of study after amendments or temporary suspension pending clearance of uncertainty.  |
| **IMPORTANCE TO GENERAL MEDICINE**  | CAP is a major public health problem and is one of the most common admitting diagnoses managed by General Physicians. The annual cost burden of patients who require admission for CAP exceeds >AUD27 million. This pragmatic study aims to involve General Physicians across multiple sites in Australia to test a potentially cheap adjunctive treatment option for CAP.  |
| **FUNDING** | No current funding. We intend to seek NHMRC funding or local institutional grants for this study. |
| **CURRENT PROGRESS** | Design and protocol development [Yes]Ethics application [No]Study in progress [No]Manuscript write-up in progress or under review [No]Accepted or published [No]Aborted N/A |
| **IMSANZ-RN OFFICE USE ONLY** | **APPROVED****APPROVAL CATEGORY: ENDORSED STUDY** |

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