ASpirin as a Treatment for Acute Respiratory Distress Syndrome - a multi-centre, randomised, double-blind, placebo-controlled trial (STAR): study protocol

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Background: Acute respiratory distress syndrome (ARDS) remains a common cause of significant morbidity and mortality in the critically ill, for which there is currently no pharmacological treatment. There is in vivo, in vitro, observational and phase I evidence suggesting aspirin may be of benefit in this condition. The aim of the STAR trial (aSpirin as a Treatment for ARDS) is to test the hypothesis that aspirin 75 mg is both safe and effective in improving important surrogate outcomes in patients with ARDS.

Methods/Design: STAR is a randomised, double-blind, allocation-concealed, placebo-controlled, multi-centred phase II trial. Patients diagnosed with ARDS, as per the Berlin Definition, will be randomised in a 1:1 ratio to receive enteral aspirin 75 mg or placebo for a maximum of 14 days. Randomisation is stratified by vasopressor requirement. The primary endpoint is to evaluate the efficacy of aspirin to improve oxygenation index at day 7. A total of 60 patients will be recruited from intensive care units (ICUs) across Northern Ireland. Plasma, bronchoalveolar lavage (BAL) and urine samples will be obtained to further investigate mechanisms by which aspirin might improve clinical outcomes in these patients.

Trial Registration: NCT02326350

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Background information

Acute respiratory distress syndrome (ARDS) is defined by the Berlin Definition as an acute onset of hypoxia (PaO_2/FiO_2 ratio ≤ 40 kPa), in the presence of a positive end-expiratory pressure (PEEP) ≥ 5 cm H_2O and with bilateral radiological opacities not solely explained by cardiac dysfunction[1].

Despite advances in treatment[2–4], mortality remains relatively high at 35-40%[5, 6] with significant post morbid functional impairment and reduction in quality of life[7, 8]. The high mortality and long-term consequences, coupled with the high financial burden, make the treatment of ARDS a healthcare priority[9]. Multiple drugs have been investigated as potential treatments, most recently simvastatin[10], but as yet there is no effective pharmacological treatment[11].

The rationale for aspirin as a treatment for ARDS

The use of aspirin as a treatment for ARDS is a novel approach. There are various pathways in which aspirin could attenuate the pathophysiology in ARDS. Firstly, through the inhibition of cyclooxygenase enzymes (COX), aspirin can prevent platelet activation[12]. Platelets play a significant role in the development of sepsis and ARDS[13], especially as the

lungs are a major site of platelet maturation and subsequent reservoirs[14]. Once activated, platelets degranulate and release a pro-inflammatory cocktail promoting further platelet degranulation and aggregation, leucocyte recruitment and oedema formation[15]. Furthermore, platelet and neutrophil aggregation is essential for the formation of neutrophil extracellular traps (NETs), which, in excess, can directly damage the lung architecture, thus escalating the inflammatory and thrombotic processes[16, 17]. In an ARDS murine model, platelet depletion resulted in reduced neutrophil migration, less oedema formation and improved outcomes[15].

Secondly, aspirin can down-regulate the production of pro-inflammatory cytokines through the inhibition of NFκB[18], with subsequent reduction in leucocyte recruitment[19]. Thirdly, aspirin promotes nitric oxide (NO) production, resulting in decreased leucocyte migration, oedema formation and micro-thrombi, all of which are important features in ARDS[20]. Finally, aspirin promotes resolution via the production of lipoxins (aspirin triggered lipoxin [ATL])[21], a feature absent in ARDS.

Both aspirin and ATL administration reduce pulmonary inflammation and improve outcomes in murine models of ARDS[22, 23]. Observational studies have shown a benefit to prior aspirin use in those admitted to ICU with ARDS or sepsis[13, 24]. In a local single centre retrospective study, aspirin was associated with reduced mortality in ARDS, with an odds ratio 0.42 (95% confidence interval, 0.18 - 0.96)[25]. Aspirin also significantly reduced bronchoalveolar lavage (BAL) neutrophil count, not only in an *ex vivo* lung perfusion (EVLP) lipopolysaccharide (LPS)-induced inflammation model of ARDS, but also in a healthy volunteer model of ARDS-induced by inhaled LPS[26]. These animal models, observational studies, and human models support the hypothesis that aspirin may have a role in the treatment of ARDS.

Aspirin has recently been investigated as a preventive agent for ARDS in high-risk patients presenting to the emergency department. However, it did not significantly reduce the incidence of ARDS at day 7[27]. On closer review, the study was underpowered, thus limiting the impact of this result.

The aim of the STAR trial is to test the hypothesis that aspirin 75 mg, when administered enterally, is both safe and effective in improving important surrogate outcomes in patients diagnosed with ARDS.

Methods/ Design

STAR is a randomised, double-blind, allocation-concealed, multi-centre, placebo-controlled phase II trial to determine if aspirin is safe and whether it improves important surrogate clinical outcomes in adult patients with ARDS.

The trial is sponsored by the Belfast Health and Social Care Trust (BHSCT). The protocol was reviewed and approved by the Office for Research Ethics Committees Northern Ireland (ORECNI) (14/NI/1093) and by the Medicines and Health Care Products Regulatory Authority (MHRA). STAR is registered with ISRCTN (NCT02326350) and with the European Union Drug Regulation Authorities Clinical Trials Database (2014-002564-32).

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (https://ichgcp.net). STAR is coordinated through the Northern Ireland Clinical Trials Unit (NICTU) and has been adopted on to the Clinical Research

Portfolio supported by the Northern Ireland Clinical Research Network (NICRN) for Critical Care.

In PICO terms:
Population: adult patients with ARDS
Intervention: aspirin 75 mg
Comparator: placebo
Outcome: safety and physiological indices of efficacy

Outcome Measures

As this is a phase II clinical study, several surrogate outcomes will be evaluated.

The primary endpoint is oxygenation index (OI) at day 7.

OI is a physiological index of the severity of ARDS, which measures both impaired oxygenation and the amount of mechanical ventilation delivered, and independently predicts mortality in patients with ARDS[28]. Day 7 was chosen as this time interval will minimise the competing effects of death and extubation, while allowing a sufficient time interval for a biological effect to occur. OI is calculated as (mean airway pressure (cm H_2O) x FiO_2 x 100) ÷ PaO_2 (kPa).

The secondary outcomes are:

1. OI at days 4 and 14

2. Physiological indices of ARDS, as measured by respiratory compliance (Crs) and P/F ratio on days 4, 7 and 14

3. Change in sequential organ failure assessment (SOFA) score from baseline to day 4, 7 and 14

4. Safety and tolerability, as assessed by the occurrence of suspected unexpected serious adverse reactions (SUSARs)

Duration of ventilation, ventilation-free-days at day 28, mortality at both day 28 and 90, as well as length of ICU stay will also be recorded. These important clinical outcomes are not included as outcome measures as the study is not adequately powered to assess them.

Safety

The frequency with which the following events occur will be reported to the Data, Monitoring and Ethical Committee (DMEC):

1. Fall in haemoglobin below 70 g/l

2. incidence of acute kidney injury

3. all adverse events (AEs), including serious adverse events (SAEs) and occurrences of suspected unexpected serious adverse events (SUSARs)

Safety monitoring blood tests including full blood count (FBC), urea and electrolytes (U&E), coagulation profile, liver function tests (LFTs) and clinical assessment is undertaken on a daily basis for 14 days. All AEs are reported up to 28 days from completing the study drug.

Biological mechanisms

An exploratory study will provide insight into the mechanism by which aspirin may be an effective treatment in ARDS. Blood, BAL and urine will be taken on days 0 and 4, with further blood and urine samples taken on days 7 and 14 while patients continue to receive the study drug. Samples will be analysed for biological markers of pulmonary and systemic
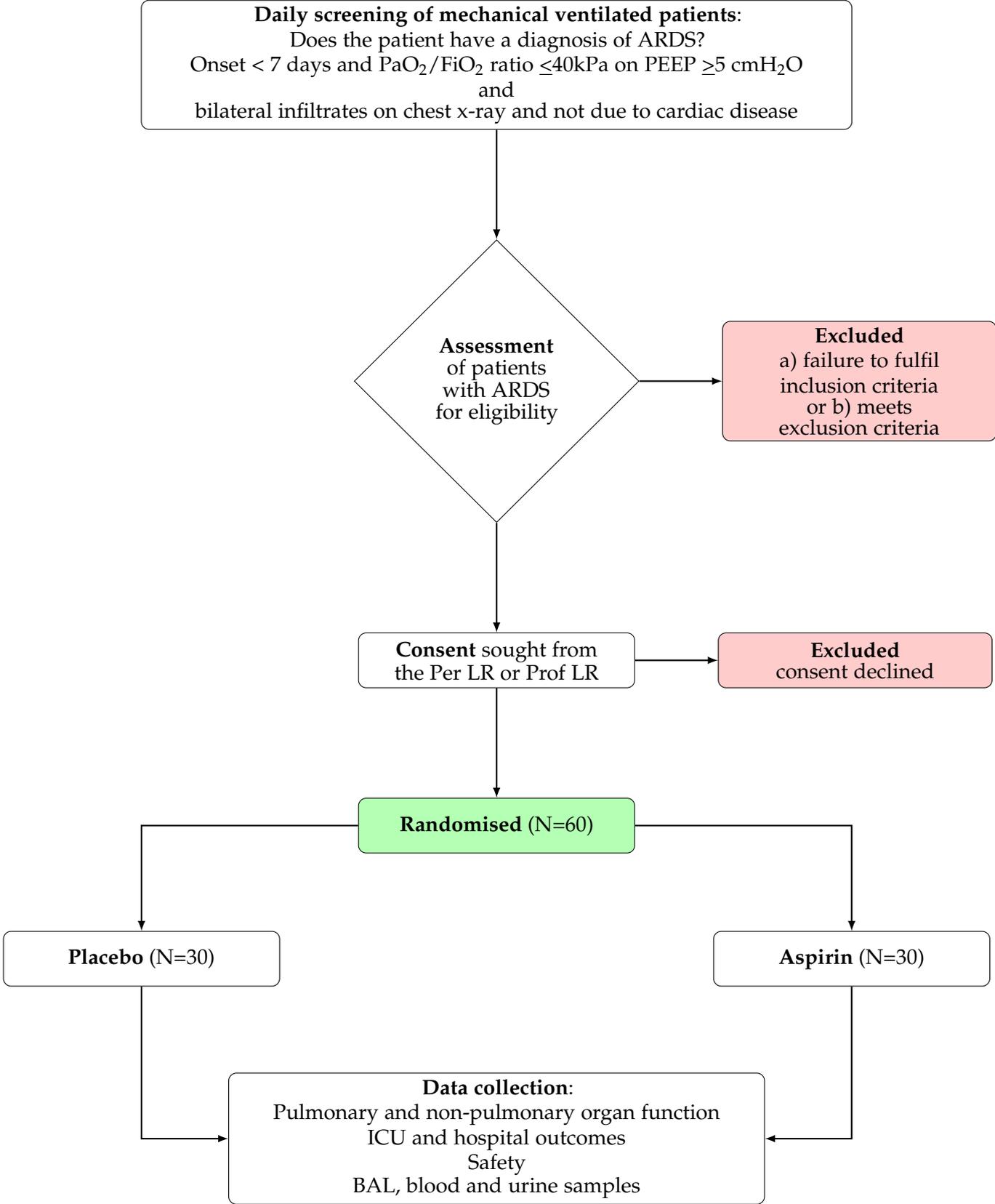
Figure 1. Trial Schematic

inflammation, as well as pulmonary and systemic epithelial and endothelial function. Furthermore, we will measure several lipid inflammatory mediators in addition to assessing the pharmacokinetics and pharmacodynamics of aspirin in the critically ill.

It may not be possible to collect all samples from all patients at all time points. If samples are not collected, this will not be recorded as a protocol violation.

Eligibility criteria

Inclusion

Patients are screened on a daily basis to determine if they fulfil the following inclusion criteria:

1. receiving invasive mechanical ventilation

2. ARDS as defined by the Berlin Definition[1]

   a) onset within 1 week of an identified insult
   b) within the same 24 hour time period
      (i) hypoxic respiratory failure (PaO$_2$/FiO$_2$ ratio $\leq$ 40 kPa on PEEP $\geq$ 5 cmH$_2$0)
      (ii) bilateral infiltrates on chest x-ray consistent with pulmonary oedema not explained by another pulmonary pathology
      (iii) no evidence of heart failure or volume overload

Exclusion

Patients fulfilling any of the criteria below will be excluded from the trial:

1. greater than 72 hours from the onset of ARDS

2. age < 16 years

3. patient is known to be pregnant

4. participation in a clinical trial of an investigational medicinal product within 30 days

5. current treatment with aspirin or within the past 4 weeks

6. platelet count < 50 x 10^9/l

7. haemophilia or other haemorrhagic disorder or concurrent therapeutic anticoagulant therapy

8. history of aspirin-sensitive asthma or nasal polyps associated with asthma

9. active, or history of, recurrent peptic ulcer and/or gastric or intestinal haemorrhage, or other kinds of bleeding, such as cerebrovascular haemorrhage

10. traumatic brain injury

11. active gout

12. currently receiving methotrexate

13. severe chronic liver disease with Child-Pugh score > 12

14. known hypersensitivity or previous adverse reaction to salicylic acid compounds or prostaglandin synthetase inhibitors

15. physician decision that aspirin is required for proven indication

16. contraindication to enteral drug administration, e.g. patients with mechanical bowel obstruction

17. treatment withdrawal imminent within 24 hours

18. consent declined.

Power and sample size

The primary outcome measure will be the difference in OI between the aspirin and placebo treated groups at day 7. Based on data from a recently completed clinical trial in ARDS, the mean (standard deviation; SD) OI at day 7 in patients with ARDS is 62 (51) cmH$_2$O/kPa[29]. A sample size of 56 subjects (28 in each group) will have 80% power, at a two-tailed significance level of 0.05, to detect a clinically significant difference of 39 cmH$_2$O/kPa in OI between groups. In a previous phase II study of similar size, we found that an intervention can demonstrate a change in OI of a similar magnitude confirming a treatment effect of this size can be achieved[29]. Although we anticipate few withdrawals or losses to follow-up, we have allowed for this in the sample size calculation. In our previous single centre study of simvastatin in ARDS, there were no withdrawals. In a multi-centre UK study of pulmonary artery catheters in ICU patients (PAC-Man), no patients were lost to follow up, and only 3% withdrew consent after recovering competency[30]. Therefore, a drop-out rate of 5% has been estimated and the study will require a total of 60 patients (30 in each group).

Trial Conduct

Consent

Informed consent will be obtained before conducting any trial specific procedures. Due to the incapacitating nature of the condition, the patients typically lack the capacity to give consent. In this situation, informed consent will be sought from a Personal Legal Representative (Per LR) or Professional Legal Representative (Pro LR), in keeping with requirements from the EU clinical trails directive. Once they regain capacity, patients will be informed of their participation in the trial, have the trial explained to them, and consent to continue in the trial will be sought. Where consent to continue is not obtained, consent from the legal representative will remain valid. Similar consent mechanisms have been used successfully in other critical care trials[10, 29, 30].

Randomisation and study drug design

Victoria Pharmaceuticals will prepare the drug packs. Aspirin 75 mg and the placebo will have an identical appearance. All trial drugs will be packaged identically and identified by a unique pack number.

After informed consent, the researcher will contact the clinical trials pharmacist who will allocate the next sequential number as per the randomisation schedule, maintaining blinding. Randomisation will be stratified by vasopressor use and subjects will be randomised in a 1:1 ratio using blocks of variable size. The researcher will then register the recruited patient with the CTU.

Study drug administration

Subjects will be randomised to receive aspirin 75 mg capsule or a placebo capsule enterally for up to 14 days. The first dose of the study drug will ideally be administered within 4 hours of randomisation and subsequent doses will be as close to 10 am as possible starting on the following calendar day. The clinical staff administering the drug will not be involved in any of the study specific assessments.

Post randomisation withdrawals and exclusions

Patients may withdraw, or be withdrawn by their representative, from the trial at any time without prejudice. Consent will be requested to use the data collected to that point. If a

Table 1. Trial Procedures

	Study day									
	0	1	2-3	4	5-6	7	8-13	14	15-42	90
Eligibility assessment	X									
Informed consent	X									
Randomization	X									
Baseline data	X									
Daily data		X	X	X	X	X	X	X		
Study drug administration		X	X	X	X	X	X	X		
Adverse events		X	X	X	X	X	X	X	X	
BAL sampling	X			X						
Blood sampling	X			X		X		X		
Urine sampling	X			X		X		X		
Clinical outcome									X	X

patient, or their representative, requests termination of the trial drug during the treatment period, the drug will be stopped but the patient will continue to be followed-up as part of the trial, unless they also explicitly request withdrawal from follow-up.

Study drug termination criteria

The study drug will be continued until one of the following is met:

1. 14 days after randomisation (maximum treatment period)

2. study drug related adverse event

3. critical care discharge

4. death or discontinuation of active treatment

5. request from Per LR or Pro LR to withdraw the patient from the study

6. decision by the attending clinician on safety grounds

7. clinical indication for treatment with aspirin e.g. myocardial infarction.

Study drug compliance

Any omission of the study drug will be recorded in the case report form (CRF) to monitor compliance.

Clinical management of patients in the trial

All patients will receive standard management with regards to nutrition, antibiotic policy, fluid management and weaning. It is recommended patients will be managed using a standardised mechanical ventilation protocol aiming for tidal volumes of 6 ml/kg predicted body weight[2]. Rescue therapies, such as extra-corporeal membrane oxygenation, can be used according to local policy.

Study procedures for unblinding

As STAR is a randomised, placebo-controlled, double-blind trial, the research staff, treating clinical staff, and patients, will be blinded as to which arm of the study the patient is allocated. All trial drugs have identical appearance and are only identified by a unique pack number. The investigator or treating physician may unblind a participant's treatment assignment in the case of an emergency, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. Emergency unblinding will be performed by telephone contact with the pharmacy in the BHSCT. The date and reason for unblinding will be recorded in the CRF.

Data collection

All data for an individual patient will be collected by the research team and recorded in the CRF. The majority of the data will be obtained from the patient's hospital record. Data will be collected from the time the patient is considered for entry into the trial through to their discharge from hospital and recorded on a secure, backed up custom database. Data censorship will occur after 90 days post randomisation.

Adverse event reporting

As STAR is recruiting in a population that is already in a life-threatening situation, it is expected that many of the patients will experience AEs. Events that are suspected in this population (i.e. events in keeping with the underlying condition) will not be reported as AEs. The adverse effects as listed in the summary of product characteristics (SmPC) for aspirin will be used as the reference safety information. AEs that occur between trial entry and up to 28 days after completion of the study drug will be reported. SAEs and SUSARs will be reported within 24 hours of becoming aware of their occurrence and the sponsor will inform the regulatory authorities as per the regulatory requirements.

End of trial

The trial will end when 60 patients have been recruited and completed 90-day follow-up. The trial will be stopped prematurely if mandated by the Ethics Committee, MHRA, or the sponsor e.g. following recommendations from the DMEC.

Statistical analysis plan

A full statistical analysis plan is available as a supplementary appendix at http://www.criticalcarehorizons.com/2018-star-protocol.

Trial oversight

The Chief Investigator will have overall responsibility for the conduct of the study. The Trial Management Group will have responsibility for the daily running of the trial. An independent DMEC will monitor the safety of the participants through regular review of AEs, deaths and any other data as requested by the DMEC. They will report any issues pertaining to safety to the Chief Investigator. It will be the responsibility of the Chief Investigator to inform the sponsor who will take appropriate action to halt the trial if concerns exist about patient safety

Trial status

The trial has been successfully initiated and as of August 2018 46 patients have been successfully enrolled. There has been one major amendment to the protocol design and eligibility criteria, which has been approved by the MHRA and local ethics committee. That amendment was to extend from a single site to a multi centre trial to ensure adequate recruitment and to adjust the absolute platelet exclusion count from 100×10^9/l to 50×10^9/l.

Author's contributions

DFM and CO'K conceived the study. All authors made a substantial contribution to the protocol development. All authors have read and approved the manuscript.

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