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Study Protocol

Glucocorticoids in adults with Acute Respiratory Distress Syndrome (GuARDS Trial)

Co-Sponsors	The University of Edinburgh & Lothian Health Board ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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Chief Investigator	Manu Shankar-Hari, Chair of Translational Critical Care Medicine, University of Edinburgh
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KEY TRIAL CONTACTS (*Protocol Authors)

Chief Investigator	
Name:	Professor Manu Shankar-Hari
Address:	Centre for Inflammation Research Queen's Medical Research Institute, University of Edinburgh EH16 4TJ
Telephone:	07879470843
Email:	manu.shankar-hari@ed.ac.uk

Lead Co-Sponsor Representative	
Name:	Tiago Santos
Address:	ACCORD, Queen's Medical Research Institute, University of Edinburgh, EH16 4TJ
Telephone:	01310 242 3353
Email:	Tiago.Santos@ed.ac.uk

Trial Manager	
Name:	Dr Kay Russell
Address:	Centre for Inflammation Research Queen's Medical Research Institute, University of Edinburgh EH16 4TJ
Telephone:	07900685570
Email:	Kay.russell@ed.ac.uk

Trial Statistician	
Name:	Professor John Norrie
Address:	Usher Institute University of Edinburgh NINE 9 Little France Road Edinburgh BioQuarter Edinburgh EH16 4UX
Telephone:	01316517895
Email:	j.norrie@ed.ac.uk

Co-investigator	
Name:	Professor Danny McAuley
Address:	Room 02.057 Wellcome-Wolfson Institute for Experimental Medicine Queen's University of Belfast 97 Lisburn Road Belfast, BT9 7AE
Telephone:	02890976385
Email:	d.f.mcauley@qub.ac.uk

Co-investigator	
Name:	Professor Charlotte Summers
Address:	Department of Medicine University of Cambridge Cambridge Biomedical Campus Hills Road Cambridge CB2 0QQ
Telephone:	+44 1223 762007
Email:	cs493@medschl.cam.ac.uk

Co-investigator	
Name:	Professor Paul Dark
Address:	Faculty of Biology Medicine and Health The University of Manchester
Telephone:	01612064718
Email:	paul.m.dark@manchester.ac.uk

Co-investigator

Name:	Professor Tamaz Szakmany
Address:	Aneurin Bevan University Health Board University of Cardiff
Telephone:	02920744852
Email:	szakmanyt1@cardiff.ac.uk

Co-investigator

Name:	Dr Dhruv Parekh
Address:	Institute of Inflammation and Ageing College of Medical and Dental Sciences Centre for Translational and Inflammatory Research New Queen Elizabeth Hospital Mindelsohn Way Birmingham, B15 2WB
Telephone:	01213717887
Email:	d.parekh@bham.ac.uk

Co-investigator

Name:	Dr Redmond Tully
Address:	Royal Oldham Hospital Northern Care Alliance NHS Trust
Telephone:	07967098997
Email:	redmond.tully@nca.nhs.uk

Co-investigator

Name:	Andrew Stoddart
Address:	Edinburgh Clinical Trials Unit Usher Institute University of Edinburgh NINE 9 Little France Road Edinburgh BioQuarter Edinburgh EH16 4UX
Telephone:	07817715362
Email:	Andrew.Stoddart@ed.ac.uk

Name:	Dr Brijesh Patel
Address:	Adult Intensive Care Unit Sydney Street Royal Brompton Campus Imperial College London
Telephone:	07870645380
Email:	brijesh.patel@imperial.ac.uk

Co-investigator

Name:	Dr Jay Naisbitt
Address:	Salford Royal NHS Foundation Trust
Telephone:	07972797730
Email:	jay.naisbitt@nca.nhs.uk

Co-investigator

Name:	Dr Anthony Rostron
Address:	Translational and Clinical Research Institute Newcastle University
Telephone:	07717708099
Email:	Anthony.Rostron@newcastle.ac.uk

Co-investigator

Name:	Hazel Milligan
Address:	Pharmacy, Royal Infirmary Edinburgh NHS Lothian
Telephone:	0131 537 1208
Email:	hazel.milligan@nhslothian.scot.nhs.uk

Co-investigator	
Name:	Mark Borthwick
Address:	Pharmacy and Clinical Care Oxford University Hospitals NHS Foundation Trust
Telephone:	01865857878
Email:	mark.borthwick@ouh.nhs.uk

Co-investigator	
Name:	Professor Mark Griffiths
Address:	Critical Care Medicine Bart Health Trust
Telephone:	07875999126
Email:	m.griffiths@ic.ac.uk

Co-investigator	
Name:	Bram Rochwerg
Address:	Juravinski Hospital 711 Concession St. Hamilton Ontario Canada
Telephone:	+1-905-515-2121
Email:	rochwerg@mcmaster.ca

Co-investigator	
Name:	Lorenzo Del Sorbo
Address:	Toronto General Hospital 585 University Ave M5G2N2 Toronto ON Canada
Telephone:	+1 416 340 4800 - 8009
Email:	lorenzo.delsorbo@uhn.ca

Patient representative	
Name:	Mr Barry Williams
Email:	bkw@alphacare.plus.com

PROTOCOL APPROVAL SIGNATURE PAGE

Glucocorticoids in Adults with Acute Respiratory Distress Syndrome: GuARDS Trial

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

Manu Shankar- Hari			
Chief Investigator	**Signature**		**Date**
John Norrie			
Trial Statistician	**Signature**		**Date**
Tiago Santos			
Lead Co-Sponsor Representative	**Signature**		**Date**

For multi-site trials, the Principal Investigator must sign below to document that the protocol has been read and understood.

Name				
Principal Investigator	**Signature**		**Site**	**Date**

CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AR	Adverse Reaction
ARDS	Acute Respiratory Distress Syndrome
CEAC	Cost Effectiveness Acceptability Curve
CI	Chief Investigator
COS	Core Outcome Set
CRF	Case Report Form
CSR	Clinical Study Report
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EQ-5D	Euroqol 5 Dimension Health Related Quality of Life Survey
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HEAP	Health Economic Analysis Plan
HFNC	High Flow Nasal Canula
HRQoL	Health Related Quality of Life
IB	Investigator Brochure
ICER	Incremental Cost-Effectiveness Ratio
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
IMV	Invasive Mechanical Ventilation
ISF	Investigator Site File

ISRCTN	International Standard Randomised Controlled Trials Number
LOS	Length of Stay
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIV	Non-Invasive Ventilation
PI	Principal Investigator
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
QA	Quality Assurance
QALY	Quality Adjusted Life Year
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SPC	Summary of Product Characteristics
SoC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom

TRIAL SUMMARY

Trial Title	***Gl**u**c**ocorticoids in adults with **A**cute **R**espiratory **D**istress **S**yndrome: A randomised, parallel-group, allocation-concealed, open label, pragmatic, group sequential design, clinical and cost- effectiveness trial with internal pilot*
Study Acronym	GuARDS Trial
Clinical Phase	Phase IV
Trial Design	Randomised, parallel-group, allocation-concealed, open label, pragmatic, group sequential design
Trial Participants	1708
Planned Number of Participants	1708
Planned Number of Sites	At least 60
Countries Anticipated to be Involved in Trial	All 4 UK Home Nations (England, Wales, Northern Ireland, and Scotland)
Treatment Duration	10 days
Follow up Duration	180 days
Total Planned Trial Duration	60 months
Primary Objective	To determine the clinical effectiveness of dexamethasone on the primary outcome of 60-day mortality,
Secondary Objectives	To determine the clinical effectiveness of dexamethasone in moderate to severe ARDS To assess the cost-efficiency of dexamethasone plus usual care versus usual care alone in the treatment of ARDS, as per NICE reference case specifications modelled over 1, 3, and 5 year, and lifetime time horizons.
Primary Endpoint	All-cause mortality at 60-days from randomisation
Secondary Endpoint	In hospital Extubation; Re-intubation; Duration of stay in intensive care unit from randomisation; duration of stay in hospital from randomisation At 60 days Health-related quality of life; Health Service Use Follow-up At 90 days All-cause mortality; Health-related quality of life; Health Service Use Follow-up At 180-days All-cause mortality; Health-related quality of life; Health Service Use Follow-up
IMP(s)	Dexamethasone
IMP Route of Administration	Intravenous

Lay Summary of Trial	**Background to the trial**: Every year about 120,000 adults who are admitted to Intensive Care Units (ICUs) require a machine, called a ventilator, to help them breathe. In patients who need ventilation, about 1 in 4 have a life-threatening condition with severe breathing difficulties called acute respiratory distress syndrome (ARDS). Unfortunately, around 40% of patients with ARDS die within 60 days of developing this condition. Breathing difficulties in ARDS happen because the lungs fill with fluid due to inflammation, which is part of the body's response to the conditions causing ARDS. Over the last 30-years, various drug treatments have been tested to reduce the inflammation in ARDS, with little success. At present, there are no drugs that cure ARDS. However, in 2020, a small research study (the DEXA-ARDS trial) in Spain looked at dexamethasone as a treatment for ARDS. Dexamethasone is a well-known steroid, which is a cheap anti-inflammatory drug that is already widely used to treat other illnesses (such as arthritis and asthma). The result of DEXA-ARDS trial showed that it may help patients survive ARDS. These results from Spain are hopeful but to help us know how effective dexamethasone is, we need to test it in a much larger group of patients who come into the NHS with ARDS. We are planning to conduct a large clinical trial across the UK. **Aim(s) of the trial:** The aims of our study is to find out if dexamethasone treatment in patients with ARDS can save lives, reduce the need for extended ICU care, improve longer term patient quality of life and find the best value for the public and health services. **Design:** The study design is called a randomised controlled trial (RCT). We plan to recruit up to 1708 adult patients with ARDS, in approximately 60 ICUs throughout the UK. We will ask patients, or their Legal Representatives if patients are unable to make decisions about their care, to agree (consent) to take part in our study. We will also ask patients if we could follow them up for 6 months after their treatment, as this will give us important information about the clinical effectiveness and cost effectiveness of the treatment. Patients who agree to take part in the trial will then be assigned at random to either dexamethasone in addition to the usual intensive care (intervention), or to usual intensive care only (control), for up to 10 days or until critical care (ICU/HDU) discharge day, whichever occurs first. We will not change other regular care provided in the NHS. The main outcome of the study is whether dexamethasone improves survival at 60-days compared with usual care. This study will be open labelled meaning that the healthcare practitioners and patients will know which group of the study they have been allocated to. Blinding is not appropriate in this case as commonly

	seen side effects of dexamethasone, such as reduced inflammatory markers and raised blood sugar, would point to which group the patient was in. **Patient and public involvement (PPI):** Patients, carers and family are an important part of our team and they have helped us establish the need for this research and to write the study protocol. Their experiences and advice also help us to design and ethically conduct the trial. They will continue to be central in the ongoing delivery and reporting of the study.

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 Acute Respiratory Distress syndrome (ARDS)

ARDS is an acute diffuse, inflammatory lung injury. There are several aetiologies that cause ARDS, including pneumonia, non-pulmonary infections, acute pancreatitis, trauma, transfusions, burns, aspiration pneumonitis, and sepsis. The resulting injury affects the resident immune cells, and alveolar capillary membrane. There is an influx of circulating immune cells. These events lead to increased pulmonary vascular and epithelial permeability, lung oedema, loss of surfactant, and atelectasis, all of which contribute to loss of aerated lung tissue. The clinical hallmarks are arterial hypoxemia and radiographic opacities associated with increased shunting, increased alveolar dead space, and decreased lung compliance. Based on the severity of hypoxaemia[1-3], ARDS is categorised into mild, moderate, and severe. Our target population of ARDS patients will be moderate to severe hypoxaemia categories defined based on either the PaO_2/FiO_2 ratio (P/F ratio) or the SpO_2/FiO_2 (S/F ratio). Moderate category is defined as P/F ratio between 100 – 200 or S/F ratio (if $SpO_2 \leq 97\%$) between 148 – 235. Severe is defined as P/F ratio between ≤ 100 or S/F ratio (if $SpO_2 \leq 97\%$) between ≤ 148.

ARDS is a common and devastating acute critical illness.
An international, multicentre, prospective cohort study of 459 ICUs from 50 countries across 5 continents undergoing invasive mechanical (IMV) or non-invasive (NIV) ventilation reported a period prevalence of 10.4% of intensive care unit admissions. This equates to an estimated potential global burden of ARDS by World Bank region of around 1 to 5 in 10,000 per-year (across World Bank regions)[4].

ARDS is a major cause of short-term mortality, and long-term morbidity and mortality.
The acute hospital mortality in ARDS increases with severity of hypoxaemia, with acute hospital mortality in excess of 40% in more severe illness. ARDS survivors also have exercise limitations, psychological sequelae, decreased physical quality of life, increased costs, and high use of health care services for up to 5 years after they recover from their acute illness[4-6].

ARDS has significant resource implications for healthcare systems.
In the NHS, ARDS accounts for a considerable proportion of ICU resource use. Every year, over 120,000 patients are admitted to UK ICUs needing IMV and ~25% of IMV patients will have ARDS.
Severe ARDS patients have a median (inter-quartile range (IQR)) duration of mechanical ventilation of 9 (4-16) days, ICU length of stay of (LOS) of 11 (5-19) and hospital LOS of 16 (6-31) days[4]. Further, patients with ARDS utilise considerable ICU/hospital capacity and cost (Cost per NHS ICU bed-day = £1932; ward= £413; mean estimated cost of ICU stay based on a UK RCT involving ARDS patients[7] was £26,857 (95 % CI £25,222–£28,491))[8]. Given the long-term sequalae described above, ARDS survivors continue to need primary care contact and ongoing rehabilitation in the community. The mean societal cost at 1 year exceeds £40K, and the total societal cost divided by the number of 1-year survivors is estimated to exceed £90K[7].

1.1.2 Current management of ARDS patients (i.e., usual care for the trial)

The current management of ARDS (i.e., usual care) consists of optimising the diagnosis and treatment of underlying conditions, the deployment of supportive measures that minimise lung injury and the prevention of the consequences of critical illness with supportive care. Thus, the current ARDS management can be broadly divided into ventilatory management, and non-ventilatory management[9,10].

Ventilatory management of ARDS
In patients who require IMV, the use of low tidal volumes (<6 ml/kg ideal body weight) and limiting the airway pressures (plateau pressure <30 cmH2O) is the current recommendation[9]. The setting of positive end expiratory pressure (PEEP) during invasive mechanical ventilation is loosely linked to the inspired oxygen fraction (FiO2), with higher PEEP often used with more severe hypoxemia. In patients with more severe ARDS, prone position ventilation is recommended as part of usual care in the NHS setting.

Non-ventilatory management of ARDS
Patients who develop more severe hypoxaemia, often require sedation, and muscle relaxants to ensure adequate oxygenation. When all the above measures fail to maintain adequate levels of gas exchange, extracorporeal membrane oxygenation (ECMO) is provided in the specialist severe respiratory failure centres in the UK.

1.2 RATIONALE FOR STUDY

1.2.1 Justification of the trial

We recently conducted a systematic review to understand the up-to-date landscape of randomised clinical trials (RCTs) in ARDS[11]. Despite 50 years of research, there are no recommended pharmacological therapies for all-cause ARDS[12].

Glucocorticoids are potent anti-inflammatory drugs, with a good risk benefit profile, and have therefore been tested previously in randomised clinical trials involving ARDS patients. The clinical effectiveness of glucocorticoids in all-cause ARDS, described in section 1.2.3 (i.e., ARDS 'not due to COVID-19') remains uncertain[9].

DEXA-ARDS[13], a multicentre RCT conducted in 17 ICUs in Spain, tested a 20 mg starting dose of dexamethasone (as dexamethasone sodium phosphate) in moderate-to-severe ARDS[1], i.e., three times higher than the dose shown to be effective in COVID-19[14]. It is important to note the following challenges about DEXA-ARDS RCT before accepting the conclusion that dexamethasone 20mg may benefit patients with all-cause ARDS[13]. The DEXA-ARDS trial stopped early after enrolling 88% of the planned sample size of 314 patients. The trial was powered for the primary outcome of ventilator-free days at 28 days. This short-term primary outcome does not capture the risk of delayed clinical deterioration requiring reintubation at ~180 days seen in the LaSRS Trial[15]. The potential long-term safety of glucocorticoid therapy was not reported in DEXA-ARDS trial, a clinically important evidence gap. It is also plausible that usual care provided in the NHS may differ from Spanish usual health care, as outcomes from critical illness are different between the two countries[16].

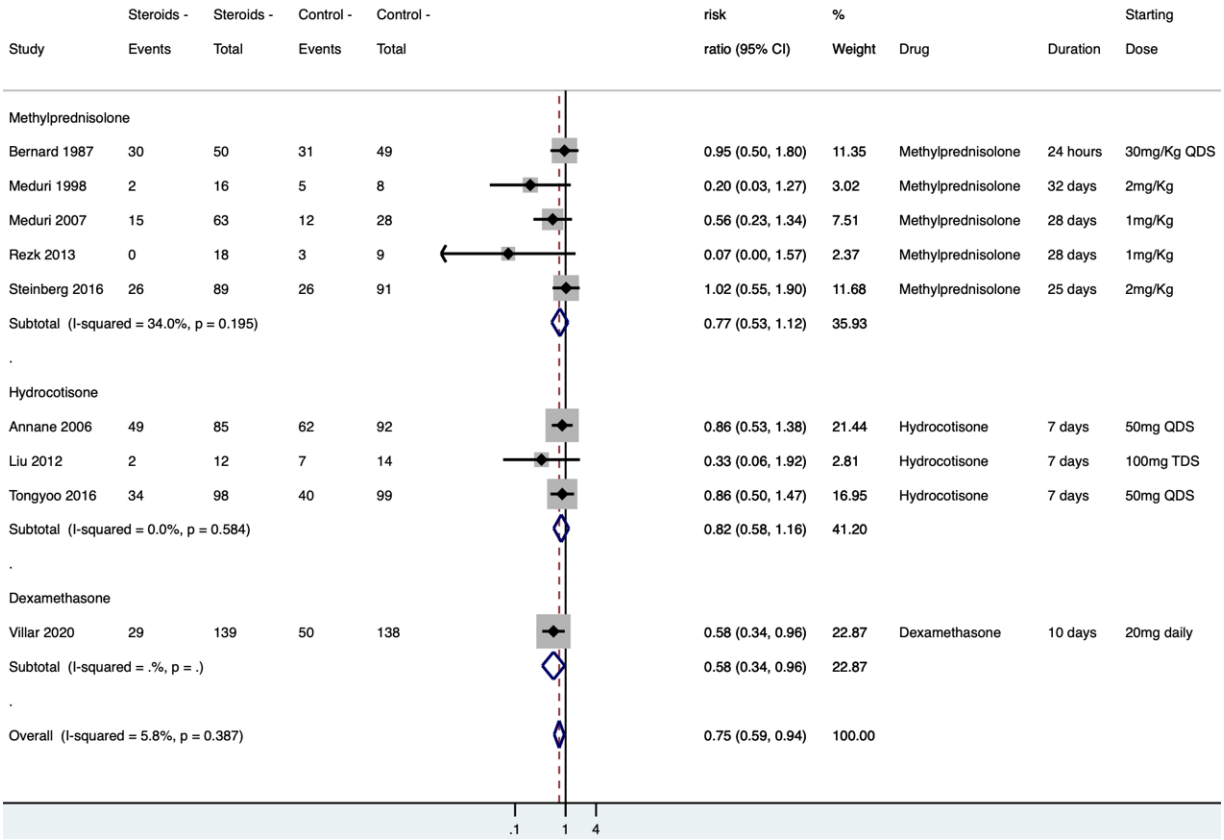
Furthermore, there are safety concerns due to paucity of RCT data on the short-term as well as the longer-term adverse effects of short course glucocorticoids in this population[9,17]. This clinical uncertainty of benefit and risk of harm is reflected in the current UK guidelines for ARDS management[9]: 'The use of glucocorticoids in established ARDS should be the subject of a suitably powered, multicentre RCT with long-term follow-up (GRADE: research recommendation[9]).'

Finally, our research question addresses - what is the role of glucocorticoids in all-cause early ARDS? – is one of the top priorities identified by NIHR-funded James Lind Alliance Intensive Care research Priority Setting Partnership as important to patients, carers and health professionals[18]: *What is the best way of preventing damage to the lungs of patients receiving respiratory support (ventilation)?*

1.2.2 Role of glucocorticoids in ARDS

Systematic reviews and meta-analyses suggest glucocorticoids might be effective in reducing 28-day mortality in patients with all-cause ARDS (1098 patients in 9 RCTs, RR (95% CI) 0.75, 95% CI 0.59–0.94 in fixed effects model, and absolute risk reduction (ARR) (95% CI) 11.9(9.9–14.2%) (p<0.001); (I^2=5.8%) (Figure-1)[19-21]. The study proposed here would be considerably larger than the current evidence base.

Figure-1: Summary of evidence informing the estimated treatment effect



The main methodological findings of our and other systematic reviews[11,19,20] were that most were small RCTs with either surrogate or short-term mortality as primary outcomes. Most RCTs studied *'early'* ARDS patients, i.e., randomised within 72 hours of ARDS onset, suffered from moderate risk of bias from lack of allocation concealment, blinding, and outcome ascertainment. Importantly, RCTs use different glucocorticoids, at different doses, for different durations adds uncertainty to this evidence. Therefore, glucocorticoids should not be used as standard of care (or usual care) currently in ARDS patients.

1.2.3 How did we choose the dosing regimen to test in the GuARDS Trial?

Amongst the different regimens reported in the literature, the dosing regimen used in the DEX-ARDS trial appears to be most promising[13]. DEX-ARDS administered 20mg Dexamethasone sodium phosphate intravenously for days 1-5 and then 10mg intravenously for days 6-10. This study forms the evidence base for this study. The 60-day mortality was 15.3% lower in the dexamethasone group. We reason that dexamethasone at the proposed dose has the highest anti-inflammatory effects compared with other glucocorticoids. Dexamethasone will have pharmacological effects from day 1 that continue beyond the 10-day treatment regime. In pharmacokinetic simulations will maintain a high glucocorticoid

receptor occupancy (trough to peak: 50-90%)[22], and will enable once daily dosing due to long biological half-life.

1.2.4 Hypothesis

Our primary hypothesis is that adult ICU patients with early ARDS (defined as within 72 hours from ARDS diagnosis), and moderate to severe hypoxaemia who are treated with dexamethasone plus usual care will have lower mortality at 60-days compared with those receiving usual care alone. Our rationale for the 'early' (defined as within 72 hours from ARDS diagnosis) treatment regime represents a balance between recruitment feasibility and biological rationale. Biological rationale is that glucocorticoids when administered at the early 'exudative' inflammatory phase, which occurs in the first 72 hours of ARDS onset will reduce inflammation, thereby preventing progressive lung oedema and lung damage[12].

1.2.5 Aim

Our aim is to conduct a multi-centre, parallel group, pragmatic RCT to investigate the clinical and cost effectiveness of dexamethasone plus usual care in patients with ARDS with moderate to severe hypoxaemia, compared with usual care of ARDS patients.

2. STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

To determine the clinical effectiveness of dexamethasone in patients with ARDS with moderate to severe hypoxaemia (referred to as patients with moderate to severe ARDS) on the primary outcome of 60-day mortality.

2.1.2 Secondary Objectives

To determine the clinical effectiveness of dexamethasone in moderate to severe ARDS on a range of clinically relevant secondary outcomes included within the CoVENT core outcome set (COS) for ventilation trials[23]

To assess the cost-efficiency of dexamethasone plus usual care versus usual care alone in the treatment of ARDS, as per NICE reference case specifications modelled over 1, 3, and 5 year, and lifetime time horizons.

2.1.3 Exploratory Objectives

To collect blood samples to evaluate the biological mechanisms in patients with moderate to severe ARDS.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

All-cause mortality at 60-days from randomisation.

2.2.2 Secondary Endpoints

Our proposed secondary outcomes (endpoints) are from the CoVENT core outcome set (COS) for ventilation rials[23]. The timing of their assessments, measurement tools, and justification are summarised in Table 1.

Table-1: Secondary endpoints description

Outcome	Measurement tool or method	Rationale and justification
In-hospital		
First successful extubation	Extubation is defined as free from all tubes, endotracheal tube, and tracheostomy. Success is defined as remaining free from tubes at 48 hrs. If discharged from hospital before the 48-hr success period, assume extubation is successful.	Defined as time from randomization until first successful extubation or the patient's death occurs. We will record the date/time of all periods of ventilation up to day 60.
Duration of mechanical ventilation	Unassisted breathing defined as no inspiratory support (includes time receiving invasive mechanical ventilation and non-invasive ventilation) or extracorporeal lung support. Success defined as remaining to breathe unassisted at 48 hr. Death prior to end of mechanical ventilation or within the 48- hour period after end of mechanical ventilation is considered censored.	Defined as time from randomization until first successful unassisted breathing or the patient's death occurs.
Reintubation	All reintubation events with date/time to report the total number of reintubations after a planned extubation in each group and the average number of reintubation events/participant in each group.	The COS recommends reintubation rates at 60-days. To capture the risk of delayed reintubation[15] we will collect this outcome for up to 180 days from randomization, censored at hospital discharge).
Duration of ICU and hospital stay	Time from randomisation until participant first leaves the relevant facility or death	Included in relevant COS
60-days		
Heath Related Quality of Life (HRQoL)	HRQoL will be measured using the EQ-5D at Baseline, 60 days and 180days. (www.euroqol.org).	HRQoL is an important participant-reported outcome. EQ-5D is recommended for health economic evaluations.
Health service use since hospital discharge	Rehospitalisation, Health service usage	Health service usage is data required for health economic analyses
90-days		
Mortality	We will record the event date/time of event, as well as date/time of randomization to enable survival analysis.	We will also be able to estimate mortality at a priori defined time point of 90-days, and 180-days.
HRQoL	As described above	As described above
Health service use since hospital discharge	As described above	As described above
180-days		

Mortality	As described above.	As described above.
HRQoL	As described above	As described above
Health service use since hospital discharge	As described above	As described above

2.2.3 Exploratory Biological evaluations

Blood samples collected at baseline and at day 3 (+2d) post randomisation will be used for future biological assessments. Further information is provided in the GuARDS Biological Sampling Work Instruction.

3. STUDY DESIGN

3.1 Study Design

GuARDS is a UK multi-centre, parallel group, allocation concealed, open label, pragmatic, group sequential design randomised controlled trial, with internal pilot where the standard of care will be compared to standard of care with additional dexamethasone treatment. Interim analysis will be performed at set points in the trial (n=4, 50%, 65%, 80%, 100% of the sample size) which will allow for statistically controlled opportunities to stop for either overwhelming evidence of benefit (where dexamethasone works) or for ineffectiveness.
Specifically, in PICO terms as an overview:

Population	Adult patients with moderate to severe ARDS
Intervention:	Intravenous Dexamethasone base 16.5mg (equivalent to Dexamethasone Phosphate 20mg) and Dexamethasone base 8.25mg (equivalent to Dexamethasone Phosphate 10mg)
Comparator	Usual care[25]
Outcome	Primary outcome for clinical effectiveness is all-cause mortality 60 days after randomisation.

3.2 Recruitment estimates

We plan to have 36 months of recruitment involving at least 60 sites and at 11/12th capacity (i.e., allow 1 month per 12 off for holidays, other reasons, etc.) gives 2145 centre months. This would result in the maximum sample size of 1708 participants (if the study continues at all interim analyses) being recruited over 2145 centre months = i.e., less than 1 per centre per month (0.8 on average).

3.3 Internal pilot stage

Our project includes an internal pilot stage. We expect a lead time of 6 months for first recruitment, to secure regulatory approvals and to set-up the first five sites. We expect to add the remaining sites at around 10 sites/month over the next 6 months from start of month 7. This internal pilot will run for the first nine months of recruitment (from month 7 to month 16) to assess feasibility and protocol fidelity, with the eventual duration driven by patient numbers. Formal commencement of the pilot stage will be defined as the date of the first recruitment. Thus, for the proposed duration of the internal pilot, we would have an expected recruitment of 268 participants (or around one sixth of the maximum sample size) with mature 60-day mortality primary outcome data to enable the proposed sample size re-estimation step.

We will use a traffic light system to guide internal pilot stage progression, as recommended in recent best practice[19]:

Green: Progress to main trial with review of screening logs and protocol and any barriers to recruitment addressed

Amber: Progress to main trial with ongoing site set-up, review of screening logs and protocol deviations, and protocol review where necessary

Red : Decision to progress to main trial made by the Trial Steering Committee and the funder (NIHR-HTA programme)

The internal pilot will reported to the funder (NIHR-HTA) using their designated management system.

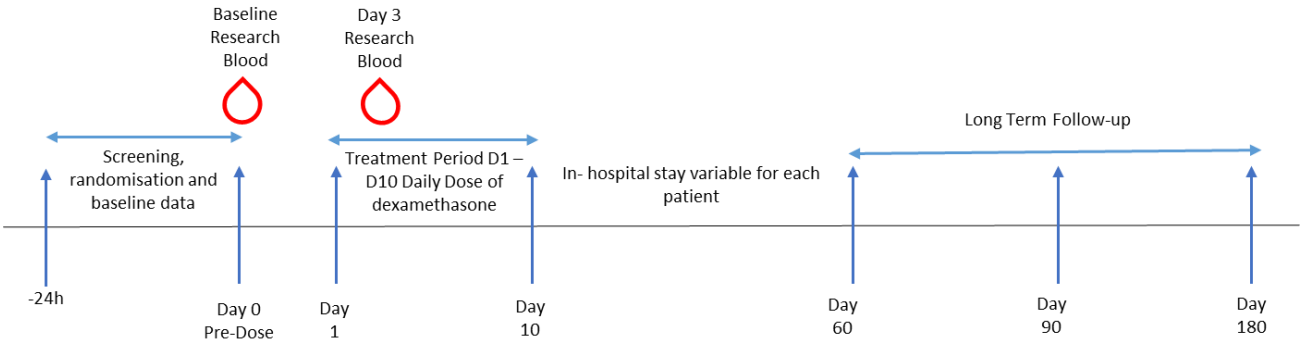
Table- 2: Detail of internal pilot phase conducted during the first 9 months of recruitment

	Red	Amber	Green
% Threshold	<60%	61-99%	100%
Recruitment rate/site/month	<0.4	<0.6	0.8
Number of sites opened	~40	41-59	~60
Total number of participants recruited	<120	<200	288

The main parameters of interest to guide the progress of the trial and inform the procedures to be used in its delivery, are recruitment rates. Participants enrolled in the pilot will be included in the analysis of the main study. If recruitment of 268 patients occurs as planned or quicker than anticipated, progression to the full trial will occur. There will no pause to trial recruitment between completion of internal pilot stage, as per standard RCT practices.

During the internal pilot, we will audit screening logs, recruitment, reasons for exclusion, and protocol compliance. We will also measure the completeness of the primary outcome, which we anticipate should be >95% and optimise the educational materials for use in the wider site recruitment and set-up. Data from recruited patients in the internal pilot phase will be assessed for representativeness, by comparing demographic, ethnic, and indices of deprivation features with corresponding reports from ICUs in England, Wales and Norther Ireland (ICNARC case-mix programme reports)[17] and Scotland (SICSAG reports)[18].

Figure-2. Trial Overview



4. STUDY POPULATION

Adult patients with ARDS, and moderate to severe hypoxaemia.

4.1 NUMBER OF PARTICIPANTS

A maximum of 1708 participants will be randomised 1:1 dexamethasone plus standard care vs, standard of care alone (around 854 per group).

4.2 INCLUSION CRITERIA

(a) Provision of informed consent
(b) Aged 16 years or older
(c) Admitted to intensive care unit or high dependency unit (ICU)
(d) Receiving respiratory support via invasive mechanical ventilation or non-invasive ventilatory support (non-invasive ventilatory support includes mask or helmet) or high flow nasal cannula (HFNC) >30L/min
(e) Within 72 hours of diagnosis of ARDS with moderate to severe hypoxaemia defined as
   i) a known acute clinical insult or new or worsening respiratory dysfunction (*Note: this includes new deterioration at any time-point during the ICU stay*), and
   ii) opacities on chest imaging not fully explained by effusions, lobar/lung collapse/atelectasis, or nodules, and
   iii) respiratory failure not fully explained by cardiac failure or fluid overload, and
   iv) assessment of hypoxaemia done with either PaO_2/FiO_2 ratio <26.7 kPa from arterial blood gases, or SpO_2/FiO_2 <235 with SaO_2<97%

4.2.1 Additional notes on inclusion criteria listed in Section 4.2

- Provision of informed consent is only required for randomisation; it is not required for including patients in the screening log for the purposes of the CONSORT diagram. The rationale we need the number of patients fulfilling the inclusion criteria.

- Patients who change from mild hypoxaemia to moderate or severe hypoxaemia are eligible.

- For this trial, patients with unilateral opacities are eligible, as they would meet the definition of acute hypoxemic respiratory failure, and often have biological changes similar to ARDS. Furthermore, it is well recognised that there are differences in interpretation of chest radiography between observers (low inter observer agreement, validity, and reliability), what may appear to be a unilateral infiltrate on chest radiograph can seem bilateral infiltrates in a CT scan; and in mechanically ventilated patients radiological infiltrates can be masked in portable chest radiographs for numerous reasons[26-30].

- We will include patients requiring other immunosuppressive drugs, provided there exists clinician equipoise for randomising such a patient.

4.3 EXCLUSION CRITERIA

(a) ARDS due to microbiologically confirmed SARS-Co-V2 infection (COVID-19 ARDS)
(b) Major upper gastrointestinal bleeding during current hospital admission, defined as requiring endoscopy and transfusion for two or more units of packed red blood cells. This exclusion criterion will exclude patients with contraindications to the glucocorticoids on the grounds of safety.
(c) High dose glucocorticoids are required for a separate proven clinical indication at the time of randomisation as withholding treatments that have been deemed clinically effective, would be unethical.
   Note: *Low dose glucocorticoid treatments for clinical indications (defined as maximum daily dose of 200mg hydrocortisone or equivalent other steroids) is not an exclusion criterion.*

(d) Known hypersensitivity to dexamethasone[31]
(e) Infections that are not being effectively treated as determined by the treating medical team.
Note: *Once infections are considered as effectively treated by the treating medical team, they are eligible for the trial.*
(f) Planned intensive care treatment withdrawal within next 24 hours as determined by the treating medical team
(g) Patients who are known to be pregnant
(h) Previous enrolment in the GuARDS trial

4.3.1 Explanatory notes on exclusion criteria listed in Section 4.3

Exclusion criterion (a) will exclude patients with COVID-19 who should be receiving glucocorticoids as part of their standard of care. There may be occasions where the reporting of COVID-19 status may be delayed and or proven clinical indications may become apparent few days after randomisation. This is likely to be a small proportion of patients. In this scenario, we will analyse on the intention to treat principles and provide additional sensitivity analyses, as appropriate.

Exclusion criterion (c): In patients receiving low dose (defined as maximum daily dose of 200mg hydrocortisone or equivalent other glucocorticoids) for clinical indications, the decision to continue this low dose glucocorticoids post randomisation in the usual care arm, and in the intervention arm will be at the discretion of the treating physicians.

Exclusion criterion (g) will exclude patients who are pregnant, as administering glucocorticoids in the first trimester of pregnancy increases the risk of cleft palate in the foetus, and in the third trimester of pregnancy, glucocorticoids are part of usual care for facilitating lung maturation in the foetus. Pregnancy tests are carried out on female patients on admission either to the emergency department, or to the hospital or when they are admitted to the ICU. This means that pregnant patients will be identified, and excluded appropriately. The SPC states that drug may pass to breast milk but no additional data is available. Lactation is not considered as an exclusion criterion as breastfeeding is highly unlikely in patients with moderate to severe ARDS in the ICU setting.

4.4 CO-ENROLMENT

Co-enrolment will be undertaken in line with the Sponsor co-enrolment policy (POL008). The CI, or delegate, and Co-sponsor Representative will complete the co-enrolment checklist (POL008-F01) where patients are already taking part in a Clinical Trial of Investigational Medicinal Product (CTIMP). Co-enrolment will also be permitted with studies investigating medical devices and non-interventional research studies on a case-by-case basis. Networks available to the CI and others will identify other studies involving ARDS patients and approaches to co-enrolment can be standardised with co-enrolment agreements where suitable.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Participants will be identified by clinical ICU teams in collaboration with research teams using regular screening of patients, as often as feasible, from the time of ICU admission.

5.2 CONSENTING PARTICIPANTS

Many patients will lack mental capacity to consent at the time of screening and enrolment as a result of critical illness and the effects of sedative drugs. The legal frameworks that govern the inclusion of adults with incapacity in research in the UK are the Medicines for Human Use (Clinical Trials) Regulations, Adults with Incapacity (Scotland) Act, and Mental Capacity Act (England, Wales and Northern Ireland).

Where a patient lacks the capacity to consent, the law allows a legal representative to give consent for the patient to participate. Those who are able to act as a legal representative in Clinical Trials of Investigational Medicinal Products (CTIMPs):

- **Personal legal representative (PerLR)** i.e. Adult's Welfare Guardian or Welfare Attorney, or if not appointed: The adult's nearest relative, if neither are reasonably contactable.
- **Professional legal representative (ProLR)** i.e. A doctor responsible for the medical treatment of the adult if they are independent of the study, or a person nominated by the healthcare provider.

In GuARDS we will seek consent from the patient if they have capacity. Where a patient does not have capacity to consent, we will seek written consent from a legal representative (defined above).

5.2.1 Informed Consent

All patients who are potentially eligible for the trial will be critically ill, and often receive medications that could affect informed decision making, such as sedative drugs intermittently or by continuous infusion. They will therefore lack mental capacity. The Investigator is responsible for ensuring agreed consent procedures are followed before any protocol specific procedures are carried out.

5.2.2 Consent process

In clinical trials that include patients with diminished capacity requiring treatment in a critical care environment, a common approach is to seek consent from a legal representative and once the participant has regained capacity, to seek retrospective informed consent. For this trial, the greatest benefit of dexamethasone treatment is anticipated in the initial 72h post development of moderate/severe ARDS whilst patients will be receiving a range of care measures. Broadly, for consent, patients will fit into two categories:

I. Some patients receiving non-invasive respiratory support (oxygen via HFNC or non-invasive ventilation) who may have capacity and can consent for themselves.
II. For all other patients, we will require someone to consent on their behalf (i.e., legal representative)

In ICUs, research teams are integrated into clinical teams and/or work closely with them. Once the clinical and/or research teams have identified a patient is eligible for enrolment in the trial, the aim is to randomise the patient and start the allocated intervention as soon as possible. This will maximise the potential benefit from the intervention and ensure it is evaluated in the manner it would be used in routine care.

There will be four scenarios through which randomisation is likely to occur:

a) Patient is able to provide consent.

In this situation the patients will be consulted and provided with the Patient Information Sheet (PIS) sheet. After the opportunity to ask questions of the research team, patients who consent will be randomised.

b) Patient's personal legal representative (PerLR) is present at the time eligibility occurs or attends within the next 48 hours.

In this situation the PerLR will be consulted and provided with the Patient Information Sheet (PIS) sheet. After the opportunity to ask questions of the research team, patients for whom consent is provided will be randomised. If the *Per*LR provides consent the patient will be randomised. From our collective experience of critical care trials, this is likely to be the default approach.

c) *Patient's personal legal representative (PerLR) is not present at the time of eligibility or in the following 48 hours.*

The patient's PerLR will be contacted via telephone. The PIS contents will be explained. They will be given the opportunity to ask questions by telephone before deciding whether to give oral consent which will be witnessed by an impartial (i.e. not on the delegation log) and recorded on the consent form. If the PerLR provides consent, the patient will be randomised. In-person consent will be obtained from the PerLR if they are present on site after the patient is randomised but still without capacity to consent. When the PerLR attends on site, they will be provided a copy of the PIS. Where the PerLR does not plan to attend site the witnessed oral consent will remain valid until the participant regains capacity. Attempts to contact the PerLR via phone will be recorded as part of the screening logs in the eCRF.

Note: As part of usual clinical practice, please ensure that the PerLR is aware that the patient was admitted to ICU before seeking consent for research.

d) *Patient's personal legal representative (PerLR) is not present at the time eligibility occurs and either does not attend within 48 hours of fulfilling eligibility criteria, or cannot be contacted via phone after 3 attempts, but a professional legal representative (ProfLR) is identified who is immediately available.*

In this situation, the ProfLR will be consulted. If the ProfLR provides consent the patient will be randomised. Retrospective consent will be obtained from the PerLR if they are present in the time from ProfLR consent and prior to the patient providing consent.
A flow diagram of the consent process is in Appendix 1.

5.2.3 Obtaining consent from participants who regain capacity.

Once a patient is deemed to have regained capacity, they will be approached by an authorised member of the site research team for informed consent to continue in the trial. This will be done as soon as practically possible.

Approach for informed consent from participants who regain capacity:

- The majority of enrolled participants will have their invasive mechanical ventilation discontinued through removal of the endotracheal tube, prior to them having demonstrated capacity and will therefore only be approached for informed consent following extubation, and sedation cessation. Of note, a minority of enrolled patients will have an endotracheal tube in place yet still be able to demonstrate capacity and be approached for informed consent prior to extubation, and sedation cessation.

- A small proportion of enrolled patients (estimated to be <10%) will have a tracheostomy performed as part of their routine clinical care and may be able to demonstrate capacity and be approached for informed consent at a time point when they are still receiving respiratory support.

- In the rare event that a patient was not approached for consent to remain in the trial prior to either ICU discharge and/or hospital discharge, the local research team will seek written consent at 60-day follow-up by sending a PIS and consent form. This will not be

considered a protocol deviation. The patient will be asked to return the signed consent form if they wish to remain in the trial, or contact the study team if they wish to be withdrawn. If the patient *neither* returns the signed consent form *nor* ask to be withdrawn from the trial, the ProfLR and/or PerLR consent will remain valid, and the patient will remain in the trial.

Process for informed consent from participants who regain capacity.
A Participant Information Sheet (PIS) will be provided to the patient by an authorised staff member who has received training in GuARDs Trial processes and procedures and in Good Clinical Practice (GCP). The PIS will provide information about the purpose of the study, what participation means for the patient (e.g. follow-up questionnaires at 60, 90 and 180 days), confidentiality and data security, and the future availability of the trial results. Patients will be given the opportunity to ask any questions they may have about participation in the GuARDs Trial. This process will be done in such a way to mitigate any potential undue influence or coercion. No therapeutic promises will be made.

After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Investigator Site File. If the patient is unable to physically sign the Consent Form (e.g. due to weakness, reduced dexterity), an independent witness can sign on their behalf.
If a patient does not wish to continue in the trial the options for withdrawal are detailed in Section 5.6 and should be recorded in the eCRF. Data collected up to the point of withdrawal will be retained.

5.3 SCREENING FOR ELIGIBILITY
Patients will be screened daily, based on the inclusion/exclusion criteria as specified in the protocol by the local ICU research team and/or members of the usual care team (where they are appropriately trained).
A screening log will form part of the eCRF and be maintained by sites. This will include no personal information but will collect data on reasons for non-enrolment to enable reporting according to the CONSORT Guidelines for parallel group randomised clinical trials.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS
Ineligible and non-recruited patients will continue to receive usual care as directed by the clinical care team.

5.5 RANDOMISATION
5.5.1 Randomisation Procedures
Randomisation will be performed by a member of the research team at each site using an automated web-based system developed by the ECTU, using variable block sizes and stratified by centre, ensuring allocation concealment. Participants will be randomised at 1:1 allocation ratio to either Usual Care alone or Dexamethasone plus Usual Care intervention. This is an open-label trial where patients, clinicians and assessors are aware of the treatment assignment post randomisation.

5.5.2 Treatment Allocation
Participants randomised to the intervention arm will be administered dexamethasone intravenously within four hours post randomisation and then daily for the next 9 days or until the time they discharged from critical care setting (ICU/HDU) to a general ward (whichever is

sooner). Participants will start on a dose of Dexamethasone base 16.5mg (equivalent to Dexamethasone Phosphate 20mg) and will then be administered 16.5mg dexamethasone base from the next calendar day after 10am and once a day up to day 5 post randomisation. From day 6 participants will be administered Dexamethasone base 8.25mg (equivalent to Dexamethasone Phosphate 10mg) per day for up to 10 days post randomisation (i.e., 5 further days - days 6, 7, 8, 9 and 10) or until the patient is discharged from ICU/HDU. Participants randomised to the usual care arm will receive the usual care as per local clinical practice and will provide follow-up data as a comparator.

5.5.3 Emergency Unblinding Procedures

GuARDS will be an open label trial, emergency unblinding procedures are not applicable.

5.6 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point. If such a withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case record form. Data collected up to the point of withdrawal will be retained by the study team. The participant will have the option of withdrawal from:

(i) **Study medication only** where continued study follow-up and collection of data by linkage permitted.
(ii) **Study medication and follow up** but data linkage permitted.
(iii) **All aspects of the trial** but continued use of data collected up to that point.
(iv) Information already collected to be used in future ethically approved research studies.

To safeguard rights, the minimum personally identifiable information possible will be collected.

Randomised participants who wish to be withdrawn from the study before they have undertaken any study related procedures will be withdrawn from the study and another participant will be recruited to replace them. Data on the original participant will be kept on the CRF/database if the participant agrees to this.

The site PI can also withdraw a participant, based on clinical reasons, often made in patient's best interests. In this scenario, the main reasons for withdrawal will need to be documented in the eCRF.

6. INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG

6.1.1 Study Drug Identification

6.1.1.1 Dexamethasone solution for injection

Several generics available in 1mL or 2mL ampoules / vials and in packs of 10 exist for Dexamethasone. As there are different salts available for dexamethasone, it should be prescribed as dexamethasone (base) 16.5mg for 5 days, then 8.25mg for 5 days.
Each site hospital pharmacy should plan to supply stock according to their local practices Site pharmacists should maintain communication with site investigators regarding available stock, to ensure that participants are only enrolled when sufficient stock is available. As IMP will be taken from local clinical stock accountability will be risk adapted, there is no requirement for trial specific accountability. Sites may document accountability in accordance with local policy/practice but this will not be monitored by the Sponsor.

6.1.2 Study Drug Manufacturer

Any preparation of dexamethasone solution for injection which has marketing authorisation in the UK and is stocked by the site hospital pharmacy, may be employed in this trial.

6.1.3 Marketing Authorisation Holder

The site hospital pharmacy can supply any generic of dexamethasone solution for injection available to them for the purposes of this trial. An example of this include:
Dexamethasone (base) 3.3mg per mL solution for injection MA Holder is hameln pharma ltd, Nexus, Gloucester Business Park, Gloucester, GL3 4AG, UK and the MA number is PL 01502 /0079.

6.1.4 Labelling and Packaging

The trial has been classified as a Type A risk adapted CTIMP as any potential risk is no higher than that of standard medical care. No specific arrangements are planned for labelling since all dexamethasone injection used in this trial will be licensed medicinal products that are currently commercially available in the UK.
The IMP will not require a study specific label as they will be taken from stock already stored in the Intensive Care Unit The drug will be prescribed by those experienced in doing so in these circumstances and it is used within the broadly licenced indications.

6.1.5 Storage

Storage and supply of the IMP will be undertaken by the site as per the standard local procedures. IMP will be stored as per the clinical stock used by the Intensive Care Unit at the local site, this may be stored in pharmacy, the Intensive Care Unit or other ward level location according to standard site practice.

Storage conditions for dexamethasone injections should be as per Summary of Product Characteristics (SmPC) for that product. Briefly, Dexamethasone (base) 3.3mg/1mL solution for injection should not be stored above 25°C. Do not freeze.
The product should be used immediately after opening but if it is not, it may be refrigerated (2 to 8°C) and used within 24 hours.
As IMP will be taken from local clinical stock, storage monitoring requirements are risk adapted, temperature monitoring will be as per local site practice. No reporting of temperature excursions to the Sponsor is required. As stock is off the shelf it is usual to follow local practice for dealing with temperature excursions in drug storage areas.

6.1.6 Regulatory Release to Site

Not applicable. Dexamethasone injections used in this trial are commercially available licensed products.

6.1.7 Destruction of Trial Drug

As dexamethasone will be taken from routine clinical stock and only be administered to participants while they are in-patients in ICU there will not any drug returned to site pharmacies. Opened ampoules will be destroyed at ward level. Site pharmacies should follow their local practice / policies for drug destruction and documentation. No approval from Sponsor is required.

6.1.8 Summary of Product Characteristics (SPC) Booklet or Investigators Brochure

The dexamethasone (base) 3.3mg/1mL injection Summary of Product Characteristics (SPC) (hameln pharma ltd, Nexus, Gloucester Business Park, Gloucester, GL3 4AG, UK) is provided in a separate document with a cover sheet and signature page (signed and verified by the CI and Co-Sponsors) and is filed in the TMF. This is a representative SPC used widely within the NHS.

6.2 PLACEBO

As an open label RCT, there is no placebo preparation in this trial.

6.3 DOSING REGIME

Each participant randomised to the intervention arm will be administered Dexamethasone base 16.5mg (equivalent to Dexamethasone Phosphate 20mg) on days 1 to 5 followed by Dexamethasone base 8.25mg (equivalent to Dexamethasone Phosphate 10mg intravenously once a day on days 6 to 10. The daily doses will be administered once a day at approximately the same time each day.

Dexamethasone solution for injection can be given without mixing or dilution. When dexamethasone solution for injection is given by intravenous infusion, glucose 5% in water and sodium chloride 0.9% have been recommended as diluents, as per site practice. Critical Care nurses with appropriate training will prepare and administer dexamethasone as per standard site practice. No weaning off the dexamethasone dose is required after the 10 days treatment period.

6.4 DOSE CHANGES

There will be no change to the dosing regimen detailed in 6.3 where patients are in the ICU/HDU. If patients are discharged from ICU/HDU before the 10-day intervention period is complete dexamethasone treatment will stop. If this occurs, participants will continue in the trial and all follow-up data will be collected where possible.

6.5 PARTICIPANT COMPLIANCE

Dexamethasone will be prescribed on the participants' in-patient drug administration chart (or equivalent) and administered to the participant by appropriately trained clinical staff in accordance with local practice. All doses given will be recorded on the chart and reasons for a dose being missed will be documented as per routine practice. The timing of each dose and compliance will be recorded in the trial database, and reasons for missing will be captured.

6.6 OVERDOSE

As the maximum daily dose is 16.5mg (as base) and is administered by appropriate clinical staff, who are trained and experienced in administering medicinal products, overdose is extremely unlikely. Reports of acute toxicity and/or deaths following overdosage with glucocorticoids are rare. No antidote is available so in the case of an overdose symptomatic treatment should be administered as per local policy.

6.7 OTHER MEDICATIONS

6.7.1 Non-Investigational Medicinal Products

Not applicable. There are no non-investigational medicinal products in this trial.

6.7.2 Permitted Medications

All other interventions will be allowed as per the clinical team including those affecting CYP3A4, because it is not clinical practice at the trial sites to change the use or dosing of

dexamethasone with concomitant use of CYP3A4 inhibitors or inducers. Concomitant administration of neuromuscular blocking agents (such vecuronium, rocuronium) could increase the risk of critical illness related muscle weakness. However, it is well recognised that patients with ARDS may require concomitant administration of these drugs to provide respiratory support, and therefore permitted[3]. Interactions with other medicinal products are contained in the SPC Section 4.5.

6.7.3 Prohibited Medications

Contraindications: Glucocorticoids which are used for a proven indication excludes the patient from this trial. There are no known contra-indications to short-term corticosteroid use. Dexamethasone interacts with several medicinal products detailed in the SPC Section 4.5 which should be considered.

7. STUDY ASSESSMENTS

7.1 SAFETY ASSESSMENTS

We will capture two key safety events – nosocomial infections, and clinically important upper gastrointestinal bleeding (UGI bleeding). Rationale being these two events are (a) recognised severe side effects of glucocorticoid treatment, and (b) critically ill patients are at risk of these two events. Nosocomial infections will be defined using the proxy of antibiotic free days during critical care stay, by collecting number of days of antibiotic therapy. Clinically important UGI bleeding will be defined as overt GI bleeding (defined as hematemesis, melena, or frank blood in the nasogastric tube or endoscopy confirmed bleeding due to peptic ulceration), needing transfusion of two or more units of packed red blood cells[32]. For these safety events, we will record the date/time of all events up to day 60 or until ICU stay if earlier than 60-days. Serious adverse events, and adverse events (SAE/AE reporting) will be captured and reported in addition to above outcomes, as per Sponsor guidance.

7.2 STUDY ASSESSMENTS

See Table 3 for a summary of all study specific assessments.

Baseline data will be recorded (Age, sex, height, index of multiple deprivation, self-reported ethnicity, smoking status in the past 6 months, hospital site, pre-existing co-morbidity; ARDS risk factor, APACHE II score; Sequential Organ failure Score; mode of ventilation and ventilator settings, measure of ARDS, use of adjunctive therapies. Baseline data thus includes key intersectional data considered within the NIHR-INCLUDE roadmap. This will enable us to monitor inclusion of under-served groups in the trial.

Daily data during ICU stay to report secondary outcomes will be recorded for all patients (mechanical ventilation status; respiratory, renal, cardiovascular organ support as defined by the UK Critical Care Minimum Data Set; length of stay (ICU (includes HDU), and hospital); non-trial glucocorticoid treatment; safety outcomes (upper GI bleed and number of days of antibiotic therapy); and adverse events as per the adverse event reporting guidance.

7.3 COMPLIANCE ASSESSMENTS

Protocol compliance will be monitored. Please also see section 6.5 for IMP compliance information.

7.4 LONG TERM FOLLOW UP ASSESSMENTS

Long term follow-ups will be checked at site. The primary objective of mortality will be checked at 60d post randomisation. At this time the HRQol will be measured using EQ-5D. Patients will be asked to complete a HRQol questionnaire at 60, 90 and 180 days post randomisation. These questionnaires will be completed in person, via phone or email. Long-term follow up data on health care use will be obtained with data linkage as described in Section-8. A health resource use questionnaire will be carried out by a phone call with the patient at 60, 90 and 180 days by a member of the research team.

Table 3: Schedule of events

Events and Procedures	Screening (Day 0)	Randomisation (Day 1)	Day 2-5	Day 6-10	ICU Stay	In hospital stay	Day 60	Day 90	Day 180
Study Procedures									
Informed consent	x								
Medical History	x								
Review and confirm eligibility	x								
Demographics	x								
Baseline data	x								
Research blood samples		x [a]	x[b]						
Intervention									
Usual Care or Dexamethasone Treatment		x	x	x					
Efficacy Measures									
First successful extubation					x	x			
Mechanical Ventilation status		x	x	x	x				
Organ support information		x	x	x	x				
AE/SAE Recording		x	x	x					
Duration of stay					x	x			
Long Term Follow-up									
HRQoL							x	x	x
Mortality							x	x	x
Health Resource Use							x	x	x

[a] Prior to first dose of the intervention
[b] On Day 3 (+2d)

7.5 STORAGE AND ANALYSIS OF SAMPLES

Research blood samples will be taken as part of the trial to evaluate the biological mechanisms in patients with moderate to severe ARDS.

Samples will be taken in both dexamethasone arm, and usual care arm of the trial, at two time points. The first sampling time point is referred to as baseline (defined as soon as possible, after consent, and randomisation, before dexamethasone administration in the intervention arm. The second sampling time point is referred to as Day-3(+2) post randomisation.

Baseline:

- One RNA tube (2.5ml)
- One Serum tube (white or brown top tube, 4ml)
- One plasma EDTA or Citrate tube (red, 2ml)

And
Day-3 (+2) post randomisation:

- One RNA tube (2.5ml)
- One Serum (white or brown top tube, 4ml)
- One plasma EDTA or Citrate tube (red, 2ml)

Further details on the sample handling, storage and analysis can be found in the GuARDS specific Biological Sample Laboratory Work Instruction. RNA and Serum samples will be sent to laboratories in IRR, University of Edinburgh and plasma samples will be sent to Institute for Experimental Medicine, Queen's University of Belfast.
RNA samples will undergo transcriptomics to understand changes in gene expression in ARDS patients. Several methods will be used to explore differences in inflammation and immune function in ARDS patient groups in the plasma and serum samples.

If a sample is not taken, reasons will be collected in the eCRF but it will not be treated as a protocol deviation.

8. DATA COLLECTION

We will use a bespoke web-based electronic case report form, with a full data dictionary, automatic and manual data queries and a full audit trail, to ensure data captured are consistent, reliable and fully compliant with all Good Clinical Practice and any other regulatory requirements. We will seek consent from patients for longer-term follow-up up to 6 months using routine databases. We have previously used this approach in critical care trials, successfully. Long-term mortality, and Health service use since hospital discharge will be collected using NHS Digital data linkage for sites in England, edRIS linkage for Scotland, SITES for Northern Ireland and SAIL Databank for Wales. For all linkages, the guidance proposed by each of the organisations will be followed.
Data will be collected by a qualified and delegated healthcare practitioner within the hospital setting or via telephone call.

8.1 Baseline data

Data including initials;; date of birth; sex at birth; height (to calculate ideal body weight);; GP Address; Postcode to determine regional index of multiple deprivation, self-reported ethnicity, hospital site; pre-existing co-morbidity; ARDS risk factor[4], APACHE II score; Sequential Organ failure Score[33]; ventilator settings at randomisation, measure of ARDS, Use of adjunctive therapies,.
Baseline data thus includes key intersectional data considered within the NIHR-INCLUDE roadmap[34]. This will enable us to monitor inclusion of under-served groups in the trial.

8.2 Daily data during ICU stay

Mechanical ventilation status, information about organ support as defined by the UK Critical Care Minimum Data Set; drug-related adverse events (upper GI bleed and days of antibiotic therapy); ICU length of stay; secondary outcome variables.

8.3 Hospital and follow-up

Data will be collected on hospital length of stay; survival; long-term follow-up outcome measures including health care usage (completed at 60, 90 and 180days), and HRQoL questionnaires (completed at 60, 90 and 180 days). Questionnaires may be carried out in person (e.g., on the ward if the patient is an inpatient in the participating hospital at the time of follow up) or via telephone by a qualified person in the research team. Data will be recorded in an eCRF. HRQoL Questionnaires may be sent via email for patients to complete in their own time with answers directly populated to the eCRF.

Long-term mortality and health care use since hospital discharge will be collected using NHS Digital data linkage for sites in England, edRIS linkage for Scotland, SITES for Northern Ireland and SAIL Databank for Wales Databank for Wales. For all linkages, the guidance proposed by each of the organisations will be followed.

Trial patients will be informed of study questionnaire via telephone and asked their preference on how to complete the questions. Where a patient is unable to complete a questionnaire, their Personal legal representative may complete on their behalf or data will be recorded as missing and not treated as protocol deviation. Sites may attempt to follow up with patients three times before they are considered lost to follow-up.

8.4 SOURCE DATA DOCUMENTATION

Source data is defined as all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records where source data are recorded for the first time. The source data will be the patient's medical records, electronic records, data collection sheets and completed questionnaires. A record of where the source data can be found will be detailed in a separate source data plan.

8.5 CASE REPORT FORMS

Study data will be recorded on the electronic CRF by members of the research team at each site. Follow-up study data collected centrally will also be recorded on the eCRF. Paper data collection sheets may be used if required by sites.

Case report forms must be reviewed and approved by the ACCORD Monitor prior to use (see ACCORD SOP CR013 CRF Design and Implementation).

NOTE: All electronic case report forms are subject to Co-Sponsor approval (see section 8.3).

8.6 TRIAL DATABASE

A trial database/ECRF developed by the Clinical Trials Unit in Edinburgh will be used to collect all study data. This will be built in accordance with ECTU SOPs. This will be hosted by the University's Enterprise Server Visualisation and Hosting Service which is physically located at the University of Edinburgh Data Centre on the King's Buildings Campus. Individuals will be issued log-in details and access will be restricted to necessary fields only. The study teams at site involved in follow-up data collection or data entry will enter data. Participants contact details will be encrypted for storage in the database. Following data analyses, the database will be archived by appropriately trained software developers at

ECTU. This archived database will be stored on University of Edinburgh servers once user access has been disabled. Access to the archived database will be controlled by the Chief Investigator.

9. DATA MANAGEMENT

9.1 Data Management Plan

All aspects of data collection, data processing (entry/uploading, cleaning, and query management), and the production of the final dataset ready for analysis and/or archiving will be detailed in a separate Data Management Plan (DMP).

9.2 Personal Data

The following personal data will be collected as part of the research:
Study ID, date of birth, sex at birth, Postcode (to determine index of multiple deprivation), self-reported ethnicity, email address, telephone number, death record, and unique hospital number (CHI/NHS). Personal data detailed will be stored on an Edinburgh Clinical Trials Unit (ECTU) secure database which is compliant with Sponsor SOPs. Only named research staff will have access. Data will be stored for a period of 5 years after the trial has finished follow-up.

Personal data required for follow up trial procedures (Study ID, date of birth, sex at birth, Postcode (to determine index of multiple deprivation), death record, telephone number and, unique hospital number (CHI/NHS) and the name of the Personal Legal Representative who gave their consent) will be stored securely by the research team at each recruiting site for up to 5 years after the trial has finished follow-up.

9.3 Data Information Flow

A bespoke web based electronic data capture system will be used, hosted by ECTU. Site staff will be given training on data entry requirements as part of site set up, and only given access to the live database after they have accessed the training database and completed the training. Written instructions for data entry will also be filed in the ISF to be used by site staff for reference.
The data manager will review the data entered, raise any data queries identified from the data management plan with the study sites and will liaise with the trial statistician to ensure all queries are raised and resolved prior to database lock. The trial manager will document database lock prior to the final dataset being sent for analysis. A separate Data Management Plan will be prepared for the trial detailing the checks to be undertaken.

9.4 Data Storage

The research team will store personal data as follows:

i) All paper files containing personal data will be held in site files. These files will be held securely at each research site. Access to the research documents will be by the research team only.

ii) Electronically on an Edinburgh Clinical Trials Unit secure database compliant with Sponsor SOPs. Named researchers will have access.

Personal data will be stored for five years to allow for inspection and audit of data if required. Data will be uploaded by a suitably qualified person at ECTU following approved standard operating procedures. This will be cross checked prior to locking of the database for analysis.

9.5 Data Retention

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

9.6 Disposal of Data

Study data will be archived by a senior software developer at ECTU following sponsor approved SOPs. This will be fully documented in the Data Management Plan.

9.7 External Transfer of Data

Data collected or generated by the study from consenting individuals may be transferred to external individuals or organisations outside of the Sponsoring organisation(s). It may be provided to researchers running other research studies out with NHS Lothian/University of Edinburgh. Organisations and researchers will only use anonymised participant information to conduct research in accordance with the UK Policy Framework for Health and Social Care Research**.** Where this information includes identifiable information, it will be held securely with strict arrangements about who can access the information.

We intend to perform data linkage with nationally held databases to find out about the participant's long term health. In order to identify them on these databases we will use their NHS/CHI number and other personal details.

9.8 Data Controller

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site).

9.9 Data Breaches

Any data breaches will be reported to the University of Edinburgh (dpo@ed.ac.uk) and NHS Lothian (Lothian.DPO@nhslothian.scot.nhs.uk) Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

10. STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE CALCULATION

10.1.1 Primary outcome event rates

We conducted a systematic review of ARDS RCTs commencing recruitment after the 1994 American European Consensus Conference ARDS definition. We identified 150 ARDS RCTs, and 28 of these RCTs used mortality as primary outcome for sample size calculations. Based on this systematic review, we expect 40% control arm mortality at 60 days[11].

10.1.2 Estimated treatment effects

To date there have been 9 RCTs (8 non-COVID ARDS RCTs[13,15,35-41], including one septic shock trial reporting glucocorticoid effects in the ARDS sub-populations). With fixed effect meta-analysis, the overall risk ratio (95% CI) was 0.75 (0.59, 0.94), favouring glucocorticoid treatment in ARDS (Figure 1). In the corresponding random effect meta-analysis, the overall risk ratio (95% CI) was 0.83 (0.70, 0.99), again favouring glucocorticoid treatment in ARDS. In the DEXA-ARDS Trial that enrolled a similar target population using the same dexamethasone dose, the absolute risk reduction (ARR) in hospital mortality was 15.3%[13].

For our sample size estimations, we have used a conservative estimate of 8% ARR for expected treatment effect. Our primary rationale being that in our systematic review of 150 ARDS RCTs[11], no ARDS RCT of pharmacological interventions to-date have reported an observed ARR of 10% or higher[42].

10.1.3 Sample size estimation

With a frequentist group-sequential design, we have planned and adjusted our sample size for four analyses of primary outcome (at 50%, 65%, 80% and 100% sample size), including three interim analyses. The design uses a Hwang-Shih-DeCani spending function, of which the lower bounds are non-binding (routine 'gsDesign' in R version 4.0.5 (2021-03-31 for Mac). Based on these considerations, to achieve a power of 90%, for the primary outcome of mortality at 60 days (binary yes/no outcome) and a (teosided type 1 error rate of 0.05 without continuity correction[43], we would require 1656 patients. Further, based on previous UK ICU RCTs, we expect less than 3% loss to follow-up at 60 days. Therefore, we propose a maximum sample size of 1708 patients (around 854 patients/arm). The first interim analysis is expected to occur when 828 have complete 60-day outcomes, the 2nd interim analysis at 1077, the 3rd at 1325 and the final at 1656 (which is 1708 assuming 3% missing vital status). This is assuming the control rate is 40%. The z-values for stopping for futility are 0.47, 0.87, 1.35 and (for the final analysis, if reached 2.02); and for stopping for efficacy 2.75, 2.62, 2.39 and 2.02 (for the scheduled interim analyses at 50%, 65%, 80%, and 100% of information achieved).

10.2 PROPOSED ANALYSES

As highlighted in Section-3 GuARDS Trial is a parallel group, allocation concealed, open label, pragmatic, group sequential design randomised controlled trial[44], with internal pilot, with frequentist analyses.

One experimental treatment (intravenous dexamethasone) is compared with usual care (control) arm. Prior to the first formal interim analysis, we will generate a detailed Statistical Analysis Plan (SAP), which will include details of how missing data will be accounted for in the analyses.

Analyses will be two-sided and tested at an a priori significance level of p=0.05. The primary analyses will be conducted on an intention-to-treat basis, with all randomised patients being analysed in the group to which they were allocated, regardless of the subsequent treatment they received. Results will be reported in accordance with Consolidated Standards of Reporting Trials guidance for parallel group clinical trials[46].

We will describe baseline characteristics, follow-up measurements and safety data, using suitable measures of central tendencies; means and medians with the associated standard deviations and interquartile ranges for continuous data; and frequencies and proportions for categorical data (including binary data).

The primary outcome for the randomised groups will be analysed using a logistic regression model, adjusted for age, and severity of hypoxaemia at baseline as two pre-defined baseline prognostic covariates. Analysis of secondary outcomes will involve fitting models appropriate to the type of outcome measure (i.e. time-to-event, binary, continuous).

Subgroup analyses will be provided on the primary outcome, for baseline patients features age category (≤65 years vs. >65 years), sex, comorbidities (number, and diabetes status), shock status, pneumonia diagnosis, baseline illness severity, and ARDS features (pulmonary

vs extra pulmonary, sepsis status, baseline mechanical ventilation status, severity of hypoxaemia, and extent of chest radiology involvement). These analyses will be based on an intention-to-treat population and will be restricted to participants with non-missing subgroup data at baseline.

10.3 Interim analyses

We plan to conduct three interim analyses (at 50%, 65% and 80% sample size), to assess efficacy of the primary outcome. These formal interim analyses allow us statistically controlled opportunities to stop for either overwhelming evidence of benefit (dexamethasone works) or for futility (given the size and direction of the treatment effect at the interim analysis, there is no realistic possibility of a statistically significant benefit being demonstrated if the study continues). The study can of course stop at any time for safety concerns.

10.4 Health Economic Evaluation

Full details of these analyses will be specified in a comprehensive Health Economic Analysis Plan (HEAP), authored by the study health economist(s), and signed off by the PI prior to analysis, however the following section offers an overview for ease of reference:

To maximise UK policy relevance, health economic analysis will follow NICE reference case recommendations[47] including: Adoption of an NHS and PSS costing perspective for primary analyses; cost-utility approach (results in terms of incremental cost per quality adjusted life year (QALY)); discount rate of 3.5% for both costs and QALYs; and the use of probabilistic sensitivity analysis (PSA) to generate cost effectiveness acceptability curves (CEACs).[48]

A decision analytic model will be developed during the early phases of the trial utilising Markov chain methodology and based around recommendations from Soares et al[49]. This is anticipated to take the form of a simple Alive/Dead partitioned survival curve model based on survival curve data from the main trial, though other options will be explored. Survival for each trial arm will be extrapolated over 1, 3, and 5 year, and lifetime horizons, with sensitivity analysis of assumed curve trajectory using common distributional assumptions (such as Weibull, Exponential, Gompertz, or log-Normal).

The systematic review by Soares et al[49] will be topped up to date of analysis to identify any subsequent studies. The results of the review and trial data will then be used to parameterise the model, applying costs based on standard UK price weights and health utilities based by preference on EQ-5D index scores where available, to the predicted survival for each trial arm. It may be necessary for targeted non-systematic reviews to be used to search for any otherwise unsourced parameters, though this is not anticipated.

Results of the cost-effectiveness analysis will be reported in a Bayesian format with no formal hypothesis testing, using a method of moments approach[48]. Incremental cost effectiveness ratios (ICERs) in terms of cost per QALY will be presented and compared to established UK thresholds. [REF] Uncertainty will be presented in the form of PSA using cost effectiveness acceptability curves (CEACs) [REF] with deterministic sensitivity analysis around key assumptions or where a probabilistic approach would be inappropriate.

11. PHARMACOVIGILANCE

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SPC) Booklet.

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. Adverse events (AE) related to the participant's critical

condition will not be collected. AE related to the side effects of dexamethasone will also not be collected (hyperglycemia, muscle weakness) during the participant's stay in ICU or for 21days as these events are common in critically ill patients, irrespective of whether they got dexamethasone treatment or not. Further detail on this can be found in Section 11.3.2.

11.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).
An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.
A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant
- is life threatening*
- requires in-patient hospitalisation** or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
**Any hospitalisation that was planned prior to enrolment will not meet SAE criteria. Any hospitalisation that is planned post enrolment will meet the SAE criteria.
A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be related to the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SPC) booklet or Investigators Brochure.

11.2 IDENTIFYING AEs AND SAEs

Aes and SAEs will be recorded from the time a participant signs the consent form until 21 days post randomisation, or death or discharge from ICU, whichever occurs earlier.
Aes and SAEs will be identified by research nurses through review of the participant's medical notes (this includes daily charts, laboratory results and other investigations undertaken as part of routine medical care).

11.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator, or another suitably qualified physician in the research team who is delegated to record and report Aes/SAEs, to review all documentation (e.g., hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the eCRF/AE log and on the SAE form (if the AE meets the criteria of serious).
Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

11.3.1 Pre-existing Medical Conditions

Pre-existing medical conditions (i.e., existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study.

11.3.2 Aes and SAEs that do not require recording in the CRF

The very nature of critical illness is that many patients' illnesses will worsen before improving, and one in three patients die. Therefore, GuARDS participants may have events that meet the

clinical trial definition of an AE or SAE, but in this patient population they are expected features of critical illness requiring ICU care.

Aes and SAEs that are considered consistent with the expected course of patient's critical illness do not require recording or reporting unless the Principal Investigator (or delegate) considers they may be related to participation in the trial.

These include, but are not limited to:
- complications of ICU procedures
- requirement for further interventions (e.g., surgery) related to the presenting diagnosis.
- reactions to co-prescribed medications
- Known side effects of dexamethasone (e.g., hyperglycaemia, muscle weakness)

Deaths within 60-days of ARDS diagnosis (either during ICU stay, during hospital stay or after hospital discharge) is expected to occur in around 40% of participants and mortality is included within the primary and secondary outcomes for the trial. Death only needs to be recorded as an AE and/or SAE if the Investigator considers that it relates to participation in the trial.

AEs and SAEs that fall within the categories listed above are anticipated and expected in this group of patients. Therefore, these events will not be recorded as AEs or SAEs on the AE log, SAE form or trial database. Details for these events will be recorded in the medical record in accordance with local practice.

11.3.3 Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition should be recorded in the patient's medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs.

11.4 ASSESSMENT OF AEs AND SAEs

Each AE must be assessed for seriousness, causality, severity and ARs must be assessed for expectedness by the Principal Investigator or another suitably qualified physician in the research team who has been delegated this role.
AEs will be assessed for usual care as well as those receiving IMP. SUSARs will be reported to REC and CA (by ACCORD).
The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

11.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 11.1.

11.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

11.4.3 Assessment of Expectedness

If the event is an AR the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SPC Booklet (Section 4.8).
The event may be classed as either:

- **Expected**: the AR is consistent with the toxicity of the IMP listed in the SPC Booklet (Section 4.8).
- **Unexpected**: the AR is not consistent with the toxicity in the SPC Booklet (Section 4.8).

Fatal and life-threatening SARs should usually be considered unexpected. Fatal SARs can only be expected for IMPs with an MA in the EU, when it is clearly stated in the list of ARs of the SPC (Section 4.8) that the IMP causes fatal SARs.

11.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE/SAR/SUSAR and record this on the CRF/AE log or SAE form according to one of the following categories:

- **Mild**: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.
- **Moderate**: an event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe**: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

11.5 RECORDING OF AEs

All adverse events for each participant will be recorded on the AE log and will be assigned the appropriate MedDRA Systems Organ Class (SOC) code.

11.6 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance ***within 24 hours****. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.*

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 11.4.2, Assessment of Causality and 11.4.3, Assessment of Expectedness.

The SAE form will be transmitted via email to safety@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

All reports sent to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

11.7 REGULATORY REPORTING REQUIREMENTS

ACCORD is responsible for pharmacovigilance reporting on behalf of the Co-Sponsors (The University of Edinburgh and NHS Lothian).

ACCORD has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD (or delegate) will inform Investigators at participating sites of all SUSARs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Investigator to prepare the Development Safety Update Report. This annual report lists all SARs and SUSARs reported during that time period. The responsibility of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with ACCORD.

11.8 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the CRF or AE log or additional information section of SAE form

.

11.9 PREGNANCY

Pregnant patients are excluded from this trial due to known side effects in the foetus. It is extremely unlikely that a new pregnancy will occur in either female participants, or partners of male participants, as all participants will be hospitalised for the duration of trial treatment. Data concerning pregnancy will not be collected other than at screening for trial eligibility.

12. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), Trial Managers and coordinating nurse.

The TMG will comprise the Chief investigators Shankar-Hari, Co-investigator D. McAuley, ECTU Director (Norrie), trial managers, and co-applicants acting as regional leads for groups of ICUs geographically close to their centres to enhance trial delivery as well as linking sites in regional proximity for additional support. The TMG will meet face to face and/or by teleconference on a monthly basis and will communicate between meetings via telephone and email as needed. The trial manager in consultation with the Chief Investigator will manage all day-to-day trial activity, providing a single point of contact for all enquiries and a single dissemination point for project communications.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial. We anticipate some centres will leave the trial due to poor recruitment and will manage this actively, considering replacement ICUs when required.
Regular teleconferences will be held with sites to monitor recruitment rates, share recruitment 'tips' and provide advice and support. This approach has been used effectively in other UK critical care trials.

12.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the Trial Steering Committee, the draft template for reporting and the names and contact details are detailed in DMC & TSC Charters.

12.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The terms of reference of the Data Monitoring Committee and the names and contact details are detailed in DMC & TSC Charters.

12.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the Co-Sponsors, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the Co-Sponsors direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

12.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the Co-Sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to trial design.

12.6 STUDY MONITORING AND AUDIT

ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan.

13. GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).
Before the study can commence, all necessary approvals will be obtained and any conditions of approvals will be met.

13.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

13.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.
Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

13.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.
Participants (or their representative) must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.
The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant (or their representative) must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.
The participant (or their representative) will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the Co-Sponsors.
The Investigator or delegated member of the trial team and the participant/representative will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant or their representative will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes.

13.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

13.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

13.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.
- ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the required documentation is available in local Investigator Site files (ISFs). Under

certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

13.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

13.3.6 Data Protection Training

All University of Edinburgh employed researchers and study staff will complete the Data Protection Training through Learn.
NHS Lothian employed researchers and study staff will comply with NHS Lothian mandatory Information Governance Data Protection training through LearnPro.
Non-NHS Lothian staff that have access to NHS Lothian systems will familiarise themselves and abide by all NHS Lothian IT policies, as well as employer policies.

13.3.7 Information Security Training

All University of Edinburgh employed researchers, students and study staff will complete the Information Security Essentials modules through Learn and will have read the minimum and required reading setting out ground rules to be complied with.
NHS Lothian employed researchers and study staff will comply with NHS Lothian mandatory Information Governance IT Security training through LearnPro.
Non-NHS Lothian staff that have access to NHS Lothian systems will familiarise themselves and abide by all NHS Lothian IT policies, as well as employer policies.

13.3.8 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the Co-Sponsors or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.3.9 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including where applicable the General Data Protection Regulation with regard to the collection, storage, processing and disclosure of personal information.
Computers used to collate the data will have limited access measures via user names and passwords.
Published results will not contain any personal data that could allow identification of individual participants.

14. STUDY CONDUCT RESPONSIBILITIES

14.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.
Proposed amendments will be submitted to the Co-Sponsors for classification and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to implementation.

14.2 PROTOCOL NON COMPLIANCE

14.2.1 Definitions

- **Deviation** - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subject's rights, safety, or well-being, or study outcomes.
- **Violation** - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

14.2.2 Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the Co-Sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

14.2.3 Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the Co-Sponsors every 3 months. Each protocol violation will be reported to the Co-Sponsors within 3 days of becoming aware of the violation. Deviation logs/violation forms will be transmitted via email to QA@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

14.3 URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the REC and the MHRA. This is defined as an urgent safety measure and the investigator must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (+44 (0) 20 3080 6456).

The Investigator will then notify the MHRA (clintrialhelpline@mhra.gsi.gov.uk), the REC and ACCORD, in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

14.4 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:
(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the Co-Sponsors (QA@accord.scot) must be notified within 24 hours. It is the responsibility of the Co-Sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

14.5 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will be destroyed with permission from the Co-Sponsors.

14.6 END OF STUDY

The end of study is defined as the last participant's last visit.
The Investigators and/or the trial steering committee and/or the Co-Sponsors have the right at any time to terminate the study for clinical or administrative reasons.
The end of the study will be reported to the REC, Regulatory Authority, R&D Office(s) and Co-Sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the Co-Sponsors via email to researchgovernance@ed.ac.uk.
In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Co-Sponsors (QA@accord.scot) and REC within 1 year of the end of the study.
Within one year of the end of trial, the Investigator will publish summary results on the public accessible database that the trial was registered with, on behalf of the Co-Sponsors.

14.7 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Trial drug will not be continued following the end of the study as participants will only receive trial drug in the 10-day treatment phase of the study. It will be recorded if patients re-start dexamethasone treatment during their stay in hospital.

14.8 INSURANCE AND INDEMNITY

The Co-Sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.
The following arrangements are in place to fulfil the Co-Sponsors' responsibilities:

- The Protocol has been authored by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The Co-Sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities. Sites which are part of the United Kingdom's National Health Service have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

15. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

15.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Co-Sponsors and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. Results of the study will be made publicly available following completion of the analysis of the data.
Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

15.3 DATA SHARING

The final trial dataset will be held by the University of Edinburgh on a secure password protected drive. Co-investigators will have the right to access the final data set for the purpose of additional analyses that are consistent with the consent provided by participants. Similarly, any external party can approach the co-investigators to request access to the trial data. In all cases, access to the trial dataset will require approval by a majority of the members of the trial management group and the sponsor (or its delegated representative).
De-identified version of the analysis data set would be made available to external parties, upon reasonable written request.
After end of the trial, a core group involving the chief investigator, co-investigators, and ECTU data sharing representative(s) will provide oversight of the data requests.

15.4 PEER REVIEW

This study was commissioned by the NIHR in response to a detailed commissioned Systematic Review, and prioritization exercise. The study underwent external peer review during the application for funding.
The study was also presented to the UK Critical Care Research Group (March 2023) and received support. The study was reviewed on multiple occasions by co-investigators and PPI collaborators during the grants application and protocol development process.

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Appendix 1: Consent Process