Clinical trial results:
Can Nebulised HepArin Reduce acuTE lung injury in Patients with SARS-CoV-2 Requiring Advanced Respiratory support in Ireland

Summary

EudraCT number	2020-003349-12
Trial protocol	IE
Global end of trial date	28 February 2022

Results information

Result version number	v1
This version publication date	24 January 2025
First version publication date	24 January 2025
Summary attachment (see zip file)	CHARTER-Ireland Summary (CHARTER-Ireland Summary.pdf)

Trial information

Trial identification

Sponsor protocol code	NUIG-2020-003

Additional study identifiers

ISRCTN number	ISRCTN12345678
ClinicalTrials.gov id (NCT number)	NCT12345678
WHO universal trial number (UTN)	U1234-5678-1234
Other trial identifiers	NUIG sponsor number: NUIG-2020-003

Notes:

Sponsors

Sponsor organisation name	National University of Ireland Galway
Sponsor organisation address	University Road, Galway, Ireland, H91 TK33
Public contact	Prof John Laffey, National University of Ireland Galway, 353 91524411, jlaffey@universityofgalway.ie
Scientific contact	Prof John Laffey, National University of Ireland Galway, 353 91524411, jlaffey@universityofgalway.ie

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 July 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2022
Global end of trial reached?	Yes
Global end of trial date	28 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Effect of nebulised heparin on d-dimer profile, assessed via d-dimer AUC and via a mixed effects model, with data collected on days 1, 3, 5 and 10.
Safety of nebulised heparin delivered by Aerogun vibrating-mesh nebuliser in patients with COVID-19 induced severe respiratory failure, as measured by the incidence of severe adverse events.

Protection of trial subjects:

Trial performed to full GCP protocol. Regulatory approval received from the Health Products Regulatory Authority (HPRA) in Ireland. Ethics approval received from Galway Research Ethics Committee. Adverse event reporting requirements detailed in the protocol. Ongoing oversight of trial operations conducted by Afortiori. The DSMB met on 4 occassion, once to review and approve the DSMB charter. The remaining three reviews were study reviews, including a cumulative review of study events. The DSMB reports were prepared by Afortiori

Background therapy:

Full standard medical therapy for severe COVID-19 respiratory Failure

Evidence for comparator:

Clinical studies of nebulised heparin in patients with Acute Respiratory Distress Syndrome (ARDS) have shown it to be a safe intervention and have shown promising results in reduction of progression of lung injury and earlier hospital discharge.(1) The COVID-19 pandemic has resulted in a high volume of patients presenting to critical care with ARDS.(2) The pathophysiology of ARDS seen includes a markedly raised D-dimer level, indicative of a hypercoagulable state. (2) Previous studies have shown microvascular thrombosis as a distinct clinical feature of ARDS, leading to hyaline membrane formation and fibrosis.(3) Furthermore, patients with a raised D-dimer have areas of hypoperfusion on lung CT perfusion scans. These patients have a markedly increased mortality compared to patients with D-dimers less than the median value of enrolled patients in these studies. (2) Heparin can alter the conformation of the SARS-CoV-2 spike protein, .(4) and has anti-inflammatory effects.(5)

References
1. Dixon B et al. Nebulised heparin for patients with or at risk of acute respiratory distress syndrome: a multicentre, randomised, double-blind, placebo-controlled phase 3 trial. The Lancet Respiratory Medicine. 2021;9(4):360-72.
2. Grasselli G, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. The Lancet Respiratory Medicine. 2020.
3. Dixon B, et al. A phase 1 trial of nebulised heparin in acute lung injury. Crit Care. 2008;12(3): R64.
4. Paiardi G, et al. The binding of heparin to spike glycoprotein inhibits SARS-CoV-2 infection by three mechanisms. J Biol Chem. 2022;298(2):101507.
5. Hochart H, et al. Low-molecular weight and unfractionated heparins induce a downregulation of inflammation: decreased levels of proinflammatory cytokines and nuclear factor-kappaB in LPS-stimulated human monocytes. Br J Haematol. 2006;133(1):62-7.

Actual start date of recruitment	01 October 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 39
Worldwide total number of subjects	39
EEA total number of subjects	39

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	39
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited in three intensive care units across Ireland between 06/01/2021 and 28/02/2022. Recruitment was organised and supervised by intensive care research and clinical research facilities within recruiting centres and in line with national and international standards and guidelines, and local standard operating procedures.

Pre-assignment

Screening details:

The research nurses, coordinators and investigators at each site work with clinicians to identify potential candidates for enrolment. All patients with severe COVID-19 in participating Critical care units were screened daily during the study period (October 2020 to February 2022).

Period 1

Period 1 title	Study Enrollment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This is an open-label trial. The standard of care group did not receive a placebo for operational reasons during COVID-19 pandemic. All patients facing study personnel were unblinded however, the statistician performing data analysis will be blinded to allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Heparin Therapy

Arm description:

This group received the treatment under study

Arm type	Experimental
Investigational medicinal product name	Unfractionated Heparin
Investigational medicinal product code	IMP Package
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Inhalation use

Dosage and administration details:

Nebulised unfractionated heparin 25000 units (5ml heparin sodium 5000 IU/ml (Pinewood laboratories, Clonmel, Ireland) was administered via the Aerogen Solo® nebuliser every 6 h from enrolment to day 10, or until discontinuation of advanced respiratory support (if sooner), with the dosage and schedule based on previous work.

Arm title	Standard Care

Arm description:

This arm received standard medical care

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Heparin Therapy	Standard Care
Started	20	19
Completed	20	19

Period 2	
Period 2 title	Outcome
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	Heparin

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Unfractionated Heparin
Investigational medicinal product code	IMP Package
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Inhalation use

Dosage and administration details:

Nebulised unfractionated heparin 25000 units (5ml heparin sodium 5000 IU/ml (Pinewood laboratories, Clonmel, Ireland) was administered via the Aerogen Solo® nebuliser every 6 h from enrolment to day 10, or until discontinuation of advanced respiratory support (if sooner), with the dosage and schedule based on previous work.

Arm title	Standard Care

Arm description:

Standard Care

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Heparin	Standard Care
Started	20	19
Completed	20	19

Baseline characteristics

Reporting groups	
Reporting group title	Heparin Therapy
Reporting group description:	
This group received the treatment under study	
Reporting group title	Standard Care
Reporting group description:	
This arm received standard medical care	

Reporting group values	Heparin Therapy	Standard Care	Total
Number of subjects	20	19	39
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	19	39
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	56.6	51.3	
standard deviation	± 11.5	± 14.9	-
Gender categorical Units: Subjects			
Female	7	8	15
Male	13	11	24
Ethnicity Units: Subjects			
Caucasian	19	17	36
Black,African,Caribbean,Ethnic Black	0	2	2
Asian, Ethnic Asian	1	0	1
COVID-19 Diagnosis Units: Subjects			
Confirmed	19	19	38
Suspected	1	0	1
Concomitant/Prior Steroids Units: Subjects			
Yes	16	18	34
No	4	1	5
Baseline Respiratory Support Units: Subjects			
High Flow Nasal Oxygen	10	8	18

Invasive Mechanical Ventilation	7	6	13
Positive Pressure Ventilator Support	3	5	8
No Advanced Respiratory Support	0	0	0
Adjunctive Therapies Units: Subjects			
Neuromuscular Blocking Drugs	6	7	13
Prone Position	12	9	21
None	2	3	5
Concomitant/Prior Antiviral medications Units: Subjects			
Yes	1	0	1
No	19	19	38
Concomitant/Prior Other Immunomodulatory Drugs Units: Subjects			
Yes	3	4	7
No	17	15	32
BMI			
Body Mass Index			
Units: kg/m2			
arithmetic mean	31.1	31.8	
standard deviation	± 5.2	± 6.4	-
First Qualifying PaO2/FiO2 Ratio Units: ratio			
arithmetic mean	179.6	133.9	
standard deviation	± 64.2	± 44.2	-
Worst PaO2/FiO2 ratio (first 24 hours) Units: ratio			
arithmetic mean	158.4	148.6	
standard deviation	± 63.2	± 58.1	-
Total SOFA Score Units: units			
median	3	4	
inter-quartile range (Q1-Q3)	3 to 8	3 to 9	-
Lowest Mean Arterial Pressure Units: mmHg			
arithmetic mean	88.5	84.5	
standard deviation	± 15	± 15.4	-
Ferritin Units: ng/mL			
median	1586.5	1239	
inter-quartile range (Q1-Q3)	728.25 to 2954.25	635.5 to 1326.0	-
C-Reactive Protein Units: mg/L			
median	65.6	43.17	
inter-quartile range (Q1-Q3)	40.55 to 81.75	25.1 to 95.96	-
Procalcitonin Units: ng/L			
median	0.12	0.11	
inter-quartile range (Q1-Q3)	0.08 to 0.18	0.09 to 0.27	-

End points

End points reporting groups

Reporting group title	Heparin Therapy
Reporting group description: This group received the treatment under study	
Reporting group title	Standard Care
Reporting group description: This arm received standard medical care	
Reporting group title	Heparin
Reporting group description: -	
Reporting group title	Standard Care
Reporting group description: Standard Care	

Primary: Tiime to separation from respiratory support

End point title	Tiime to separation from respiratory support
End point description:	
End point type	Primary
End point timeframe: Duration of Respiratory Support	

End point values	Heparin	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: days				
median (inter-quartile range (Q1-Q3))	9 (4 to 28)	5 (2 to 28)		

Statistical analyses

Statistical analysis title	Survival analysis
Comparison groups	Heparin v Standard Care
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.7

Primary: Length of ICU stay

End point title	Length of ICU stay

End point description:

End point type	Primary

End point timeframe:

Duration of Stay in Intensive Care Unit

End point values	Heparin	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: days				
median (inter-quartile range (Q1-Q3))	10.5 (5.42 to 12.4)	7.8 (4.1 to 19.7)		

Statistical analyses

Statistical analysis title	Survival Analysis
Comparison groups	Heparin v Standard Care
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.931
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.99

Primary: Length of Hospital Stay

End point title	Length of Hospital Stay

End point description:

End point type	Primary

End point timeframe:
Duration of Hospital Stay

End point values	Heparin	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: days				
median (inter-quartile range (Q1-Q3))	22.8 (14.35 to 32.05)	21.6 (14.72 to 33.27)		

Statistical analyses

Statistical analysis title	Survival analysis
Comparison groups	Standard Care v Heparin
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.974
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	2.13

Primary: 28-day mortality

End point title	28-day mortality

End point description:

End point type	Primary

End point timeframe:
28 days from randomisation

End point values	Heparin	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: subjects	1	1		

Statistical analyses

Statistical analysis title	Relative Risk
Comparison groups	Heparin v Standard Care
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	Relative Risk
Parameter estimate	Risk ratio (RR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	14.13

Secondary: 60-day Mortality

End point title	60-day Mortality

End point description:

End point type	Secondary

End point timeframe:

60 days from randomisation

End point values	Heparin	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: subjects	3	2		

Statistical analyses

Statistical analysis title	Relative Risk
Comparison groups	Heparin v Standard Care

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.712
Method	Relative Risk
Parameter estimate	Risk ratio (RR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	7.61

Secondary: Any Adverse Events	
End point title	Any Adverse Events
End point description:	

End point type	Secondary
End point timeframe:	
At any stage during participation	

End point values	Heparin	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: subjects	16	14		

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Heparin v Standard Care
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.663
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.54

Secondary: Any Serious Adverse Events	
End point title	Any Serious Adverse Events
End point description:	

End point type	Secondary
End point timeframe:	
During study participation	

End point values	Heparin	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: subjects	9	5		

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Heparin v Standard Care
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.249
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	5.73

Secondary: Any Haemorrhage	
End point title	Any Haemorrhage
End point description:	

End point type	Secondary
End point timeframe:	
During study participation	

End point values	Heparin	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: subjects	5	3		

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Heparin v Standard Care
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.512
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	5.73

Secondary: Requiring blood transfusion

End point title	Requiring blood transfusion

End point description:

End point type	Secondary

End point timeframe:

During study participation

End point values	Heparin	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Thromboembolic Event

End point title	Thromboembolic Event

End point description:

End point type	Secondary

End point timeframe:

During study participation

End point values	Heparin	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: subjects	1	1		

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Heparin v Standard Care
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.974
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.974
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	14.13

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During study participation

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Heparin Treatment
Reporting group description: -	
Reporting group title	Standard Care
Reporting group description: -	

Serious adverse events	Heparin Treatment	Standard Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 20 (45.00%)	5 / 19 (26.32%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events	3	2	
Investigations			
Elevated Liver Function Tests	Additional description: Elevated Liver Function Tests		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Episode of desaturation, dyspnea and altered consciousness.	Additional description: Episode of desaturation, dyspnea and altered consciousness.		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Episode of desaturation, respiratory arrest call put out, readmitted to Intensive Care Unit	Additional description: Episode of desaturation, respiratory arrest call put out, readmitted to Intensive Care Unit		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Brachial Artery occlusion with arterial dissection	Additional description: Brachial Artery occlusion with arterial dissection		

subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac Tamponade	Additional description: Cardiac Tamponade		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Right arm tingling and numbness	Additional description: Right arm tingling and numbness		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting	Additional description: Vomiting		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
acquired pneumonia	Additional description: acquired pneumonia		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chest pain	Additional description: Chest pain		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective Exacerbation of COPD	Additional description: Infective Exacerbation of COPD		

subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right vocal cord palsy	Additional description: Right vocal cord palsy		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severe respiratory failure	Additional description: Severe respiratory failure		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Shock Liver	Additional description: Shock Liver		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol Withdrawal	Additional description: Alcohol Withdrawal		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Worsening Acute Kidney Injury requiring renal replacement therapy	Additional description: Worsening Acute Kidney Injury requiring renal replacement therapy		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Unresolved Covid-19 Pneumonitis	Additional description: Unresolved Covid-19 Pneumonitis		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Unresolved Covid-19 pneumonitis leading to Multi organ failure.	Additional description: Unresolved Covid-19 pneumonitis leading to Multi organ failure.		

subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Worsening Covid pneumonitis requiring Extra Corporeal Membranous Oxygenation	Additional description: Worsening Covid pneumonitis requiring Extra Corporeal Membranous Oxygenation		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Worsening of Covid pneumonitis	Additional description: Worsening of Covid pneumonitis		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Weight Loss	Additional description: Weight Loss		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Heparin Treatment	Standard Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 20 (65.00%)	14 / 19 (73.68%)	
Vascular disorders			
copious blood stained secretions	Additional description: copious blood stained secretions		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	5 / 20 (25.00%)	3 / 19 (15.79%)	
occurrences (all)	5	4	
Haematuria	Additional description: Haematuria		
subjects affected / exposed	0 / 20 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Haemoptysis	Additional description: Haemoptysis		

subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Hypotension	Additional description: Hypotension		
subjects affected / exposed	1 / 20 (5.00%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Swelling to right arm	Additional description: Swelling to right arm		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Deterioration in Medical Condition	Additional description: Worsening of condition resulting in re-admission to ICU		
subjects affected / exposed	1 / 20 (5.00%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Immune system disorders			
Allergic Reaction to betalactams	Additional description: Allergic Reaction to betalactams		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
bronchospasm	Additional description: bronchospasm		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Candida Albicans in sputum- worsening of medical history	Additional description: Candida Albicans in sputum- worsening of medical history		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Coughing episode	Additional description: Coughing episode		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Enterobactor Colocea-Ventilator Acquired Pneumonia	Additional description: Enterobactor Colocea-Ventilator Acquired Pneumonia		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Hafnia Alvei in sputum	Additional description: Hafnia Alvei in sputum		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Hospital acquired pneumonia	Additional description: Hospital acquired pneumonia		

subjects affected / exposed	0 / 20 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Numbness to nose	Additional description: Numbness to nose		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
patient complaining of intermitant pain to costal region	Additional description: patient complaining of intermitant pain to costal region		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Pneumomediastinum	Additional description: Pneumomediastinum		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Pneumothorax	Additional description: Pneumothorax		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
probable ventilator associated pneumonia	Additional description: probable ventilator associated pneumonia		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Pulmonary Embolism	Additional description: Pulmonary Embolism		
subjects affected / exposed	1 / 20 (5.00%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
query new pneumonia	Additional description: query new pneumonia		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Right sided pnemothorax	Additional description: Right sided pnemothorax		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
severe hiccups	Additional description: severe hiccups		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
severe hypoxemic respiratory failure	Additional description: severe hypoxemic respiratory failure		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
supraglottic oedema	Additional description: supraglottic oedema		

subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
sore throat	Additional description: sore throat		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Ventilator Aquired Pneumonia	Additional description: Ventilator Aquired Pneumonia		
subjects affected / exposed	1 / 20 (5.00%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Worsening of MSSA in sputum	Additional description: Worsening of MSSA in sputum		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Investigations			
Abnormal Liver function test	Additional description: Abnormal Liver function test		
subjects affected / exposed	3 / 20 (15.00%)	2 / 19 (10.53%)	
occurrences (all)	3	2	
Blood cultures positive for gram negative bacilli and pseudomonas aeruginosa	Additional description: Blood cultures positive for gram negative bacilli and pseudomonas aeruginosa		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Elevated Creatinine Kinase	Additional description: Elevated Creatinine Kinase		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Elevated Trigylcerides	Additional description: Elevated Trigylcerides		
subjects affected / exposed	1 / 20 (5.00%)	2 / 19 (10.53%)	
occurrences (all)	1	2	
Elevated Troponin	Additional description: Elevated Troponin		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Gram Negative Bacilli on Cultures	Additional description: Gram Negative Bacilli on Cultures		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
T Wave Inversion	Additional description: T Wave Inversion		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Worsening Elevated Liver function tests	Additional description: Worsening Elevated Liver function tests		

subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Bleeding from tracheostomy site	Additional description: Bleeding from tracheostomy site		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Injection site bleeding	Additional description: Injection site bleeding		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
surgical emphsema	Additional description: surgical emphsema		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial Fibrillation	Additional description: Atrial Fibrillation		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Fast Atrial Fibrillation	Additional description: Fast Atrial Fibrillation		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Sinus tachycardia	Additional description: Sinus tachycardia		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Symptomatic Atrial Fibrillation	Additional description: Symptomatic Atrial Fibrillation		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Left Hand Numbness	Additional description: Left Hand Numbness		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Lockjaw sensation	Additional description: Lockjaw sensation		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
right sided weakness	Additional description: right sided weakness		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Seizure like activity	Additional description: Seizure like activity		

subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
anaemia	Additional description: anaemia		
subjects affected / exposed	0 / 20 (0.00%)	3 / 19 (15.79%)	
occurrences (all)	0	3	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	0 / 20 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Eye disorders			
papillioedema	Additional description: papillioedema		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Ulceration to tongue	Additional description: Ulceration to tongue		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Left big toe mottled	Additional description: Left big toe mottled		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute Kidney Injury	Additional description: Acute Kidney Injury		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Nephrolithiasis	Additional description: Nephrolithiasis		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence	Additional description: Urinary incontinence		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Worsening of acute kidney injury	Additional description: Worsening of acute kidney injury		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Infections and infestations			
deteriorating sepsis	Additional description: deteriorating sepsis		

subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Oral thrush	Additional description: Oral thrush		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Pansinusitis	Additional description: Pansinusitis		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
worsening of herpes simplex virus	Additional description: worsening of herpes simplex virus		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
gross Metabolism acidosis requiring re-intubation	Additional description: gross Metabolism acidosis requiring re-intubation		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
hyperkalemia	Additional description: hyperkalemia		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Hypernatremia	Additional description: Hypernatremia		
subjects affected / exposed	0 / 20 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2020	• NCT number has been added • Secondary outcomes divided into secondary and 'other' outcomes • Exclusion Criteria # 15 has been added. • Changes have been made to the IMP section 9 to make the section more explicit • Changes made to section 15.2 Auditing and Monitoring to outline the process further • Other minor changes.
25 August 2020	In response to HPRA Queries: • Exclusion criteria changed to platelet count 50 from 20 • Clarification of exclusion criteria regarding premorbid state • Clarification in Introduction Summary – our group changed to our Australian colleagues… • We have added some extra information justifying the dose selected in Introduction: "Bleeding and blood transfusion"
09 September 2020	In Response to further HPRA Queries: • Edits to introduction section on: • Treatment of pulmonary microvascular thrombosis and hyaline membranes • SARS-CoV-2 inactivation by heparin • Added paragraph "D-dimer as an outcome measure" • Edits to sections Safety and tolerability of nebulised heparin and Bleeding and blood transfusion • Additional exclusion criteria : Any other specific contraindication to anticoagulation including prophylactic anticoagulation not otherwise listed here
25 September 2020	• Amendment of Safety Outcomes to include recording of all episodes of clinically relevant non-major bleeding (CRNMB), according to the definition of the International Society on Thrombosis and Haemostasis • Amendment of Exclusion criterion #3 from 'APTT>120 seconds and this is not due to anticoagulant therapy' to read 'APTT>100 seconds and this is not due to anticoagulant therapy'
01 October 2020	• Amendment to exclusion criteria number 3, to remove the phrase "and this is not due to anticoagulant therapy" to just APTT > 100 seconds
25 January 2021	• Substantial changes were made to the protocol to extend the inclusion criteria to patients with COVID respiratory failure receiving other forms of advanced respiratory support in addition to invasive mechanical ventilation. • There are also some smaller changes such as to measurements but they are largely a reflection of the changed inclusion criteria or to correct formatting and typographical errors. • Specific exclusion criteria of systemic anticoagulation other than prophylactic anticoagulation including additional text in sections 8.8 and 8.9.
22 February 2021	• The title of the trial has changed from 'mechanical ventilation' to 'Advanced Respiratory support'. • Inclusion criteria altered to include patients on therapeutic anticoagulation with heparin or LMWH • Exclusion criteria updated to remove any therapeutic anticoagulation, other changes made throughout the protocol • Details of new EU MAH added to drug supplier due to Brexit • The person undertaking the role of the Vice President of Research in NUI Galway has changed personnel. This resulted in an update to the named Sponsor person. • Other minor changes have been made to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This was an early phase study and was not powered for efficacy

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36104785

http://www.ncbi.nlm.nih.gov/pubmed/39186127

http://www.ncbi.nlm.nih.gov/pubmed/35106809