PROTOCOL

A multicentre randomised, double-blind, placebo-controlled trial to evaluate the effect of intravenous infusions of salbutamol versus placebo on 28-day mortality in patients with acute respiratory distress syndrome

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For Collection and Use of Human Biological samples
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<td>ATPase</td>
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<td>cAMP</td>
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<td>Hydrogen ion</td>
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<td>Suspected unexpected serious adverse reaction</td>
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1. Background

1.1 Acute Respiratory Distress Syndrome

1.1.1 Terminology

The acute respiratory distress syndrome (ARDS) is a condition characterised by a failure of pulmonary oxygen exchange due to increased alveolar-capillary permeability and resultant lung oedema. It can be caused by primary lung conditions such as aspiration, pneumonitis, or can arise as a complication of non-pulmonary conditions such as severe sepsis. Ashbaugh and colleagues first described the syndrome in 1967 in a group of 12 patients with acute onset of dyspnoea, tachypnoea, refractory hypoxiaemia, reduced pulmonary compliance and diffuse alveolar shadowing on their chest radiographs. All the patients required positive pressure mechanical ventilation with positive end expiratory pressure to maintain arterial oxygenation. Post mortem examination of the lungs of the seven patients who died revealed widespread atelectasis, vascular congestion and intra-alveolar haemorrhage, severe pulmonary oedema and formation of hyaline membranes in the alveolar space. Four years later, the term “Adult Respiratory Distress Syndrome” was used to describe the condition. Subsequently the syndrome was renamed as the Acute Respiratory Distress Syndrome (ARDS) because the syndrome also occurs in children. The current definition of ARDS arose from the American-European Consensus Conference in 1994 and requires an oxygen exchange deficit, typical chest radiograph changes and the absence of cardiogenic causes of pulmonary oedema.

1.1.2 Pathophysiology

The pathological findings during the acute stage of ARDS result from diffuse damage to the alveolar capillary barrier causing increased permeability and flooding of the alveolar with proteinaceous exudates. Macroscopically the lungs are oedematous and heavy with a uniform solid red cut surface appearance. Microscopically, there is evidence of an exudative process with extensive epithelial and endothelial barrier damage, alveolar flooding with proteinaceous liquid, inflammatory cells (neutrophils and alveolar macrophages) and fibrin. Hyaline membrane formation is seen in the alveolar spaces. The recovery from ARDS is variable, in some patients there is rapid reabsorption of alveolar oedema fluid and repair of the injured region of the alveolar epithelium, followed by clinical recovery from respiratory failure. However, in other patients alveolar oedema persists followed by organisation of hyaline membranes and gradual appearance of intra-alveolar (interstitial) fibrosis. The development of interstitial fibrosis distorts the normal architecture of the lung. The alveoli fill with cellular debris, leucocytes, red cells and fibrin and fibroblasts proliferate in the interstitial and alveolar space. These processes result in extreme narrowing or even obliteration of the airspaces and prevent normal gas exchange. With the passage of time, fibrin and cell debris are progressively replaced by collagen leading to the development of fibrosis and scarring. Recent evidence suggests there is a much greater overlap of the inflammatory and fibroproliferative phases than was initially thought. As early as 24 hours after the initiation of ventilation evidence of collagen turn-over and lung remodelling can be found in the lavage fluid of patients with ARDS.

1.1.3 Formation and Resolution of Pulmonary Oedema

The alveolar epithelium and the endothelium of the pulmonary capillaries together form the alveolar capillary barrier. The normal alveolar epithelium is composed of two different cell types. The flat type I cells make up 90 percent of the alveolar surface and are easily injured. The remaining 10 percent of cells consist of the cuboidal type II cells. These cells are more
resistant to injury and have important functions such as surfactant synthesis and secretion, ion transport and proliferation and differentiation to type I cells after injury. Both tight and gap junctions couple Type I and Type II cells, providing barrier functions and pathways for intercellular communication. In ARDS, alterations to alveolar-capillary permeability, pulmonary capillary hydrostatic pressures and oncotic pressure leads to flooding of the alveolus with protein rich oedema fluid and the development of non-cardiogenic pulmonary oedema, as outlined above. This interferes with the matching of ventilation to perfusion (V/Q matching) with resulting hypoxaemia, reduced pulmonary compliance and thus acute respiratory failure.

The clearance of oedema fluid is dependent on the balance between oedema formation and re-absorption processes. Oedema formation is governed by Starling forces and the integrity of the alveolar capillary barrier whilst fluid re-absorption is dependent on the active transport of sodium and electrolytes, which drives water re-absorption. Attempts to clear oedema fluid by reducing pulmonary capillary hydrostatic pressure using diuretics, vasoactive agents or extracorporeal membrane oxygenation have been largely unsuccessful. Matthay was the first to demonstrate that alveolar fluid clearance was not governed by Starling forces but occurs via the active transport of sodium across the alveolar epithelium. Sodium / potassium adenosine-triphosphatase (Na$^{+}$/K$^{+}$ ATPase) pumps located on the basolateral surface of type I and type II alveolar epithelial cells pump sodium out of the cell and potassium into the cell against their respective concentration gradients. The Na$^{+}$/K$^{+}$ ATPase consists of two subunits, the alpha subunit, containing the catalytic activity and ion binding sites and the beta subunit, which contributes to the stability of the alpha/beta complex and its insertion into the basolateral membrane of the alveolar epithelial cell. The active transport of sodium by the Na$^{+}$/K$^{+}$ ATPase leads to the development of a concentration gradient across the basolateral surface of the alveolar epithelial cell. Sodium then enters the cell through channels located on the apical surface of the cell. Several different types of channels have been characterised and include amiloride sensitive (e.g. non-selective cation channel, highly selective cation channels and epithelial sodium channel) and non-amiloride sensitive channels. The amiloride sensitive channels contribute towards at least 50-60% of the fluid clearance capacity of the alveolar epithelium. The active transport of sodium across the alveolar epithelial cells creates an osmotic gradient which in turn drives fluid movement from the alveolar to interstitial space leading to the resolution of alveolar oedema.

1.2. Rationale for Beta Agonists in ARDS

1.2.1 A High Burden of Disease and Lack of Effective Therapies

ARDS is common, 13.3% of patients who require mechanical ventilation have ARDS, which is up to 40 times as high as previous studies have indicated. ARDS is frequently fatal; in-Intensive Care Unit (ICU) mortality is estimated at 41-46%, corresponding to about 2,200 deaths per year in the UK. ARDS is costly in health economics terms: these patients consume significantly more resources than matched patients without ARDS since they require a longer ICU and hospital stay (median 17 vs 8 days and 31 vs 25 days, respectively), and convalescence on the ward and subsequent rehabilitation in the community. The quality of life after ARDS is significantly reduced with 35% unable to return to work 24 months after hospital discharge. ARDS has no primary treatments proven to improve outcome other than supportive care with a lung-protective ventilator strategy.
1.2.2 Basic Science Data Support a Clinical Trial of a $\beta_2$ Agonist in ARDS

Experimental studies in animals, as well as in the *ex-vivo* human lung, have demonstrated that $\beta$ adrenergic agonists accelerate the rate of alveolar fluid clearance predominantly through stimulation of the $\beta_2$ receptor on alveolar type I and II cells. $^{14}$ $\beta_2$ receptor activation increases intracellular cAMP resulting in increased sodium transport across alveolar cells by up-regulation of the apical sodium and chloride pathways, $\text{Na}^+/\text{K}^+$ ATPase and probably cystic fibrosis transmembrane conductance regulator. $^1$ This leads to the development of a micro-osmotic gradient between the alveolar space and interstitium which drives the movement of water and accelerates alveolar fluid reabsorption.

$\beta_2$ agonists have been shown to reduce neutrophil sequestration, activation and inflammatory cytokine production *in-vitro* and in animal models of ARDS. $^{22}$ In humans, inhaled salmeterol (long acting $\beta_2$ agonist) given prior to lipopolysaccharide inhalation reduces neutrophil influx, degranulation and tumour necrosis factor-$\alpha$ release. $^{23}$

In ARDS, $\beta_2$ agonists reduce endothelial permeability in animal models and humans $^{24,25}$ and afford a degree of epithelial cytoprotection from infection related epithelial cell injury. $^2$ In BALTI 1, we found *in-vivo* evidence of reduced alveolar capillary permeability $^{26}$ (fig 1) and *in-vitro* evidence of enhanced epithelial monolayer wound repair in patients treated with salbutamol $^{27}$ (fig 2). This effect is protein kinase A dependent and occurs predominantly due to cell migration/spreading.

These data suggest that, in addition to enhancing alveolar fluid clearance, $\beta_2$ agonists may maintain alveolar-capillary integrity, thereby reducing alveolar flooding and the development of ARDS or promote alveolar capillary repair in those with established ARDS.

**Figure 1.**

**Figure 2.**

1.2.3 Lack of Published Randomised Controlled Trials of $\beta_2$-Agonists in Patients with ARDS

In 2004, we conducted an electronic search of the on-line bibliographic databases Medline, PubMed, Current Contents, Clinical Evidence, the Cochrane Library, EBM and bmj.com for all publications in English using key words “acute lung injury” (or “ALI”), “ARDS”, “alveolar epithelium”, “$\beta_2$ agoists” and “pharmacotherapy” in the title, abstract, or Medical Subject Headings. A ‘hand search’ of the full reference lists from review articles and individual relevant papers in peer reviewed English language respiratory and critical care journals was also performed in order to cross check the quality of the computer retrieval method. The results were published as a review. $^{22}$ Three clinical studies (one randomised controlled cross over trial $^{28}$ and two non-randomised studies $^{29,30}$) using $\beta_2$-agonists in patients with ARDS were identified. These studies examined the effects of nebulised $^{28,29}$ or intravenous (IV) $^{30}$ $\beta_2$-agonists on the respiratory mechanics of artificially-ventilated patients with ARDS and found that $\beta_2$-agonists reduced airway resistance, peak and plateau airway pressures. There were no clinical studies addressing the effects of $\beta_2$-agonists on alveolar fluid clearance, or on outcome.
Recently, we conducted a further literature search (unpublished), using the same keywords combined with terms to identify randomised controlled trials, to identify any recent studies of the treatment of human ALI or ARDS with $\beta_2$-agonists. No studies using IV Salbutamol infusion were identified. A retrospective case review of 86 patients with ALI was the only relevant publication. The patients with ALI who also received high dose nebulised Salbutamol (2.5–6.4 mg day$^{-1}$) had a significantly more days alive and free of ALI (n=22, 12.2 (4.4) days) compared with the group receiving $\leq$ 2.4 mg day$^{-1}$ (n=64, 7.6 (1.9) days) although both groups had similar hospital mortality rates of 48% vs 50%.

1.2.4 A Pilot Study of the $\beta_2$ Agonist Salbutamol in ARDS Confirms Laboratory Findings

After an initial dose-ranging study to determine the maximum infusion rate for salbutamol that did not cause tachydysrhythmias in patients with ARDS we undertook a single centre randomised, double blind, placebo-controlled phase II study (BALTI 1) in 40 adult patients with ARDS to determine if an intravenous infusion of salbutamol 15 $\mu$g kg$^{-1}$ hr$^{-1}$ for 7 days would accelerate clearance of alveolar oedema. As shown in the figure below, salbutamol significantly reduced lung water (left) (day 7: mean (SD), 9.2 (6) (●) vs 13.2 (3) (▲) ml kg$^{-1}$, P=0.038) and plateau airway pressures (right) compared to placebo, and trend towards reduced lung injury score.

![Graph showing reduction in lung water and airway pressures](image)

Patients with ARDS who have impaired alveolar fluid clearance have a higher hospital mortality than those with normal clearance (fig 3). This association suggests that the improved clearance of extravascular lung water seen in the salbutamol-treated patients in the BALTI 1 study may lead to a survival benefit. We could not demonstrate this as the study was powered to detect a reduction in extravascular lung water. Therefore, a large-scale definitive trial with a survival endpoint is required.

1.2.5 The Research Proposed is Supported by the Worldwide Critical Care Community

The American European Consensus Conference on ARDS in 1998 first supported the hypothesis that $\beta_2$ agonists could accelerate alveolar fluid clearance in ARDS and called for a clinical trial to investigate if $\beta_2$ agonists would alter outcomes in ARDS. The National Heart, Lung and Blood Institute Working Group considered the future research directions in ARDS in 2002 and concluded that clinical trials to investigate strategies targeting alveolar fluid clearance were required. More recently, Professors Matthay and Abraham, two leading American critical care physicians, endorsed the need for a clinical trial with $\beta_2$ agonists in ARDS in their editorial which accompanied the BALTI 1 publication.

![Graph showing hospital mortality by alveolar fluid clearance](image)
The BALTI 1 trial was funded and heavily supported by the West Midlands Intensive Care Society. At a national critical care research strategy meeting in November 2005, held by the UK Intensive Care Society (ICS), to assess the feasibility of undertaking ICU based multi-centre randomised clinical trials, the BALTI 2 trial was most highly ranked by over 50 active ICU researchers and the expert panel. The ICS funded a feasibility and pilot study on BALTI 2 for one year which has allowed the piloting and refinement of the trial protocol.

1.2.6 Reliable Drug Delivery

The optimal route for delivering \( \beta_2 \) agonists in patients with ARDS with a goal of increasing alveolar fluid clearance has not been determined. Nebulising drugs into the breathing circuits of mechanically ventilated patients appears attractive as it results in high lung concentrations but low blood concentrations and so may reduce the incidence of systemic side effects compared to parenteral treatment. \(^{28}\) However, nebulised drugs might not reach the alveolar space in the consolidated and poorly ventilated lungs found in patients with ARDS.

Prior to the BALTI 1 study we conducted a dose-ranging study to determine the maximum tolerable dose of intravenous salbutamol that critically-ill patients could receive without an increase in ventricular or atrial ectopy. The maximal tolerable dose was 15\( \mu \)g kg ideal body weight\(^{-1}\) hour\(^{-1}\) which is the maximal recommended dose for the treatment of airflow obstruction in acutely ill patients. This dose was used in the BALTI 1 study. This dose achieved plasma levels of salbutamol (10\(^{-6}\)M) which are associated with 100\% increase in basal alveolar fluid clearance in animal models of ARDS. \(^{37}\)

1.2.7 Acceptable Tolerability and Side Effects

The administration of \( \beta_2 \)-agonists can lead to important cardiovascular, metabolic and renal complications. Stimulation of cardiac and vascular \( \beta_1 \) and \( \beta_2 \) receptors causes tachycardia, arrhythmias, exacerbation of myocardial ischaemia, pulmonary vasodilatation and loss of hypoxic pulmonary vasoconstriction. \(^{38,39}\) Metabolic sequelae include hypokalaemia, hyperinsulinaemia and hyperglycaemia. \(^{40}\) The use of intravenous \( \beta_2 \) agonists for tocolysis during pregnancy has been associated with the development of maternal pulmonary oedema. \(^{41,42}\) Studies investigating this phenomenon in vivo in rabbits and humans found that intravenous injection of \( \beta_2 \)-agonists caused reduced sodium, potassium and water excretion leading to a reduced haematocrit and intravascular hypervolaemia. \(^{43,44}\) These adverse effects are usually more marked following intravenous rather than nebulised administration. However, in general, these drugs are well tolerated in the critically ill. These potentially deleterious effects may limit the potential beneficial effects of \( \beta_2 \)-agonists described in this review.

In BALTI 1 treatment was generally well tolerated. \(^{7}\) There was a trend towards higher heart rates in the salbutamol group at day 4 (means (SD), 103(22) vs 88(16) beats min\(^{-1}\), salbutamol vs placebo, \(p=0.06\)) and day 7 (94(14) vs 86(22), \(p=0.264\)). 19 patients received intravenous salbutamol for a total of 2148 hours. During salbutamol or placebo infusions, seven patients (n=5 – salbutamol, n=2 – placebo, \(p=0.164\)) developed new onset of supraventricular tachycardia. These arrhythmias did not cause significant hemodynamic compromise and were short lived. No patients sustained serious ventricular arrhythmias. There were no substantial differences in electrolyte concentrations or acid-base balance between salbutamol and placebo for K\(^+\), Mg\(^{++}\) H\(^+\) or glucose as shown in Figure 4:
1.2.8 Lactic acidosis

Lactic acidosis is reported in the literature as a recognised side effect of intravenous and nebulised β₂ agonists. This effect is probably mediated by β₂-adrenoreceptors and is hypothesised as being due to an increase in skeletal muscle glycolysis leading to a rise in peripheral lactate production. Splanchnic glucose production and lactate extraction are also increased, probably secondary to increases in hepatic glycogenolysis and gluconeogenesis. Acidosis does not develop until the bicarbonate buffering system is saturated, and this usually does not occur until lactate concentrations exceed 5 mmol L⁻¹.

There was no significant difference in lactate levels between placebo and treatment arms in the BALTI-1 study and no patients required discontinuation of the trial drug due to lactic acidosis. Two patients (out of 53) recruited to the BALTI-2 pilot study developed a lactic acidosis which the treating clinicians attributed to the trial drug and discontinued the infusion. In both cases, the lactic acidosis resolved spontaneously after discontinuation of the trial drug over the next 6 hours.

1.2.9 The Intervention is Simple and Cheap

Salbutamol is a low cost treatment, and is readily available from generic drug manufacturers. A seven day infusion for a 70 kg patient will cost just £98. By comparison the NHS Reference cost for a day ICU care (2004) is £1,328.

1.3 Good Clinical Practice

The trial will be carried out in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org), the EU Clinical Trials Directive and UK legislation.

1.4 CONSORT Guidelines

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).
2. Trial Design

2.1 Trial Summary

BALTI-2 is a multicentre, pragmatic, randomised, double-blind, placebo-controlled clinical trial. Patients fulfilling the American-European Consensus Conference Definition of ARDS will be randomised in a 1:1 ratio to receive an IV infusion either of salbutamol (15 µg kg ideal body weight\(^{-1}\) hr\(^{-1}\)) or placebo (0.9% sodium chloride solution), for a maximum of seven days. Allocation to randomised groups will use minimisation to ensure balance with respect to hospital of recruitment, age group (<64, 65-84, >85 years) and PaO\(_2\)/FiO\(_2\) ratio (≤6.7, 6.8-13.2, ≥13.3 kPa). The trial will be fully blinded and all drugs will be packaged identically, so that neither patients, clinicians or investigators will know which patients are in each arm. Data will be recorded by participating ICUs until hospital discharge, and all surviving patients will be followed up by post at six and twelve months post randomisation. The primary outcome is mortality at 28 days after randomisation; secondary outcomes are mortality in ICU, mortality in hospital, number of ventilator-free days, number of organ failure-free days, mortality at twelve months post-randomisation, quality of life at six and twelve months, length of stay in ICU, length of stay in hospital, adverse effects (tachycardia and arrhythmia). 1,334 patients will be recruited from about fifty ICUs in the UK, and an economic evaluation will be conducted alongside the trial.

2.2 Trial objectives

2.2.1 Primary Objective

The primary objective of the trial is to assess whether an intravenous (IV) infusion of salbutamol given at 15 µg (kg ideal body weight\(^{-1}\) hour\(^{-1}\) for up to seven days reduces 28 day all-cause mortality in patients with ARDS compared with a placebo (0.9% sodium chloride) infusion.

2.2.2 Secondary Objectives

The secondary objectives of the trial are:
- To evaluate the effects of IV salbutamol on mortality in ICU, mortality in hospital, ventilator-free days, organ failure-free days, length of ICU and hospital stay, mortality up to twelve months after randomisation, and health related quality of life six and twelve months after randomisation
- To evaluate the safety of IV salbutamol for ARDS patients
- To evaluate the cost-effectiveness of IV salbutamol for patients with ARDS
- To explore whether the effects of salbutamol vary between patients of different age, initial disease severity, mortality risk at ICU admission, and ARDS aetiology.

2.3 Outcome measures

2.3.1 Efficacy

1) Primary outcome: All cause mortality 28 days after randomisation
2) Secondary outcomes:
   - Mortality at (first) discharge from ICU
   - Mortality at (first) discharge from hospital
   - Number of ventilator-free days
   - Number of organ failure-free days
   - Mortality at twelve months post randomisation
Ventilator-free days (VFDs) are often used as a trial outcome in addition to mortality. They are defined as the number of calendar days after initiating unassisted breathing to day 28 after randomisation, assuming a patient survives for at least 48 consecutive hours after initiating unassisted breathing. For example, if a patient initiates unassisted breathing on day 16 and survives to day 28, he/she will be assigned a value of 12 VFDs. If a similar patient begins unassisted breathing on day 16 but dies on day 25, the number of VFDs is 9. If a patient survives for >48 consecutive hours of unassisted breathing but requires assisted breathing (for any reason) before day 28, the number of VFDs is the number of days of unassisted breathing before day 28. Patients who die without initiating unassisted breathing or before 48 consecutive hours of unassisted breathing will be assigned a value of zero VFDs. Patients transferred to another hospital or other health care facility prior to day 28 (intermediate care, nursing home etc.) while still on positive pressure ventilation will be followed to assess this efficacy measure.

In the assessment of VFDs, unassisted breathing is defined as:
1. Extubated with face mask, nasal prong oxygen, or room air, OR
2. T-tube breathing, OR
3. Tracheostomy mask breathing, OR
4. CPAP = 5 cm H2O without PS or IMV assistance.

Organ failure-free days are defined as the number of days in the first 28 days after randomisation that the patient has none of: respiratory support, cardiovascular support, renal support, or neurological support, according to Critical Care Minimum Dataset definitions.

2.3.2 Safety
1) Tachycardia sufficient to stop treatment with trial drug
2) New arrhythmia sufficient to stop treatment with trial drug
3) Other side effects sufficient to stop treatment with trial drug
4) Serious adverse events and suspected unexpected serious adverse reactions

2.3.3 Others
1) Health related quality of life: EQ-5D and SF-12 at six and twelve months after randomisation
2) Resource use: Length of stay in Critical Care Unit
Length of stay in Hospital
Health service contacts up to twelve months after randomisation
Patient out of pocket expenditure and time away from work
2.4 Flow Diagram of Trial Design

**PATIENT ADMITTED TO ICU**
**PATIENT INTUBATED AND VENTILATED**
Does this patient have a $\text{PaO}_2/\text{FiO}_2$ ratio $\leq 26.7$ kPa?

- **YES**
  - Patient assessed by primary caring ICU clinician for the diagnosis of ARDS (acute onset, bilateral infiltrates on CXR, no evidence of left atrial hypertension)
  - **YES**
    - Patient assessed for other inclusion criteria and exclusion criteria
    - **YES**
      - Trial discussed with patient / Personal legal representative (PerLR) / Professional legal representative (Prof LR). Patient Information Sheet provided
      - **YES**
        - Consent obtained from patient, PerLR or ProfLR
          - **YES**
            - Randomisation Service telephoned.
            - Randomisation minimised by centre, age group (<64; 65 to 84; $\geq$85 years) and $\text{PaO}_2/\text{FiO}_2$ ratio ($\leq$6.7; 6.8 to 13.2; $\geq$13.3 kPa).
            - Patient allocated numbered treatment drug pack.
          - **NO**
            - Patient or PerLR / ProfLR refuses consent – patient treated in usual way.
    - **NO**
      - NO
  - **NO**
    - **NO**

- **NO**
  - NO

**SALBUTAMOL (Solution for IV Infusion (1mg ml$^{-1}$)) or PLACEBO (0.9% Sodium Chloride Injection)**
Treating prepared by diluting two ampoules of study drug with 40ml saline. Treatment given at a constant infusion rate of 0.075 ml kg ideal body weight$^{-1}$ hour$^{-1}$ for maximum of seven days to supply either 15µg salbutamol kg ideal body weight$^{-1}$ hour$^{-1}$ or saline

- Daily collection of data on ventilation, organ support and safety monitoring. ICU and hospital discharge date and status recorded.

- **FOR PATIENTS CONSENTED BY PerLR/ProfLR**
  - When the patient is fully conscious and has the capacity to understand the Patient Information Sheet they will be provided with information about the trial and asked for consent to continue in later follow-up

- **NO**
  - Patients who refuse to continue to participate in the clinical trial or follow-up will be withdrawn from the trial.

- Patient contacted by post at six and twelve months after randomisation and asked to complete EQ-5D and SF-12 quality of life questionnaires
2.5 Eligibility Criteria

Patients are eligible to be included in the trial if they meet the following criteria:

2.5.1 Inclusion Criteria:

1. Patient intubated and ventilated
2. Within 72 hours of onset of ARDS
3. ARDS according to American European consensus conference definition
   a) Acute onset
   b) Severe hypoxaemic respiratory failure (PaO$_2$/FiO$_2$ ratio ≤ 26.7 kPa)
   c) Bilateral infiltrates on the chest radiograph in the absence of clinical evidence of left atrial hypertension.
4. Age ≥ 16 years

2.5.2 Exclusion Criteria:

1. Patient known to be pregnant
2. Current treatment with IV β$_2$-agonists or requirement for on-going regular nebulised/inhaled β$_2$-agonists (see Note below)
3. Current treatment with β-adrenergic antagonists (“β-blockers”)
4. Treatment withdrawal imminent
5. Chronic liver disease, defined as Child-Pugh grade C (Appendix 2)
6. Enrolled in another clinical trial of an investigational medicinal product in the last 28 days.
7. Patient or Personal Legal Representative or Professional Legal Representative unwilling to give informed consent.

Note: Many critically ill patients with respiratory failure may receive nebulised/inhaled beta agonists during their initial resuscitation and stabilisation as part of their clinical care. This does not render a patient ineligible for BALTI-2. The clinician considering enrolling a patient in BALTI-2 should determine whether, at the time of assessment of eligibility, the patient has an on-going requirement for regular nebulised/inhaled beta agonists. The most common situations for this will be a patient with an acute exacerbation of asthma or COPD. If, in the opinion of the treating clinician, the patient does require on-going regular nebulised/inhaled beta agonists, then they should be excluded from the trial. If the patient is not deemed to require such treatment they may be enrolled in the trial provided all other eligibility criteria are met. Once a patient is enrolled in the trial, they are not prevented from having as required (PRN) nebulised/inhaled bronchodilators if their clinical status deteriorates. This covered in section 2.10.2 of the protocol on page 25.

Advice for management of a patient with a baseline tachycardia (heart rate (HR) > 140 beats min$^{-1}$) is provided in section 2.9.7 on page 22. Tachycardia at the time of recruitment does not make a patient ineligible for the trial.

2.6 Screening of Patients Not Suitable for Trial

Brief details of all patients admitted to ICUs with, or who develop, ARDS but who do not fulfill the eligibility criteria will be recorded on a Patient Screening Log at each collaborating unit.
2.7 Consent

The Principal Investigator is responsible for ensuring that informed consent for trial participation is given by each patient or a legal representative. Appropriate signatures and dates must be obtained on the informed consent documentation prior to collection of trial data and administration of the trial drug. If no consent is given a patient cannot be randomised into the trial.

Consent will be sought from the patients themselves if this is possible, but it is recognised that in the majority of cases patients will be unable to give informed consent due to alterations in their level of consciousness caused by illness and therapeutic sedation. In this situation informed consent will be sought from a Personal Legal Representative or Professional Legal representative.

2.7.1 Patient Consent

Whenever possible, informed consent will be obtained from the patient. The patient will be informed about the trial by the responsible clinician or a member of the research team and given a copy of the Patient Information Sheet (PIS). Informed patients will be given an adequate amount of time to consider their decision on trial entry. If the patient decides to enter the trial they will be asked to sign two copies of the Patient Consent Form which will then be counter signed by the responsible clinician. The patient will retain one copy of the signed Consent Form. The second copy will be photocopied and the photocopy placed in the patient’s medical records whilst the original will be retained in the Trial Site File.

2.7.2 Personal Legal Representative Consent

If the patient is unable to give consent, informed consent will be sought from the patient’s ‘Personal Legal Representative’ (PerLR) who may be a relative, partner or close friend. The PerLR will be informed about the trial by the responsible clinician or a member of the research team and provided with a copy of the Covering Statement for Personal Legal Representative with an attached PIS and asked to give an opinion as to whether the patient would object to taking part in such medical research. If the PerLR decides that the patient would have no objection to participating in the trial they will be asked to sign two copies of the PerLR Consent Form which will then be counter signed by the responsible clinician. The PerLR will retain one copy of the signed Consent Form. The second copy will be photocopied and the photocopy placed in the patients’ medical records whilst the original will be retained in the Trial Site File.

2.7.3 Professional Legal Representative Consent

If the patient is unable to give informed consent and no PerLR is available, a doctor who is not connected with the conduct of the trial may act as a Professional Legal Representative (ProfLR). The doctor will be informed about the trial by the responsible clinician or a member of the research team and given a copy of the PIS. If the doctor decides that the patient is suitable for entry into the trial they will be asked to sign two copies of the Professional Legal Representative Consent Form. The doctor will retain one copy of the signed Consent Form. The second copy will be photocopied and the photocopy placed in the patient’s medical records; the original will be retained in the Trial Site File.
2.7.4 Retrospective Patient Information

Patients for whom consent is given by a PerLR or ProfLR will be informed of their participation in the trial by the responsible clinician or a member of the research team once they regain capacity to understand the details of the trial. The responsible clinician will discuss the study with the patient and the patient will be given a copy of the PIS to keep. The patient will be asked for consent to participate in the trial and to sign the Consent to Continue Form. If the patient does not give consent, data collected about the patient will not be entered into the analysis.

2.7.5 Withdrawal of Consent

Patients may withdraw or be withdrawn (by PerLR or ProfLR) from the trial at any time without prejudice. Data recorded up to the point of withdrawal will be included in the trial analysis. If a patient or PerLR requests termination of infusion of the trial drug during the treatment period, the drug infusion will be stopped but the patient will continue to be followed-up as part of the trial. If a patient or a PerLR withdraws consent during trial treatment, the trial drug will be stopped but permission will be sought to access medical records for data related to the trial. If a patient or PerLR wishes to withdraw from the trial after completion of trial treatment, permission to access medical records for trial data will be sought.

2.8 Randomisation

Once written, informed consent has been obtained for the patient to participate in the trial the patient will be randomised to treatment with salbutamol or placebo. Patients will be randomised using a 24-hour telephone randomisation service located at the University of Aberdeen.

Randomisation will be minimised by centre, PaO2 /FiO2 ratio (≤6.7, 6.8 to 13.2, ≥13.3kPa), and age (<64, 65 to 84, ≥85 years) because of the expected differences in mortality among these strata. The randomisation service will ask to be provided with the patients’ initials, date of birth and recruitment centre, confirmation that the patient fulfills the trial entry criteria and data for minimisation. The randomisation service will allocate a numbered treatment pack to each patient. This pack will contain all drugs for giving a complete course of trial treatment to one patient.

At the time of randomisation, each patient will be allocated a unique Patient Trial Number which will be used throughout the trial for patient identification. The number will consist of six digits, the first two will correspond to the Trial Centre Number and the last four to the number of the drug box allocated.

2.9 Trial Treatments

2.9.1 Test Treatment

Active ingredient: Salbutamol Sulphate
Trade name: Ventolin™ Solution for Intravenous Infusion
Concentration: 1 mg ml⁻¹
Excipient: Sodium chloride, sodium hydroxide and Water for Injection
Container: Clear glass ampoules, 5ml
Pharmaceutical Form: Sterile injection
Manufacturer: GlaxoSmithKline Manufacturing S.p.A.

2.9.2 Control (Placebo) Treatment

Name: Sodium chloride Injection BP 0.9% w/v
Concentration: 9 mg ml⁻¹
Container: Clear glass ampoules, 5ml
Pharmaceutical Form: Sterile injection
Manufacturer: Hameln Pharmaceuticals Ltd

2.9.3 Diluent

Name: Sodium chloride Injection BP 0.9% w/v
Concentration: 9 mg ml⁻¹
Pharmaceutical Form: Sterile injection

2.9.4 Drug Pack Preparation and Supply

Patient drug packs will be prepared by Bilcare GCS (Europe) Limited (Elvicta Business Park, Crickhowell, Powys, UK). Salbutamol and sodium chloride ampoules will be supplied to Bilcare. Each ampoule will have a randomised black out label applied and 50 ampoules of either salbutamol or placebo will be packaged in a white cardboard box in ten trays containing five ampoules each. Boxes will be sealed and labelled. Each box will contain sufficient material for the treatment of one patient for seven days. All trial drugs will be packaged identically and identified only by number.

Drug boxes will be stored by Bilcare and dispatched by them to participating Hospital pharmacies.

2.9.5 Dispensing of Drug Packs

Hospital pharmacies will dispense the trial drugs to their ICU. Because patients may be recruited into the trial outside normal pharmacy opening hours, two or more patient drug packs (at least one each of salbutamol and placebo) need to be available on each hospital ICU at all times. When a patient is recruited, the randomisation service will inform the recruiting clinician of the drug pack number to be allocated to the current patient and the number of the next drug pack to be obtained from pharmacy. A retrospective prescription will be completed by the recruiting physician when the drug pack has been allocated to a patient along with a request form for the next pack required.

2.9.6 Calculation of Infusion Rate

Salbutamol and placebo infusions will be administered through a dedicated intravenous line at a rate of 0.075 ml (kg ideal body weight)⁻¹ hour⁻¹ (equivalent to 15 µg salbutamol(kg ideal body weight)⁻¹ hour⁻¹). Ideal body weight will be calculated from the patient’s height. The patient will be measured in centimetres from heel to vertex using a soft tape measure and the ideal body weight and infusion rate obtained from the conversion table below:
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<th>Female IBW (kg)</th>
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2.9.7 Treatment Preparation and Administration

Prior to infusion, two ampoules of trial drug will be diluted with 40ml of saline in a 50ml syringe. Infusion syringes should be made up immediately prior to use.

Trial drug infusions should be started immediately after randomisation. If at the time of attempting to commence the trial drug the patient’s heart rate exceeds 140 beats min\(^{-1}\), the administration should be delayed until the heart rate is less than 140 beats min\(^{-1}\) for at least 30 minutes. Every attempt should be made to complete the treatment infusion without interruption for a maximum of seven days (i.e. until 168 hours after randomisation).

2.9.8 Alteration of Infusion Rate

Sinus tachycardia or arrhythmias are known side effects of intravenous salbutamol administration. If a patient receiving a trial drug infusion is noted to have tachycardia (HR > 140 beats min\(^{-1}\)) or any new arrhythmia occurs, the dose rate of drug will be adjusted according to the flow diagram (page 23). Dose adjustments for renal or hepatic failure will be driven by the cardiovascular response to the infusion rather than on the degree of renal or hepatic impairment. Standard anti-arrhythmic therapy will be given if indicated in addition to alteration of infusion rate.
Example 1 - Patient develops sinus tachycardia rate 145 beats min\(^{-1}\), sustained for greater than 30 minutes without haemodynamic compromise. Infusion running at rate A.

Action – sedation and analgesia requirements reviewed; other causes of tachycardia sought but not identified. Infusion reduced to rate B. One hour later HR 118 beats min\(^{-1}\). Infusion continued at rate B.

Example 2 – Patient with pre-existing atrial fibrillation develops tachycardia (AF) rate 160 beats min\(^{-1}\). Infusion running at rate A.

Action – sedation and analgesia requirements reviewed; other causes of tachycardia sought but not identified. Infusion reduced to rate B. One hour later HR 148 beats min\(^{-1}\) (AF). Infusion stopped. Clinical decision taken to treat AF with anti-arrhythmic according to unit protocol. Patient reassessed 12 hours later. HR 80 beats min\(^{-1}\) (AF). Infusion restarted at rate C. If further tachycardia or new arrhythmia infusion should be stopped and remaining drug returned to pharmacy.

Example 3 – Patient develops new onset atrial fibrillation. Infusion running at rate A.

Action – Stop infusion. Check electrolytes, record 12 lead ECG. Clinical review and decision taken to treat AF with anti-arrhythmic according to unit protocol. Patient reassessed 12 hours later. HR 80 beats min\(^{-1}\) (sinus rhythm) Infusion restarted at rate B. If further tachycardia or new arrhythmia infusion should be stopped and remaining drug returned to pharmacy.
2.9.9 Infusion Termination Criteria

Termination of the infusion is defined as discontinuation of the trial drug infusion without intention to restart the infusion at a later time. Patients whose infusion is terminated before 7 days after randomisation are not withdrawn from the trial, but will remain in the trial until twelve months after randomisation or death. Trial drug infusion will be terminated in the following circumstances:

- Death
- Heart rate >140 beats min^{-1} despite two adjustments in infusion rate
- New arrhythmias despite adjustment in infusion rate
- Development of a significant lactic acidosis, which in the opinion of the treating clinician is attributable to infusion of the trial drug
- 24 hours after discontinuation of mechanical ventilation (of any sort)
- Discharge from Critical Care environment
- Discontinuation of active treatment
- Request to withdraw from PerLR or patient
- Decision by the attending clinician that the infusion should be discontinued on safety grounds
- 7 days (168 hours) after randomisation

2.9.10 Treatment Compliance

Treatment will be administered by site personnel with relevant training and experience at the hospital. Trial infusions will be recorded in the Case Report Forms to monitor treatment compliance.

2.9.11 Drug Accountability

Hospital pharmacies will be responsible for recording trial drug packs dispensed to the ICU. Preparation of all drug infusions will be recorded on the Nursing Staff Drug Accountability Form and drug administration on the patients prescription chart. The trial drug packs will include a sheet on which the fate of all ampoules will be recorded (infused, opened but not infused, discarded, unused). At the end of the treatment period any remaining unused drug will be returned to the hospital pharmacy for recording and will then be destroyed.

2.10 Clinical Management of Patients in the Trial

Patients involved in the BALTI 2 trial will be managed according to best practice established locally on each unit. Particular care to monitor electrolytes (K⁺, Mg^{++}) and glucose is required, with electrolyte supplementation/insulin administered as clinically indicated.

The only specific trial requirement is that patients are not routinely administered nebulised beta agonists or other intravenous beta agonists such as isoprenaline. The uncontrolled use of nebulised bronchodilators in the control group will limit the ability of the trial to detect a significant difference in outcomes and the use in the treatment group exposes the patients to a risk of toxicity. There is no definitive evidence at the current time that routine nebulisation of bronchodilators improves outcomes in patients with acute lung injury.
2.10.1 Acute Bronchospasm

In the event of acute bronchospasm, where the clinician feels that a nebulised bronchodilator is required, nebulised ipratropium bromide may be given. If nebulised ipratropium is insufficient to treat the bronchospasm, then salbutamol may be given as a rescue therapy. This will be recorded on the relevant case report form.

2.10.2 Ventilatory Management

There are no specific guidelines for ventilatory management. Clinicians will be encouraged to use a low tidal volume strategy of ventilation based on ideal body weight. Rescue therapies such as high frequency oscillatory ventilation, nitric oxide and extracorporeal membrane oxygenation can be used according to local policy.

2.10.3 Blinding and Procedures for Unblinding Patients

As a placebo controlled, double-blind trial, patients, clinicians and investigators will be blinded to each patient’s allocation. All trial drugs, whether salbutamol or placebo, will be packaged identically and identified only by number.

Emergency unblinding may be requested on grounds of safety by any Investigator. Emergency unblinding will be performed by telephone contact with the randomisation service in Aberdeen. This option may be used ONLY if the patient’s future treatment requires knowledge of the treatment assignment. If a Principal Investigator decides that there is justification to unblind a patient, they should make every attempt to contact the Trial Co-ordinating Centre, who will arrange for them to discuss the necessity of unblinding with a clinical member of the study team.

2.11 Post Infusion Follow-up

Any patients who remain in the Intensive Care Unit or High Dependency Unit for more than seven days post randomisation (the end of the expected drug infusion period), will continue to be monitored on daily basis until discharged to a ward. The date and place of hospital discharge will be obtained from hospital records.

All patients discharged from hospital will be followed-up six and twelve months after randomisation by postal questionnaire. The questionnaire will collect data on disability and health-related quality of life, using the EQ-5D and SF-12 questionnaires.

2.12 Adverse Event Management

2.12.1 Definitions

2.12.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with the treatment. The following are expected adverse events and will be recorded on the CRF:

- Termination of trial drug due to tachycardia
- Termination of trial drug due to new arrhythmia
- Termination of trial drug due to lactic acidosis
- Termination of the trial drug for any other reason

These events will be included as part of the safety analysis for the trial and do not need to be reported separately to the Trial Co-ordinating Centre.
2.12.1.2 Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

A serious adverse event is defined as an adverse event that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Results in congenital abnormality or birth defect
- Requires medical intervention to prevent one of the above, or is otherwise considered medically significant.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are also unexpected i.e. their nature or severity is not consistent with the Summary of Product Characteristics (Appendix 3), and are considered to be caused by the study drug.

Because BALTI-2 is recruiting a population that is already in a life-threatening situation, it is expected that many of the participants will experience SAEs. Events that are expected in this population and those that are collected as outcomes of the trial should not be reported as SAEs. This includes:

- Death
- Organ failure

Other SAEs or SUSARs that occur between trial entry and 30 days after the end of the trial drug infusion will be reported using the mechanism described in Section 2.12.1.3. The following events should be reported:

- Unexpected SAEs (SUSARs)
- Side effects of salbutamol sufficiently severe to be fatal or immediately life-threatening.

2.12.2 Reporting of SAEs and SUSARs

SAEs and SUSARs will be reported using the SAE form in the patient’s CRF. The Principal Investigator in each centre must report any SAEs and SUSARs to the Trial Co-ordinating Centre within 24 hours of becoming aware of them. To do this, the SAE form should be completed and faxed to the trial’s secure fax number (02476 150549). Subsequently, the Principal Investigator will be required to submit a full report on the resolution of the event. The Trial Co-ordinating Centre is responsible for reporting adverse events to the sponsor, ethics committee and MHRA within required timelines. The Principal Investigator’s assessment of causality of SAEs (i.e. their relationship to trial treatment) will be reported on the Serious Adverse Event form.

2.13 End of Trial

The trial will end when 1334 patients have been recruited and completed twelve month follow-up.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Mandated by the Medicines and Healthcare products Regulatory Agency (MHRA)
Following recommendations from the Data Monitoring and Ethics Committee (DMEC)

Funding for the trial ceases

The Main Research Ethics Committee (MREC) that originally gave a favourable opinion of the trial and the MHRA that issued the Clinical Trial Authorisation will be notified in writing if the trial has been concluded or terminated early.

3. Data Management

3.1 Training Issues

To ensure accurate, complete and reliable data, the Trial Co-ordinating Centre will do the following:

- Provide instructional material to the trial site(s)
- Provide an Initiation training session to instruct the Investigators and trial nurses. This session will give instructions on the protocol, the completion of Case Report Forms and trial procedures.
- Make periodic visits to the trial site
- Be available for consultation and stay in contact with the trial site personnel by mail, telephone and/or fax.
- Review and evaluate Case Report Form (CRF) data, detect errors in data collection and request data collection

3.2 Data Collection and Management

All data for an individual patient will be collected by each Principal Investigator or their delegated nominees and recorded in the CRF. Patient identification in the CRF will be through their unique Patient Trial Number allocated at the time of randomisation and initials. Data will be collected from the time the patient is considered for entry into the trial through to their discharge from hospital. In the event that a patient is transferred to another hospital, the trial team will liaise with the receiving hospital to ensure complete data collection.

APACHE II scores will be used as part of the description of the trial population. For centres that participate in the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme (CMP), the APACHE II scores can be obtained from ICNARC; therefore these centres will need to supply only the CMP number for BALTI-2 participants. Centres that do not contribute to the CMP will need to collect all of the data to allow calculation of the APACHE II score.

Data will be collected in duplicate using non-carbon required forms. Once a patient has been discharged from hospital and all data entered into the CRF, the top copy of each form will be returned to the Trial Co-ordinating Centre. The bottom copy of the CRF will be retained at the recruiting centre. The trial number, name, address and other contact details of all patients who survive will be supplied to the Trial Co-ordinating Centre at the time of hospital discharge to allow follow-up questionnaires to be posted to the patients at six and twelve months.
Submitted data will be reviewed for completeness and entered onto a secure, backed-up custom database. Due care will be taken to ensure data safety and integrity, and compliance with the Data Protection Act 1998.

3.3 Follow-up at Six and Twelve months

All survivors will be followed up at six and twelve months after randomisation by postal questionnaire. Any deaths after discharge from hospital will be identified using the NHS Strategic Tracing Service (NSTS), to avoid sending questionnaires to patients who have died. Trial patients will be asked to let the Co-ordinating Centre know if they move house at any time after hospital discharge; NSTS will enable us to locate any who move without informing the Co-ordinating Centre. The follow-up questionnaire will collect data on disability and health-related quality of life, using the EQ-5D and SF-12 questionnaires. If questionnaires are not returned a maximum of two telephone contacts will be made to the trial patient to check that the questionnaire has been received and the patient is happy to complete it, followed by a second copy of the questionnaire and telephone contacts in the event of non-return. If the second questionnaire is not returned the patient will be contacted and the outcome data collected over the telephone.

3.4 Data Storage

All essential documentation and trial records will be stored by WMSCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

3.5 Archiving

Trial documentation and data will be archived for at least five years after completion of the trial.

4. Data Analysis

4.1 Sample size calculation

The estimated sample size is 1334 patients (667 in each arm).

Published estimates of the mortality rate among ARDS patients range from about 34% to 60%. Two cohort studies that included UK data estimated that hospital mortality was 53.9% (95% CI 49.0, 58.7%) and 60.9% (95% CI 55.9, 65.9%). However, it is likely that mortality has declined since these studies were conducted (1999) because of the introduction of protective ventilation strategies after the publication of a large RCT in 2000. From unpublished ICNARC data for 2005, the hospital mortality among 37,726 patients with ARDS in the UK was 41.2%. The primary outcome for BALTI-2 is 28-day mortality, which is likely to be similar to or slightly higher than hospital mortality because most deaths will occur in ICU within a short period after randomisation, and most patients leave hospital before 28 days. In BALTI-1 the placebo group 28-day mortality rate was 67% (95% CI 0.45, 0.83). A reasonable conservative estimate of the 28-day mortality to be expected in BALTI-2 is 40-50%.

Losses to follow-up for the primary outcome are expected to be very low; in the recently-completed PAC-Man trial 2.4% of recruited patients were lost (mainly because of withdrawal
of consent) between randomisation and hospital discharge. We have therefore conservatively assumed a 3% loss of patients for the primary outcome. The table below shows the sample sizes necessary for 80% and 90% power to detect a real risk ratio of 0.80 between the salbutamol and placebo arms, using a significance level of 0.05.

**Required sample sizes for 80 and 90% power, RR 0.80, 3% losses.**

<table>
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<th>Placebo mortality</th>
<th>Salbutamol mortality</th>
<th>80% power</th>
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<tr>
<td>40%</td>
<td>32%</td>
<td>1164</td>
<td>1558</td>
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<tr>
<td>42%</td>
<td>33.6%</td>
<td>1076</td>
<td>1440</td>
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<td><strong>44%</strong></td>
<td><strong>35.2%</strong></td>
<td><strong>998</strong></td>
<td><strong>1334</strong></td>
</tr>
<tr>
<td>46%</td>
<td>36.8%</td>
<td>926</td>
<td>1238</td>
</tr>
<tr>
<td>48%</td>
<td>38.4%</td>
<td>860</td>
<td>1148</td>
</tr>
<tr>
<td>50%</td>
<td>40%</td>
<td>798</td>
<td>1068</td>
</tr>
</tbody>
</table>

We will adopt a target sample size of 1334, which will give 90% power to detect a risk ratio of 0.8 if the placebo group mortality rate is 44%, over 85% power if it is 40%, and more than 90% if it exceeds 44%. The 28-day mortality in the placebo group will be monitored (via the DMEC), to ascertain whether the assumptions made in the sample size calculations are correct. If not, the DMEC will advise on modification to the sample size.

**4.2 Statistical Analysis**

**4.2.1 General Analysis**

All analyses will be by intention to treat i.e. all patients will be analysed in their randomised group regardless of the treatment actually received, and we will seek to include all randomised patients in the analyses. The primary outcome and other dichotomous outcomes will be compared using risk ratios and 95% confidence intervals. Time to event outcomes such as length of stay and will use survival analysis techniques and compare the groups using hazard ratios and 95% confidence intervals.

A detailed Statistical Analysis Plan will be written by the trial statisticians and approved by the DMEC before the end of the trial.

**4.2.2 Subgroup Analysis**

Subgroup analyses will use a statistical test for interaction and will be reported using 99% CI.

Four subgroup analyses are pre-specified, stratifying by:

1. APACHE II score at ICU admission: 0-16, 17-21, 22-26 and 27-49.
2. Severity of hypoxaemia; the lowest PaO$_2$/FiO$_2$ ratio between onset of ARDS and randomisation of ≤6.7, 6.8-13.2, ≥13.3kPa.
3. Age: ≤64, 65-84 and ≥85 years.
4. Direct versus indirect aetiology of ARDS.

**4.2.3 Frequency of Analyses**

Interim analyses will be conducted every 12 months during the period of recruitment, or more frequently if requested by the DMEC.
4.3 Economic Evaluation

4.3.1 Objective
To calculate the expected incremental cost effectiveness of IV salbutamol compared to standard care in the treatment of patients with ARDS, admitted to ICUs in the UK.

4.3.2 Economic Analyses
Two economic analyses will be undertaken:

1. A within-trial cost effectiveness analysis comparing the costs and outcomes of patients in each arm of the trial at 12 months.

The perspective for this analysis will be that of the NHS and Social Services. The primary outcome for this analysis will be the Quality Adjusted Life Years (QALY’s). Utilities will be measured using the EQ-5D at 6 and 12 months follow-up. Within ICU resource use will be identified through a detailed costing study undertaken at a sample of ICUs recruiting to the trial. Use of other hospital services will be abstracted from the trial CRFs. Use of primary, community and social care services will be recorded via a patient diary completed at six and 12 months follow-up. Particular effort will be made to identify place of residence at 12 months follow-up and whether this is funded by health, social services or privately. Out of pocket expenditure and time away from work data will also be collected using the same patient diary. Unit costs will be obtained from national sources such as the NHS reference costs and the PSSRU Unit Costs of Health and Social Care. Where national costs are not available, unit costs will be identified in consultation with finance departments of trusts recruiting to the trial. Parameter uncertainty will be addressed using probabilistic sensitivity analysis. Outputs from the analysis will include the expected incremental cost effectiveness ratio (ICER), a scatterplot on the cost effectiveness plane, cost effectiveness acceptability curve and incremental net benefit assuming lambda=£20,000 per QALY.

2. As there is potential for a difference in mortality between the groups, a lifetime horizon is required to fully capture the cost and benefits of IV salbutamol compared to usual care. Therefore, we will construct a cost effectiveness model with a lifetime time horizon. This will model the expected long term difference in QALY’s lived and health and social care resource utilised by two hypothetical cohorts of patients with ARDS; one treated with IV salbutamol the other not. The age distribution of these cohorts will reflect the age profile of ARDS patients actually seen in UK ICUs. Life expectancy post hospital discharge will be modeled using national age specific life expectancy data adjusted to reflect published evidence on the reduced life expectancy of ICU ‘survivors’. Long-term quality of life will be estimated using published age-specific utility data adjusted to reflect any published evidence of a divergence in health related quality of life in ICU ‘survivors’. In the absence of evidence to the contrary, the model will assume that the treatment modality does not impact upon the long terms non-ARDS-related health care costs. Costs and outcomes will be discounted in line with best practice recommendations at the time of the analysis. Parameter uncertainty will be addressed using probabilistic sensitivity analysis. Outputs from the analysis will include the expected ICER, a scatterplot on the cost effectiveness plane, cost effectiveness acceptability curve and incremental net benefit assuming lambda=£20,000 per QALY.
4.4 Publication of Results

The success of the trial depends on the collaboration of doctors, nurses and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial office team, and the final version will be agreed by the Steering Committee before submission for publication, on behalf of the collaboration.

Due to limited resources, it will be not be possible to provide each surviving patient with a personal copy of the results of the trial. If the patients require a copy of the results they should contact the Principal Investigator.

5. Trial Organisation

5.1 Sponsor

The Heart of England NHS Foundation Trust acted as sponsor for the pilot trial. The Heart of England Foundation NHS Trust and University of Warwick will act as co-sponsors for the main trial.

Local agreements will be drawn up with individual participating hospitals to ensure that Investigators and patients are indemnified for against negligent harm.

5.2 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced critical care personnel and trialists as well as a ‘lay’ representative. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMEC
- Informing and advising on all aspects of the trial

5.3 Data Monitoring and Ethics Committee (DMEC)

A DMEC will be appointed comprising two clinicians with experience in undertaking clinical trials / caring for critically ill patients and a statistician who are independent of the trial.

During the period of recruitment into the trial, interim analyses of the proportion of patients alive at 28 days and analyses of deaths from all causes at 28 days will be supplied, in strict confidence, to the chairman of the DMEC, along with any other analyses that the committee may request. The intervals for these analyses will be determined by the committee.
The DMEC will advise the Chairman of the Steering Committee if, in their view, the randomised comparisons have provided both (i) 'proof beyond reasonable doubt' that for all, or some, the treatment is clearly indicated or clearly contra-indicated and (ii) evidence that might reasonably be expected to materially influence future patient management.

Following a report from the DMEC, the Steering Committee will decide what actions, if any, are required. Unless the DMEC request cessation of the trial the Steering Committee and the collaborators will remain ignorant of the interim results.

5.4 Administration

The trial will be co-ordinated at the Warwick Medical School Clinical Trials Unit with support from the West Midlands Critical Care Research Network and Intensive Care Society Clinical Trials Group.

All day-to-day co-ordination of the trial will be the responsibility of the trial manager. All clinical co-ordination of the trial will be the responsibility of Professor Fang Gao.

The trial is managed by a multi-disciplinary team (page 3).

The trial office team will assist and facilitate the setting up of centres wishing to collaborate in the trial. In addition the trial office team will:

- Distribute the standardised data collection forms to collaborators
- Organise the telephone randomisation service for formal trial entry
- Monitor the collection of data, process data and seek missing data
- Train local staff with regards to data collection
- Ensure the confidentiality and security of all trial forms and data
- Conduct extensive data checking and cleaning
- Organise any interim and main analyses
- Organise Steering Committee, DMEC and Collaborators meetings

The trial office will receive completed data forms, via the postal service. Upon receipt, data forms will be checked for completeness and entered into a trial-dedicated computer programme which will check the data validity.

Patient confidentiality will be maintained at every stage and we comply with the Data Protection Act (1998).

5.5 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to patients by the design of the research protocol.
5.6 Monitoring and Safety Procedures

5.6.1 Safety and Well-being of Trial Patients

The safety and well-being of trial patients are protected by implementation of the sponsoring organisation’s Standard Operating Procedures (SOP’s) as set out in the Research Governance Framework and The Medicines for Human Use (Clinical Trials) Regulations 2004.

Individual sites will ensure that all investigators are able to demonstrate that they are qualified by education, training and experience to fulfill their roles. Systems and procedures are in place which can assure the quality of every aspect of the trial.

If new safety information becomes available, trial patient or personal legal representative will be informed of this and asked if they wish to continue in the trial. If the patient continues in the trial, a revised Patient Information Sheet and a new Consent Form will require completion.

Early termination of the trial in response to safety issues will be addressed via the DMEC.

Day to day management of the trial will be undertaken via a Trial Management group which includes the Chief Investigator. They will meet on a regular basis to discuss trial issues.

5.6.2 Safety of Investigators

Each Trust and The University of Warwick has Health and Safety Policies applicable to all employees. All personnel should also ensure they adhere to any other Health and Safety Regulations relating to their area of work. The Principal Investigator at each site will ensure that all personnel involved in the trial have been appropriately and adequately trained to undertake their specific tasks.

As the trial fits closely to standard practice, there are few risks identified which are hazardous to Investigators. Individual sites will be responsible for ensuring all staff have received Good Clinical Practice (GCP) training prior to start up.

5.6.3 Monitoring of Trial Conduct

The Trial Manager and Recruitment Facilitators will undertake site visits to ensure that the trial protocol is adhered to and that necessary paperwork (CRF’s, Patient Consent) are being completed appropriately.

5.6.4 Ethics and Regulatory Approval

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Approval from a Multi-Centre Research Ethics Committee (MREC) approval and Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) are needed before the start of the trial.

Following detailed discussion of the trial, written, informed consent will be obtained from each patient. In line with The Medicines and For Human Use (Clinical Trials) Regulations 2004 and to comply with the Research Governance Framework, consenting processes are standardised and will be reinforced via training prior to trial start up.
The trial is registered with the International Standard Randomised Controlled Trial Number register, number ISRCTN38366450.

The trial has been registered with the UK National Institute for Health Research (NIHR) Clinical Research Portfolio. In order that the trial remains on the NIHR Portfolio and receives the appropriate level of support through the relevant Local Research Network, accrual data on patient recruitment will be forwarded to the UKCRN Co-ordinating Centre on a monthly basis from the Trial Co-ordinating Centre.
Reference List


Ref Type: Personal Communication


(49) The ARDS Network Clinical Coordinating Center. ARDSNet definitions and recommendations. 2005.
Ref Type: Report

APPENDIX 1: Literature search: Beta Agonists in ARDS

<table>
<thead>
<tr>
<th>Authors</th>
<th>Pesenti[	extsuperscript{30}]</th>
<th>Wright[	extsuperscript{50}]</th>
<th>Morina[	extsuperscript{29}]</th>
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<td>66% placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50.0% high dose arm</td>
<td>58% salbutamol</td>
</tr>
<tr>
<td>Complications</td>
<td>None reported</td>
<td>Tachycardia and hypertension</td>
<td>None reported</td>
<td>None reported</td>
<td>Trend to greater tachycardia and arrhythmia in Salbutamol arm</td>
</tr>
</tbody>
</table>
APPENDIX 2: Child-Pugh Classification


The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

<table>
<thead>
<tr>
<th></th>
<th>Points scored</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Serum bilirubin µmol/l</td>
<td>&lt;35</td>
</tr>
<tr>
<td>Serum albumin g/l</td>
<td>&gt;35</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Coagulation</td>
<td>PT secs. prolonged</td>
</tr>
<tr>
<td></td>
<td>INR</td>
</tr>
</tbody>
</table>

Grade A: 5-6 points
Grade B: 7-9 points
Grade C: 10-15 points

Encephalopathy grades are scored as follows:

Grade 1 - Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition.
Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior; impaired performance of subtraction
Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation
Grade 4 - Coma (unresponsive to verbal or noxious stimuli).
# APPENDIX 3: Summary of Product Characteristics

**Ventolin Solution for IV Infusion**

## Table of Contents

1. **NAME OF THE MEDICINAL PRODUCT**
   - Ventolin\textsuperscript{TM} Solution for Intravenous Infusion 5mg in 5ml (1mg/ml).

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
   - Ventolin Solution for Intravenous Infusion 5mg in 5ml (1mg/ml) is presented as ampoules of 5ml, each containing 5mg salbutamol as Salbutamol Sulphate BP in a sterile isotonic solution.

3. **PHARMACEUTICAL FORM**
   - Clear, colourless or pale straw-coloured solution for intravenous infusion.

4. **CLINICAL PARTICULARS**

   4.1 **Therapeutic indications**
   Ventolin Solution for Intravenous Infusion should be administered under the direction of a physician. It is indicated for two distinct clinical situations:
   a) For the relief of severe bronchospasm.
   b) In the management of premature labour; to arrest uncomplicated labour between 24 and 33 weeks of gestation in patients with no medical or obstetric contra-indication to...
tocolytic therapy. Data suggest that the main effect of tocolytic therapy is a delay in delivery of up to 48 hours. This delay may be used to administer glucocorticoids or to implement other measures known to improve perinatal health.

4.2 Posology and method of administration
Ventolin Solution for Intravenous Infusion is used to prepare an infusion solution. It should not be injected undiluted. Ventolin Solution for Intravenous Infusion should not be administered in the same syringe or infusion as any other medication.

1) In severe bronchospasm.
Adults: A suitable solution for infusion providing 10 micrograms salbutamol/ml is prepared by diluting 5ml Ventolin Solution for Intravenous Infusion to 500ml with an infusion solution such as Sodium Chloride and Dextrose Injection BP. Other suitable diluents are Water for Injections BP, Sodium Chloride Injection BP or Dextrose Injection BP.
Infusion rates providing 3 to 20 micrograms salbutamol/minute (0.3 to 2ml/minute of the above infusion solution) are usually adequate. Higher doses have been used with success in patients with respiratory failure. Children: There are insufficient data to recommend a dosage regime for routine use.

2. In the management of premature labour.
The infusion, prepared as described below, should be administered as early as possible after the diagnosis of premature labour, and after evaluation of the patient to eliminate any contra-indications to the use of salbutamol (see Contra-indications). During infusion the maternal pulse rate should be monitored and the infusion rate adjusted to avoid excessive maternal heart rate (above 140 beats/minute).
It is essential that the volume of infusion fluid is kept to a minimum to control the level of hydration and so avoid the risk of maternal pulmonary oedema (see Undesirable effects). A controlled infusion device, preferably a syringe pump, should be used.
Infusion rates providing 10 to 45 micrograms salbutamol/minute are generally adequate to control uterine contractions. A starting rate of 10 micrograms/minute is recommended, increasing the rate at 10-minute intervals until there is evidence of patient response shown by diminution in strength, frequency or duration of contractions. Thereafter, the infusion rate may be increased slowly until contractions cease. Once uterine contractions have ceased the infusion rate should be maintained at the same level for one hour and then reduced by 50% decrements at six hourly intervals. If labour progresses despite treatment the infusion should be stopped. If contractions have been successfully inhibited by the infusion, treatment may be continued orally with Ventolin Tablets 4mg given three or four times daily.

Dilution: The recommended diluent is 5% Dextrose (see precautions for use in diabetic patients).
For use in a syringe pump: Prepare a solution providing 200 micrograms salbutamol/ml by diluting 10ml Ventolin Solution for Intravenous Infusion with 40ml diluent. An infusion rate of 10 to 45 micrograms/minute is equivalent to 0.05 to 0.225ml/minute of this solution.
Other infusion methods: Prepare a solution providing 20 micrograms salbutamol/ml by diluting 10ml Ventolin Solution for Intravenous Infusion with 490ml diluent. An infusion rate of 10 to 45 micrograms/minute is equivalent to 0.5 to 2.25ml/minute of this solution.

Instructions to open the ampoule
Ampoules are equipped with the OPC (One Point Cut) opening system and must be opened using the following instructions:
• hold with the hand the bottom part of the ampoule as indicated in picture 1
• put the other hand on the top of the ampoule positioning the thumb above the coloured point and press as indicated in picture 2
Picture 1
4.3 Contraindications

Although Ventolin Solution for Intravenous Infusion and occasionally salbutamol tablets, are used in the management of premature labour uncomplicated by conditions such as placenta praevia, ante-partum haemorrhage or toxaemia of pregnancy, salbutamol preparations should not be used for threatened abortion. Ventolin Solution for Intravenous Infusion is contra-indicated in patients with a history of hypersensitivity to any of the components. Salbutamol should not be used as a tocolytic agent in patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease.

4.4 Special warnings and precautions for use

Bronchodilators should not be the only or main treatment in patients with severe or unstable asthma. Severe asthma requires regular medical assessment, including lung-function testing, as patients are at risk of severe attacks and even death. Physicians should consider using the maximum recommended dose of inhaled corticosteroid and/or oral corticosteroid therapy in these patients. The dosage or frequency of administration should only be increased on medical advice. Patients being treated with Ventolin Solution for Intravenous Infusion may also be receiving short-acting inhaled bronchodilators to relieve symptoms. Increasing use of bronchodilators, in particular short-acting inhaled $\beta_2$-agonists to relieve symptoms, indicates deterioration of asthma control. The patient should be instructed to seek medical advice if short-acting relief bronchodilator treatment becomes less effective, or more inhalations than usual are required. In this situation the patient should be assessed
and consideration given to the need for increased anti-inflammatory therapy (e.g. higher doses of inhaled corticosteroid or a course of oral corticosteroid). Severe exacerbations of asthma must be treated in the normal way. The use of Ventolin Solution for Intravenous Infusion in the treatment of severe bronchospasm does not obviate the requirement for corticosteroid therapy as appropriate. When practicable, administration of oxygen concurrently with parenteral Ventolin is recommended, particularly when it is given by intravenous infusion to hypoxic patients. In common with other β-adrenoceptor agonists, salbutamol can induce reversible metabolic changes such as hypokalaemia and increased blood glucose levels. Diabetic patients may be unable to compensate for the increase in blood glucose and the development of ketoacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

Therefore, diabetic patients and those concurrently receiving corticosteroids should be monitored frequently during intravenous infusion of Ventolin so that remedial steps (e.g. an increase in insulin dosage) can be taken to counter any metabolic change occurring. For these patients it may be preferable to dilute Ventolin Solution for Intravenous Infusion in Sodium Chloride Injection BP rather than in diluents containing dextrose. Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of myocardial ischaemia associated with salbutamol.

Tocolysis
Salbutamol should be used with caution in tocolysis and supervision of cardiorespiratory function, including ECG monitoring, should be considered. Treatment should be discontinued if signs of myocardial ischaemia (such as chest pain or ECG changes) develop. Salbutamol should not be used as a tocolytic agent in patients with significant risk factors for or pre-existing heart disease (see section 4.3).

Respiratory indications
Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving salbutamol should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Salbutamol should be administered cautiously to patients suffering from thyrotoxicosis. Potentially serious hypokalaemia may result from β2-agonist therapy, mainly from parenteral and nebulised administration. Particular caution is advised in acute severe asthma as this effect may be potentiated by hypoxia and by concomitant treatment with xanthine derivatives, steroids and diuretics. Serum potassium levels should be monitored in such situations.

As maternal pulmonary oedema has been reported during or following treatment of premature labour with β2-agonists, careful attention should be given to fluid balance and cardio-respiratory function monitored. In patients being treated for premature labour by intravenous infusion of salbutamol, increases in maternal heart rate of the order of 20 to 50 beats per minute usually accompany the infusion. The maternal pulse rate should be monitored and not normally allowed to exceed a steady rate of 140 beats per minute. Maternal blood pressure may fall slightly during the infusion; the effect being greater on diastolic than on systolic pressure. Falls in diastolic pressure are usually within the range of 10 to 20mmHg. The effect of infusion on fetal heart rate is less marked, but increases of up to 20 beats per minute may occur. In the treatment of premature labour, before Ventolin Solution for Intravenous Infusion is given to any patient with known heart disease, an adequate assessment of the patient's cardiovascular status should be made by a physician experienced in cardiology. In order to minimise the risk of hypotension associated with tocolytic therapy, special care should be taken to avoid caval compression by keeping the patient in the left or right lateral positions throughout the infusion.

4.5 Interaction with other medicinal products and other forms of interaction
Ventolin Solution for Intravenous Infusion should not be administered in the same syringe or infusion as any other medication. Salbutamol and non-selective β-blocking drugs such as propranolol, should not usually be prescribed together.

4.6 Pregnancy and lactation
Administration of drugs during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus. As with the majority of drugs, there is little published evidence of the safety of salbutamol in the early stages of human pregnancy, but in animal studies there was evidence of some harmful effects on the fetus at very high dose levels. As salbutamol is probably secreted in breast milk, its use in nursing mothers requires careful consideration. It is not known whether salbutamol has a harmful effect on the neonate, and so its use should be restricted to situations where it is felt that the expected benefit to the mother is likely to outweigh any potential risk to the neonate.

4.7 Effects on ability to drive and use machines
None reported.

4.8 Undesirable effects
Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse have been reported very rarely. Enhancement of physiological tremor may occur with Ventolin Solution for Intravenous Infusion. This effect is caused by a direct action on skeletal muscle and is common to all β-adrenergic stimulants. Tachycardia, with or without dilatation of peripheral arterioles leading to a small reduction in arterial pressure, may occur. Increases in heart rate are more likely to occur in patients with normal heart rates and these increases are dose-dependent. In patients with pre-existing sinus tachycardia, especially those in status asthmaticus, the heart rate tends to fall as the condition of the patient improves. In common with other β2-agonists, cardiac arrhythmias (including atrial fibrillation, Supraventricular tachycardia and extrasystoles) have been reported in association with the use of salbutamol, usually in susceptible patients. Maternal pulmonary oedema has been reported in association with use of β-agonists, including salbutamol, for the management of premature labour; in some cases this has proved fatal. Predisposing factors include fluid overload, multiple pregnancy, pre-existing cardiac disease and maternal infection. Close monitoring of the patient's state of hydration is essential. If signs of pulmonary oedema develop (e.g. cough, shortness of breath), treatment should be discontinued immediately and diuretic therapy instituted. Headaches have occasionally been reported. There have been very rare reports of muscle cramps. Potentially serious hypokalaemia may result from β2-agonist therapy. In the management of premature labour, intravenous infusion of Ventolin has occasionally been associated with nausea, vomiting and headaches.

Respiratory indications:

Unknown: Myocardial ischaemia* (see section 4.4)

Obstetric indications:

Uncommon: Myocardial ischaemia**
* reported spontaneously in post-marketing data therefore frequency regarded as unknown.
** In the management of pre-term labour with salbutamol solution for infusion.

4.9 Overdose
The preferred antidote for overdosage with Ventolin is a cardio-selective beta-blocking agent but beta-blocking drugs should be used with caution in patients with a history of bronchospasm. Hypokalaemia may occur following overdose with salbutamol. Serum potassium levels should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Salbutamol is a selective $\beta_2$-agonist which acts on the $\beta_2$-adrenoceptors of the bronchi and uterus.

5.2 Pharmacokinetic properties
Salbutamol administered intravenously has a half-life of 4 to 6 hours and is cleared partly renally and partly by metabolism to the inactive 4'-0-sulphate (phenolic sulphate) which is also excreted primarily in the urine. The faeces are a minor route of excretion. Most of a dose of salbutamol given intravenously, orally or by inhalation is excreted within 72 hours. Salbutamol is bound to plasma proteins to the extent of 10%.

5.3 Preclinical safety data
No additional preclinical safety data are included here.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride, sodium hydroxide, sulphuric acid and Water for Injections.

6.2 Incompatibilities
None stated.

6.3 Shelf life
36 months.
24 hours after mixing with infusion fluids.

6.4 Special precautions for storage
Store below 30°C and keep container in the outer carton.

6.5 Nature and contents of container
Clear, neutral glass ampoules, available in boxes of 10 ampoules or 5 ampoules.

6.6 Special precautions for disposal and other handling
Ventolin Solution for Intravenous Infusion must be diluted before use. The recommended diluents are Water for Injections BP, Sodium Chloride Injection BP, Sodium Chloride and Dextrose Injection BP and Dextrose Injection BP. (See Posology and method of administration.)
All unused admixtures of Ventolin Solution for Intravenous Infusion with infusion fluids should be discarded twenty-four hours after preparation.

Administrative Data
7. MARKETING AUTHORISATION HOLDER
Glaxo Wellcome UK Ltd,
trading as Allen & Hanburys,
Stockley Park West,
Uxbridge,
Middlesex,
UB11 1BT.
8. MARKETING AUTHORISATION NUMBER(S)
   PL 10949/0087

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   11 September 2000

10. DATE OF REVISION OF THE TEXT
    5 June 2007

11. Legal Status
    POM.
    Ventolin™ is a trade mark of the Glaxo Wellcome Group of Companies
Translational Research Project version June 2007
For Collection and Use of Human Biological samples
(Protocol Amendment 2: Approved 29th June 2007)

The Translation Research Project will only be undertaken in selected centres by prior arrangement with the Sponsors.

Background

The pathophysiological processes involved in ARDS are complex and incompletely understood. The BALTI-2 trial provides a unique opportunity to investigate the inflammatory and repair processes involved in ARDS and to elucidate the potential mechanisms through which beta agonists function in this condition.

The decline in extravascular lung water found in the salbutamol arm of BALTI 1 did not occur as expected within a matter of hours of the onset of treatment, it was instead delayed for 72 hours. We hypothesise that this was due to ongoing alveolar flooding through a damaged alveolar capillary barrier exceeding the ability of the alveolar epithelium to clear fluid even with beta agonists augmentation.

Previous data have suggested that beta agonists may have a role to play in promoting repair of the alveolar capillary barrier. The drugs have an effect both on reducing endothelial permeability but may also promote alveolar repair. Preliminary data obtained from the BALTI-1 study support this hypothesis in that we were able to demonstrate a significant reduction in alveolar capillary permeability (measured by PiCCO permeability index and protein selectivity in BAL fluid). Moreover, lavage fluid from patients treated in the salbutamol arm stimulated wound repair in an in-vitro epithelial cell lung injury model.

Aim of Sub Study

The aim of the genetic study is to investigate the contribution of polymorphisms on the beta agonist receptor to the rate of alveolar fluid clearance induced by salbutamol. Recently it has become apparent that single nucleotide polymorphisms (SNPs) of the β2 adrenoceptor gene contain haplotypes. 13 SNPs are organised into only 12 haplotypes out of 8192 statistically possible combinations. These haplotypes are functionally important in both normal individuals and asthmatics. The purpose of this research is to determine if β2-adrenoceptor haplotype predisposes sepsis patients to lung injury and whether the polymorphisms help determine any response to salbutamol. This research will also address whether these genetic differences remain functionally active by looking at β2 receptor expression, salbutamol induced cAMP production, and salbutamol induced L-selectin shedding in circulating monocytes.

Additional interventions required for this sub-study

This sub-study will require the collection and storage of blood and bronchoalveolar lavage fluid samples. This will be undertaken at centres that have the necessary expertise and processing facilities (e.g. University Hospital Birmingham and Heart of England NHS trust). Blood samples will be obtained from existing indwelling catheters and so will be a painless procedure. Bronchoalveolar lavage (lung fluid sampling) is routinely undertaken in critically ill patients with ARDS to look for evidence of infection. Our previous experience suggests that positive culture results arise from 1/3 of samples despite the use of antibiotics. Patients
will be already heavily sedated due to their underlying medical condition so the procedure will not cause discomfort or distress.

Blood (30mls) and lavage fluid will be collected on days 0, 4 and 7 when possible. Lavage fluid will also be sent to the NHS microbiology laboratory to allow clinical evaluation for infection. The average duration of ventilation for ARDS exceeds 7 days. The small number of patients that may have recovered and are no longer on a ventilator will only have blood samples collected.

Part of the blood samples collected will be processed to extract genetic material to investigate the impact of genetic make up on response to treatment and recovery from ARDS. Separate consent will be gained for the storage of genetic material.

Reference List


