STAR

ASpirin as a Treatment for ARDS (STAR): A Phase 2 Randomised Control Trial

Protocol number: 14043DMcA-AS
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STATISTICAL ANALYSIS PLAN

Version 1.0

Northern Ireland Clinical Trials Unit
First Floor Elliot Dynes Building
The Royal Hospitals
Belfast
BT12 6BA
Tel: +44 (0)28 9063 5794
Fax: +44 (0)28 9063 3328
Email: info@nictu.hscni.net

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Contacts
Evie Gardner – Head of Statistics
Rejina Verghis – Study Statistician
Susan McMullan – Data Manager

This document and all preceding versions will be stored in the Trial Master File for this trial

TABLE OF CONTENT

1. BACKGROUND AND DESIGN

The trial hypothesis under investigation is that treatment with aspirin is safe and improves important surrogate clinical outcomes in adult patients with ARDS.

The objective of the trial is

1. To conduct a prospective randomised, double-blind, allocation concealed, placebo-controlled phase 2 trial of aspirin as a treatment for ARDS.
2. To study the biological effects of aspirin on pulmonary and systemic
    a. inflammatory responses,
    b. epithelial and endothelial function and injury and
    c. lipid inflammatory mediators

Subjects will be randomised to receive aspirin 75mg capsule or a placebo capsule enterally for up to 14 days. Subjects will be randomised in a 1:1 ratio using blocks of variable size. 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.

Patients will be eligible to participate in the study if they fulfil the following criteria:

Inclusion criteria:

1. Patients receiving invasive mechanical ventilation.
2. ARDS as defined by the Berlin definition.
    a. Onset within 1 week of identified insult.
    b. Within the same 24 hour time period
        i. Hypoxic respiratory failure (PaO_2/FiO_2 ratio $\leq$ 40kPa on PEEP $\geq$ 5 cmH_2O)
        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

The time of onset of ARDS is when the last ARDS criterion is met.

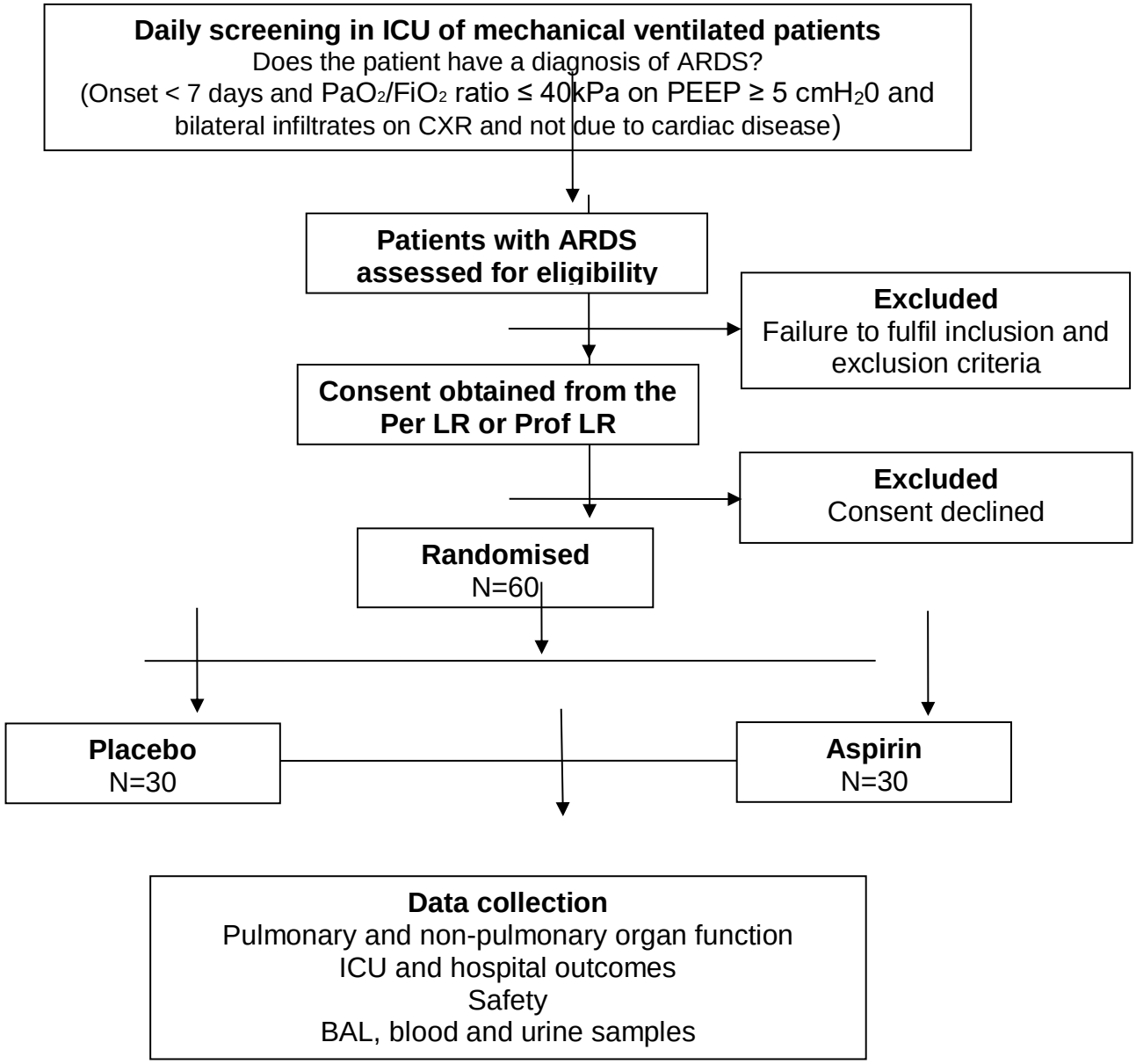
Exclusion criteria:

1. More 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/ 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.

The trial is summarised in Figure 1.

Figure 1. Trial schematic diagram



Full details of the background to the trial and its design are presented in the protocol.

2. OUTCOME MEASURES

As this is a phase 2 clinical study, several outcomes will be evaluated to determine whether treatment with aspirin shows efficacy for important surrogate clinical outcomes.

2.1 Primary outcome measure

The primary outcome measures OI at day 7. OI is a physiological index of the severity of ARDS and measures both impaired oxygenation and the amount of mechanical ventilation delivered. We and others have shown OI is independently predictive of mortality in patients with ARDS. We have chosen day 7 as we expect this time interval will minimise the competing effects of death and extubation, while allowing a sufficient time interval for a biological effect to occur.

2.2 Secondary outcome measures

The following secondary clinical outcomes will also be assessed:

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. Organ failure as measured by change in sequential organ failure assessment (SOFA) score from baseline to days 4, 7 and 14
4. Safety and tolerability as assessed by the occurrence of adverse events/reactions (AE/AR), serious adverse events/reactions (SAE/SAR) and suspected unexpected serious adverse reactions (SUSAR).

Outcomes will be measured at baseline and daily up to day 14 or until the patient is discharged from ICU or the patient dies. Although duration of ventilation, ventilation free days at day 28 and 28 and 90-day mortality as well as length of ICU stay will be recorded, these important clinical outcomes are not included as major outcome measures as the study is not adequately powered to assess these outcomes.

2.3 Exploratory analyses

In order to determine the potential mechanism of action of aspirin, the study will investigate the biological effect of aspirin on pulmonary and systemic:

1. Inflammatory responses
2. Indices of epithelial and endothelial function and injury
3. Lipid inflammatory mediators

2.4 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
- Mandated by the MHRA
- Mandated by the sponsor e.g. following recommendations from the DMEC

3. DATA

3.1 CRF Forms and variables

Full details of data collection and timing are described in the trial protocol (version 3, 20/07/2015). A copy of the CRF is presented in the Trial Master File.

3.2 Management of datasets

Below is the standard policy for management of data in the CTU as given in the CTU SOPs, at the time of analysis (including DMEC reports/Interim analysis (if required)):

The trial database will be stored in MACRO:

DMEC reports: - In collaboration with the Statistician, the Data Manager will create MACRO output files to support the analysis. This will act as the frozen dataset. It is the responsibility of the statistician to accurately record the date of freezing and ensure all data is retrieved. If there are no errors, the study database will be re-opened for further data entry.

If there are errors, the Study Statistician will report these to the Data Manager. The Data Manager in consultation with the Study Statistician, Data Project Manager and Senior Study Statistician will resolve the errors and determine which of the database closure activities are required to be undertaken. The Data Manager will re-create the MACRO output files to support the analysis.

Database closure & lock: The same process for DMEC reporting will be followed for database closure and lock, the only difference being when the MACRO output files are created and there are no errors found for final analysis, the database should be locked as per Section 4.2 SOP DM09.

3.3 Data completion schedule

The following table describes the time points for completion of clinical record forms.

Table. Error! Use the Home tab to apply 0 to the text that you want to appear here..**1. Data Completion Schedule**

CRF	Day									
	0	1	2-3	4	5-6	7	8-13	14	15- 42	90
Eligibility assessment	X									
Informed consent	X									
Randomisation	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

3.4 Data verification

Data verification, consistency and range checks will have been performed at the data entry stage by the CTU, as well as checks for missing data (copies can be found in the Trial Master File). Additional range, consistency and missing data checks will be performed, as appropriate, when the analysis is performed (and when the datasets for analysis are constructed). All variables will be examined for unusual, outlying, unlabelled or inconsistent values.

Given the thorough nature of our follow-up procedure we expect the issue of missing data to be relatively minimal. We anticipate high compliance with initial data collection as this is close to the time of patient registration. If any data is missing imputation will not be done.

Any problems with trial data will be queried with the Trial Managers, Data Managers, or statisticians, as appropriate. If possible, data queries will be resolved, although it is accepted that due to administrative reasons and data availability a small number of problems will continue to exist. This will be minimised.

3.5 Data coding

The variable codings will be as specified on the CRF.

4. DEFINITION OF TERMS

Term	Definition
Vasopressors	Vasopressors are defined as any inotropic/vasopressor agent except dopamine < 6mcg/kg/min.
SAP II	New Simplified Acute Physiology Score
Murray Lung Injury Score	Scoring system using radiology, PF ratio, PEEP and respiratory compliance to assess the extent of adult lung injury.
APACHE II score	Acute Physiology and Chronic Health Evaluation II score. A disease severity classification system.
Predicted Body Weight (Kg)	$PredictedBodyWeight = \begin{cases} 50 + 0.91 * (Height - 152.4) for Male \\ 45.5 + 0.91 * (Height - 152.4) for Female \end{cases}$
Oxygenation Index (cmH_2O/ kPa)	$OI = \frac{(MAP * FiO_2)}{PaO_2} * 100$
Total SOFA Score	Guideline 13: SOFA Score v1.0 Final 04/02/2016
Respiratory Compliance (ml/ cmH_2O)	$RespiratoryCompliance = \frac{TidalVolume}{[PlateauPressure - PEEP]}$
PF ratio (kPa)	$PFratio = \frac{PaO_2}{FiO_2}$
Unassisted breathing	Unassisted breathing is defined as; extubated with supplemental oxygen, or room air, or open T-tube breathing, or tracheostomy mask breathing, or CPAP ≤ 5 cm H2O without pressure support for a calendar day. Patients receiving pressure support via non-invasive ventilation will be defined as

	receiving ventilatory support. The date recorded will be the first calendar day of the final period of ventilation free days
Ventilator free days (VFDs)	The number of days alive and free from ventilation between final successful weaning and day 28 after study enrolment. $$VFD = \begin{cases} (28 - x), if patient alive at day 28 \wedge x \leq 27 \\ 0, if patient died within 28 days \vee x > 27 \end{cases}$$ Where x is number of days until patient achieved unassisted breathing
Duration of ventilation (days)	$$Duration of ventilation = \begin{cases} Date of unassisted breathing - Date of randomisation, if the patient achieved unassisted breathing \\ Date of death - Date of randomisation, if the patient died prior \end{cases}$$ This calculation will be censored at day 90.
Duration of ICU stay (days)	$$Duration of ICU stay = \begin{cases} Date of first ICU discharge - Date of randomisation, if the patient is alive at ICU discharge \\ Date of death - Date of randomisation, if the patient died prior \end{cases}$$ Discharge from critical care is defined as discharge to a medical ward in the hospital or another hospital, A transfer between ICUs is not considered as a discharge from critical care. This calculation will be censored at day 90.
Duration of hospital stay (days)	$$Duration of hospital stay = \begin{cases} Date of first hospital discharge - Date of randomisation, if the patient is alive at hospital discharge \\ Date of death - Date of randomisation, if the patient died prior \end{cases}$$ Hospital discharge is the first date that the patient is discharged to home/community, a transfer between hospitals is not considered as a hospital discharge. This calculation will be censored at day 90.

5. SAMPLE SIZE CALCULATIONS

The primary outcome measure is the difference in OI at day 7, between aspirin and placebo treated groups. Based on our 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_2O/kPa. 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_2O/kPa in OI between groups. In a previous phase 2 study of similar size, we have found that an intervention can demonstrate a change in OI of a similar magnitude confirming a treatment effect of this size can be achieved.

Although we anticipate few withdrawals or loss 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. This is in keeping with our local data. Therefore, a drop-out rate of 5% has been estimated and the study will require a total of 60 patients (30 in each group). All calculations assume 80% power at a two-tailed significance level of 0.05.

6. ANALYSIS PRINCIPLES

Primary outcome measure is the OI at day 7. Unadjusted (primary analysis) and adjusted analysis will be carried out to test whether there is a statistically significant difference between the aspirin & placebo groups. Secondary analysis will be carried out, if the day 7 OI values are missing, using last value carry forward method.

Secondary outcome measures are OI, CRs, PF ratio, and SOFA score at day 4, 7, 14 and safety. Unadjusted and adjusted analysis will be carried out on OI, CRs, PF ratio, SOFA score, to test whether there is a statistically significant difference between the groups.

Unadjusted analysis will be carried out using Independent sample t-test. Adjusted analysis will be carried out using ANCOVA or mixed modelling technique, based the number of data points available at each time point. Estimates & 95% confidence interval will be reported.

The number of AE, ARs, SAE, SARs, SUSARs and number (%) of patient experiencing the events will be reported. Fisher's exact test and proportion test will be used to check whether incidences of adverse events differ between the groups. Relative risk and 95% CI will be reported.

Exploratory analysis on mediators will be carried out using student t-tests or non-parametric alternative and Fishers Exact Test, presented by day where applicable. The estimates & 95% CIs will be reported. Statistical diagnostic methods will be used to check for violations of the assumptions, and transformations will be performed if required. For binary outcome measures, risk ratios and associated 95% CI will be calculated. Survival analysis technique will be used for time-to-event data. Median survival time & 95% CI will be estimated using Kaplan-Meier estimation method and the Kaplan-Meier plots will be presented. In all time-to-event analyses, patients that did not experience the event in question (e.g. death) were censored on the date last seen or 90 days. The equality of survivorship function of aspirin & placebo group will be tested

for significance using a log-rank $\chi 2$ test. Hazard ratios (HRs) & 95% CIs will be reported if the proportionality assumption holds.

Correlations between changes in the biological markers measured and physiological and clinical outcomes will be assessed by appropriate graphical and statistical methods including Pearson's (or Spearman's) correlation coefficient.

A secondary analysis excluding patients identified to have aspirin resistance will also be undertaken.

Analyses will be conducted according to intention to treat principle. All statistical tests will be 2-sided and a p-value of 0.05 will be considered as statistically significant, unless adjustment for multiple testing was needed. A single analysis is planned at the end of the trial. Every effort will be made to minimise missing baseline and outcome data in this trial. Any ad-hoc analysis will be reported as per the regulatory requirement.

7. ANALYSIS DETAILS

The results of the analyses will be reported following the principle of the ICH E3 guidelines on the Structure and Content of Clinical Study Reports and CONSORT reporting guidelines.

7.1 Recruitment and follow-up patterns

- The number of withdrawals by treatment group

7.2 Baseline Characteristics

The randomisation is stratified by vasopressor requirement. Refer to table A1. Baseline characteristics at trial entry

7.3 Trial treatment

Refer to table A2. Treatment after trial entry

7.4 Main Clinical Endpoints

- Oxygenation Index (OI) at day 7 or the last available OI prior to patient discontinuation from the study, Mean ± SD by treatment arm
- Oxygenation index (OI) at days 4 and 14, Mean ± SD by treatment arm
- Respiratory compliance (CRs) at days 4, 7 and 14, Mean ± SD by treatment arm
- P/F ratio at days 4, 7 and 14, Mean ± SD by treatment arm
- Sequential organ failure assessment (SOFA) score from baseline to day 4, 7, and 14, Mean ± SD by treatment arm

Refer to table A 1. Main Clinical Outcome Variables: PF Ratio, Oxygenation Index, SOFA, Respiratory Compliance at each visit

7.5 Toxicity/ Symptoms

- Adverse Events (AEs), Serious adverse events (SAEs), Suspected unexpected serious adverse reactions (SUSARs), and Death, no. (%) by treatment arm

Refer to table A7. Adverse events/reactions (AE/AR), serious adverse events/reactions (SAE/SAR) & suspected unexpected serious adverse reactions

8. ADDITIONAL INFORMATION

8.1 Trial management group (TMG)

The CI will take responsibility for the need to change the protocol for any reason, reviewing relevant information from other sources and considering recommendations from the DMEC. Day to day management will be undertaken via a trial management group composed of the CI and supporting staff. They will meet on a monthly basis to discuss study issues. The NICTU will be the Trial Co-ordinating Centre. Statistician's report on the accrual rate will be held in the Statistics section of the trial master file.

8.2 Data Monitoring and Ethics Committee (DMEC)

A DMEC will be appointed. The committee will be independent of the study team and will comprise Dr P Glover, an intensive care clinician, Prof. P. McKeown a clinician with experience in undertaking clinical trials with aspirin, as well as Prof. M. Clarke Director of the

All Ireland Hub for Trials Methodology, an experienced clinical trialist. The DMEC will meet to agree conduct and remit. The sponsor has recommended the DMEC meet once patient recruitment reaches 5, 20, 40 & 60. Accumulating information relating to recruitment, data quality will be presented at the open session of the DMEC. Toxicity details based on pooled data and total numbers of events for the primary outcome measure and other outcome measures may be presented to open session, at the discretion of the DMC. In addition to all the material available in the open session, the closed session material will include safety data by treatment group. It may include efficacy data by treatment group, depending on the planned interim analysis. Data reported by treatment group should be blinded where possible, unless the DMC requests otherwise. In the event of an occurrence of an unexpected severe adverse reaction an additional unplanned DMEC meeting will be convened. As this is a phase 2 trial, an interim analysis of efficacy is not planned although this issue can be discussed by the DMEC as required. The DMEC will function primarily as a check for safety, reviewing adverse events. 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. Statisticians (Closed and open) reports will be held in the Statistics section of the trial master file.

9. SIGNATURES OF APPROVAL

Date: 13/June/2017

Version: Draft 0.16

This document has completed a final review and is understood and approved by the following:

Chief investigator	*Chief Investigator signature*	Date dd/mm/yyyy
Head of Statistics	*Head of Statistics signature*	Date dd/mm/yyyy
Trial Statistician	*Trial Statistician Signature*	Date dd/mm/yyyy

APPENDIX 1. EXAMPLE DRAFT SUMMARY TABLES

Table A1. Baseline characteristics at trial entry

Variable		A	B	Total
		N = <n>	N = <n	N = <n
Age (years)		xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
Gender				
	Male	n (xx.x%)	n (xx.x%)	n (xx.x%)
	Female	n (xx.x%)	n (xx.x%)	n (xx.x%)
Height (cm)		xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
Weight (kg)		xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
Vasopressor Requirement				
	No	n (xx.x%)	n (xx.x%)	n (xx.x%)
	Yes	n (xx.x%)	n (xx.x%)	n (xx.x%)
Worst PaO2:FiO2 ratio (kPa) (pre-randomisation)		xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
PaO2:FiO2 ratio (kPa) [+]		xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
Plateau Pressure (cmH_2O) [+]		xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
Lowest Platelets ($x10^9/L$) [+]		xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
Tidal Volume (ml/kg PBW) [+]				
All patients		xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
Controlled ventilation		xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
Tidal Volume (ml/kg PBW) Day 1				
All patients		xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
Controlled ventilation		xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
Aetiology of ARDS*				
	Smoke/toxin inhalation	n (xx.x%)	n (xx.x%)	n (xx.x%)
	Gastric content aspiration	n (xx.x%)	n (xx.x%)	n (xx.x%)
	Near drowning	n (xx.x%)	n (xx.x%)	n (xx.x%)
	Thoracic trauma	n (xx.x%)	n (xx.x%)	n (xx.x%)
	Pneumonia	n (xx.x%)	n (xx.x%)	n (xx.x%)
	Sepsis	n (xx.x%)	n (xx.x%)	n (xx.x%)
	Cardiopulmonary bypass	n (xx.x%)	n (xx.x%)	n (xx.x%)
	Pancreatitis	n (xx.x%)	n (xx.x%)	n (xx.x%)
	Non-thoracic trauma	n (xx.x%)	n (xx.x%)	n (xx.x%)
	Other	n (xx.x%)	n (xx.x%)	n (xx.x%)
Mode of Ventilation[+]				
	Controlled ventilation	n (xx.x%)	n (xx.x%)	n (xx.x%)
	PS	n (xx.x%)	n (xx.x%)	n (xx.x%)
	Other	n (xx.x%)	n (xx.x%)	n (xx.x%)
SAPs score (predicted mortality %)		xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
APACHE II Score		xx.x ± x.x	xx.x ± x.x	xx.x ± x.x

Variable	A	B	Total
	N = <n>	N = <n	N = <n
Murray Lung Injury Score (LIS)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
Total SOFA Score+	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
Oxygenation Index (cmH_20/kPa) +	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
Lowest Mean Arterial Pressure (mmHg) +	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x

Mean ± SD presented for continuous variables and no. (%) for categorical variables.

+ At randomisation

* <##> patient had more than one cause

Table A2. Treatment after Trial Entry

			Aspirin N = <n>	**Placebo N = <n>**
Number of patients who received at least one dose of treatment			**n**	**n**
Duration of study drug (days)			**xx.x ± x.x**	**xx.x ± x.x**
Time from randomisation to start of study drug (hours)			**xx.x (xx.x to xx.x)**	**xx.x (xx.x to xx.x)**
Reasons for termination of study drug				
	14 days after randomisation		n	n
	Study drug related adverse event		n	n
	Discharge from critical care		n	n
	Death		n	n
	Discontinuation of active medical treatment		n	n
	Request for discontinuation of trial drug by patient or legal representative		n	n
	Decision by a physician on safety grounds		n	n
	Clinical indication for treatment with Aspirin		n	n
	Other		n	n
Protocol deviations/ violations				
	Eligibility		n (xx.x%)	n (xx.x%)
	Study Drug Administration			
		Did not receive allocated treatment[a]	n (xx.x%)	n (xx.x%)
		Received treatment of other group[b]	n (xx.x%)	n (xx.x%)
		Study drug omitted in error[c]	n (xx.x%)	n (xx.x%)
		Study drug given in error	n (xx.x%)	n (xx.x%)
	Other		n (xx.x%)	n (xx.x%)

Mean ± SD or Median (p25 to p75) presented for continuous variables and no. or no. (%) for all categorical variables [a]- Numbers based on study drug administration data, [b]- Numbers based on the randomisation listing held by trial Statistician, [c]- Numbers based on Protocol deviation data

Table A3. Main Clinical Outcome Variables: PF Ratio, Oxygenation Index, SOFA, Respiratory Compliance at each visit

	Unadjusted, Mean ± SD			Mean Difference	p-value	Adjusted, Mean ± SE		Mean Difference (95% CI)	p-value
	All patients	Aspirin	Placebo	(95% CI)		Aspirin	Placebo		
Primary outcome; OI at day 7									
Observed values (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx
Imputed values(n=<n>)*	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx
Oxygenation Index									
Baseline (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx				
Day 4 (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx
Day 14 (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx
Respiratory compliance									
Baseline (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx				
Day 4 (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx
Day 7 (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx
Day 14 (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx
PF ratio									
Baseline (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx				
Day 4 (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx
Day 7 (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx
Day 14 (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx
SOFA									
Baseline (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx				
Day 4 (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx
Day 7 (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx
Day 14 (n=<n>)	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx	xx.x ± x.x	xx.x ± x.x	xx.x (xx.x to xx.x)	0.xxx

* Last value carried forward

Table A4. Mixed model Estimates (Clinical outcomes, Haemodynamic & Oxygenation parameters and laboratory variables)

Variable	Estimate (95% CI)	df	P>chi2
Group	x.xx (x.xx to x.xx)	n	0.xxx
Day	x.xx (x.xx to x.xx)	n	0.xxx
Group*Day	x.xx (x.xx to x.xx)	n	0.xxx

Table A5. Oxygenation parameters

		Baseline		Day 4		Day 7		Day 14	
		n	**Mean±SD**	n	**Mean±SD**	n	**Mean±SD**	n	**Mean±SD**
Mean airway pressure (cm H_2O)									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx
Expiratory Tidal volume (ml/kg PBW)									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx
PEEP (cmH20)									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx
Plateau pressure (cm H_2O)									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx
pH									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx
pCO2									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx
Standard Base Excess									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx
Lactate mmol/L									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx

[#] **p values for ANCOVA or mixed model**

Table A6. Fluid Balance

		Baseline		Day 4		Day 7		Day 14	
		n	**Mean±SD**	n	**Mean±SD**	n	**Mean±SD**	n	**Mean±SD**
Total Fluid In (ml)									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
Total Fluid Out (ml)									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x

Fluid Balance									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx

[#] p values for ANCOVA or mixed model

Table A7. Summary statistics for clinical Laboratory Assessments, by Treatment Grouo

		Baseline		**Day 4**		**Day 7**		**Day 14**	
		n	**Mean±SD**	n	**Mean±SD**	n	**Mean±SD**	n	**Mean±SD**
Highest ALT (U/L)									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx
Highest AST (U/L)									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx
Highest ALP (U/L)									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx
Highest CRP mmol/L									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx
PT (s)									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx
APTT (s)									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx
Fibrinogen (g/l)									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#|]				0.xxx		0.xxx		0.xxx
Hb (g/L)									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]				0.xxx		0.xxx		0.xxx
WBC (x10^9/L)									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x

		Baseline		Day 4		Day 7		Day 14	
		n	**Mean±SD**	n	**Mean±SD**	n	**Mean±SD**	n	**Mean±SD**
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]			0.xxx		0.xxx		0.xxx	
Neutrophils(x10^9/L)									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]			0.xxx		0.xxx		0.xxx	
Highest Urea mmol/L									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]			0.xxx		0.xxx		0.xxx	
Lowest eGFR mL/min									
	Aspirin	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	Placebo	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x	n	xx.x ± x.x
	p-value[#]			0.xxx		0.xxx		0.xxx	

[#] p values for ANCOVA or mixed model

Table A 2.. Adverse events/reactions (AE/AR), serious adverse events/reactions (SAE/SAR) & suspected unexpected serious adverse reactions

		Number of Events			Number of Patients				
		Total	**Aspirin**	**Placebo**	**Total N=<n>**	**Aspirin N=<n>**	**Placebo N=<n>**	**RR (95%I)**	**p-values**
AE/AR, SAE/SAR and SUSAR	Total number of adverse events (AEs)	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Total number of adverse reactions (ARs)	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Total number of serious adverse events (SAEs)	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Total number of serious adverse reactions (SARs)	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Total number of events related to study drug and unexpected (SUSAR)	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
AEs	Blood and lymphatic system disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Cardiac disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Gastrointestinal disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Hepatobiliary disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	General disorders and administration site conditions	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Infections and infestations	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Injury, poisoning and procedural complications	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Musculoskeletal and connective tissue disorders/Elevated Creatinine Kinase	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Investigations	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Nervous system disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Renal and urinary disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Respiratory, thoracic and mediastinal disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Skin and subcutaneous tissue disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
SAEs	Blood and lymphatic system disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Cardiac disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Gastrointestinal disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Hepatobiliary disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	General disorders and administration site conditions	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Infections and infestations	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Injury, poisoning and procedural complications	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx

		Number of Events			Number of Patients				
		Total	**Aspirin**	**Placebo**	**Total N=<n>**	**Aspirin N=<n>**	**Placebo N=<n>**	**RR (95%I)**	**p-values**
	Musculoskeletal and connective tissue disorders/Elevated Creatinine Kinase	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Investigations	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Nervous system disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Renal and urinary disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Respiratory, thoracic and mediastinal disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx
	Skin and subcutaneous tissue disorders	n	n	n	n (%)	n (%)	n (%)	x.xx (x.xx to x.xx)	x.xx

Table A 3. Age & Kidney Function

Status		**All patients**	**Treatment Group**		**T-tes p-values**
			Aspirin	**Placebo**	
Number (%) of patients Age>65		n (xx.x%)	n (xx.x%)	n (xx.x%)	0.xxx
Number (%) of patients aged > 65 starting RRT after randomisation		n	n	n	0.xxx
Baseline					
	EGFR *	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	0.xxx
	Creatinine	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	0.xxx
Change from baseline to day 7					
	EGFR *	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	0.xxx
	Creatinine	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	0.xxx

Table A 6. Survival data and length of ventilation and stay data

	Aspirin	Placebo	p value
Ventilator free days (days)	n; xx.x ± x.x	n; xx.x ± x.x	0.xxx
Duration of ventilation (days)			
All patients	n; xx.x ± x.x	n; xx.x ± x.x	0.xxx
ICU survivors	n; xx.x ± x.x	n; xx.x ± x.x	0.xxx
ICU non-survivors	n; xx.x ± x.x	n; xx.x ± x.x	0.xxx
Duration of ICU stay (days)			
All patients	n; xx.x ± x.x	n; xx.x ± x.x	0.xxx
ICU survivors	n; xx.x ± x.x	n; xx.x ± x.x	0.xxx
ICU non-survivors	n; xx.x ± x.x	n; xx.x ± x.x	0.xxx
Duration of hospital stay (days)			
All patients	n; xx.x ± x.x	n; xx.x ± x.x	0.xxx
ICU survivors	n; xx.x ± x.x	n; xx.x ± x.x	0.xxx
ICU non-survivors	n; xx.x ± x.x	n; xx.x ± x.x	0.xxx
All-cause mortality 28 days post randomisation	n (xx.x%)	n (xx.x%)	0.xxx
All-cause mortality 90 days post randomisation	n (xx.x%)	n (xx.x%)	0.xxx

Mean ± SD & n (%) presented for treatment arms