NETSCC, HTA

22 June 2010

MAGnesium NEbuliser Trial In Children (MAGNETIC) – A randomised, placebo controlled study of nebulised magnesium in acute severe asthma in children.

Version 6.1, 18 January 2010

Identifying Numbers: SPON408-07
HTA 05/503/10
ISRCTN81456894
EudraCT 2007-006227-12

Authorised on behalf of the Sponsor:

Signed: _____ Date: 19/1/10

Name
Title

Dr Kathryn Pittard Davies
Deputy Director and Head of Research Policy and Management
Research and Commercial Division
Cardiff University

General Information

This document describes the MAGNETIC trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Medicines for Children Research Network Clinical Trials Unit [MCRN CTU], Liverpool), using email (magnetic@mcrnctu.org.uk) to confirm they have the most up to date version of the protocol. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via the MCRN CTU.

Statement of Compliance

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, MCRN CTU Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments.

Contact Details: Institutions

Funder:	Sponsor:	Clinical Trials Unit:
The NHS R&D National Coordinating Centre for Health Technology Assessment Mailpoint 728, Boldrewood University of Southampton Bassett Crescent East Southampton SO16 7PX Tel: 023 8059 5586 Fax: 023 8059 5639 Email: hta@hta.ac.uk	Cardiff University Cardiff Wales CF10 3XQ UK Tel: 029 208 79274 Fax: 029 208 79280 Email: davieskp2@cardiff.ac.uk	Medicines for Children Research Network Clinical Trials Unit (MCRN CTU) Institute of Child Health Royal Liverpool Children's Hospital, Alder Hey Liverpool L12 2AP Tel: 0151 282 4724 Fax: 0151 282 4721 Email: ctu@mcrn.org.uk Director: Professor Paula Williamson, prw@liv.ac.uk

Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**	**Medical Expert who will Advise on Safety Reports in the absence of the CI:**
Dr Kathy Pittard Davies Deputy Director and Head of Research Policy and Management Research and Commercial Division Cardiff University 30-36 Newport Road Cardiff CF24 0DE Tel: 029 208 79274 Fax: 029 208 79280 Email: davieskp2@cardiff.ac.uk	Dr Colin Powell Senior Lecturer in Child Health and Honorary Consultant Paediatrician School of Medicine Cardiff University Children's Hospital for Wales Heath Park Cardiff CF14 4XW Tel: 00 44 (0) 2920747747 ex 8732 Fax: 00 44 (0) 2920744822 Email: Colin.Powell@CardiffandVale.wales.nhs.uk powellc7@cardiff.ac.uk	Dr Iolo Doull Consultant Respiratory Paediatrician Children's Hospital for Wales University Hospital of Wales Heath Park Cardiff CF14 4XW Tel: 00 44 (0) 2920747747 ex 8732 Fax: 00 44 (0) 2920744822 Email: Iolo.doull@uhw-tr.wales.nhs.uk
Head of Health Economics Team:	**Director of Clinical Trials Unit:**	**Head of Statistics Team for MAGNETIC trial:**
Dr Stavros Petrou Health Economics Research Centre University of Oxford Rosemary Rue Building Old Road Campus Headington Oxford OX3 7LF Tel: 00 44 (0) 1865 289278 Fax: 00 44 (0)1865 289701 Email: stavros.petrou@npeu.ox.ac.uk	Professor Paula Williamson Medicines for Children Clinical Trials Unit Institute of Child Health Royal Liverpool Children's Hospital, Alder Hey Liverpool L12 2AP Tel: 00 44 (0) 151 794 7069 Fax: 00 44 (0) 151 252 4721 Email: prw@liv.ac.uk	Professor Paula Williamson Medicines for Children Clinical Trials Unit Institute of Child Health Royal Liverpool Children's Hospital, Alder Hey Liverpool L12 2AP Tel: 00 44 (0) 151 794 7069 Fax: 00 44 (0) 151 282 4721 Email: prw@liv.ac.uk
Trial Health Economist:	**Head of Trial Management Team:**	**Trial Manager:**
Ms Angela Boland Liverpool Reviews and implementation Group Rm 2.61 Sherrington Building Ashton Street University of Liverpool Liverpool L69 3GE Tel: 00 44 (0)151 794 5067 Fax: 00 44 (0)151 794 5585 Email: a.boland@liv.ac.uk	Ms Helen Hickey Medicines for Children Clinical Trials Unit Institute of Child Health Royal Liverpool Children's Hospital, Alder Hey Liverpool L12 2AP Tel: 00 44 (0) 151 252 5240 Fax: 00 44 (0) 151 252 4721 Email: h.hickey@liv.ac.uk	Mr John Lowe Medicines for Children Clinical Trials Unit Institute of Child Health Royal Liverpool Children's Hospital, Alder Hey Liverpool L12 2AP Tel: 00 44 (0) 151 282 4522 Fax: 00 44 (0) 151 282 4721 Email: j.lowe2@liverpool.ac.uk

Independent Oversight Committees

Data and Safety Monitoring Committee		
Professor David R Jones Professor of Medical Statistics Adrian Building Room 218 University of Leicester University Road Leicester LE1 7RH Tel: 00 44 (0)116 229 7275 Fax: 00 44 (0)116 229 7250 Email: drj@leicester.ac.uk	Dr Peter Weller Consultant in Respiratory Medicine Department of Respiratory Medicine Birmingham's Children Hospital Steelhouse Lane Birmingham West Midlands B4 6NH Tel: 00 44 (0)121 333 8205 Fax: 00 44 (0)121 333 8201 Email: peter.weller@bch.nhs.uk	Dr Ian Balfour-Lynn Consultant in Paediatric Respiratory Medicine Royal Brompton Hospital Sydney Street London SW3 6NP Tel: 00 44 (0)20 7351 8509 Fax: 00 44 (0)20 7351 8763 Email: I.balfourlynn@ic.ac.uk

Independent members of the Trial Steering Committee*

Professor Ian Russell School of Medicine Swansea University Swansea SA2 8PP Tel: 00 44 (0)1792 602939 Fax: 00 44 (0)1792 513423 Email: i.t.russell@swansea.ac.uk	Dr Colin M Gelder Consultant Respiratory Physician University Hospital of Coventry & Warwickshire NHS Trust Coventry CV2 2DX Tel: 00 44 (0)2476967696 Fax: 00 44 (0) 2476967696 Email: colin.gelder@uhcw.nhs.uk	Dr Bob Dinwiddie Consultant Respiratory Paediatrician 1 Circle gardens Merton Park London SW19 3JX Tele: 00 44 (0)2085431833 Fax: 00 44 (0)2078138514 Email: rdinwiddie@doctors.org.uk	Mrs Sue Sibert (mother of child with asthma) 1 Church Avenue Penarth CF64 1AZ Tel: 02920711381 Email:jo.sibert@virgin.net

* Non-independent members listed in section 16.

Table of Contents

List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASS	Asthma Severity Score
BTS	British Thoracic Society
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
GCP	Good Clinical Practise
GP	General Practitioner
Hrs	Hours
ICH	International Conference on Harmonisation
IDSMC	Independent Data and Safety Monitoring Committee
IEC	Independent Ethics Committee
ISF	Investigator Site File
LREC	Local Research Ethics Committee
MCRN CTU	Medicines for Children Research Network Clinical Trials Unit
MHRA	Medicines and Healthcare Products Regulatory Authority
MREC	Multi-centre Research Ethics Committee
NCR	No Carbon Required
PIC	Patient Informed Consent
PI	Principal Investigator
PICU	Paediatric Intensive Care Unit
PISC	Patient Information Sheet and Consent Form
QoL	Quality of Life
R&D	Research & Development
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

1 PROTOCOL SUMMARY

Title: **MAGnesium NEbuliser Trial In Children (MAGNETIC)** – A randomised, placebo controlled study of nebulised magnesium in acute severe asthma in children

Phase: III

Population: The target population will be children (aged 2-15 years) presenting to hospital emergency departments and acute paediatric inpatient units with severe acute asthma

Number of Sites: 30 - 35 sites throughout the United Kingdom

Study Duration: Total study duration for each child is 240 minutes with a follow-up assessment after one month. Children will be screened at presentation, provided with information about the trial if potentially eligible, and treatment initiated according to BTS guidelines. Twenty minutes after presentation a trial screening assessment will be undertaken and written informed consent obtained for eligible patients. Trial assessments reflect those routinely performed in this patient population and will be completed at randomisation, prior to administration of randomised therapy, and at 20, 40, 60, 120, 180 and 240 minutes post randomisation. Follow-up questionnaires will be sent to the patient's home one month later.

Description of Agent/ Intervention: All patients recruited into the study will have standard treatment as per BTS guidelines, plus either nebulised magnesium sulphate or placebo.

Children aged 2-5 years will be randomised to receive nebulised salbutamol 2.5mg and ipratropium bromide 0.25mg mixed with either 2.5ml of isotonic magnesium sulphate (250mmol/L, tonicity 289 mOsm; 151 mg per dose) or 2.5ml of isotonic saline on three occasions at twenty-minute intervals.
Children 6 years and over will receive 5mg of nebulised salbutamol and ipratropium bromide 0.25mg mixed with either 2.5ml of isotonic magnesium sulphate (250mmol/L, tonicity 289 mOsm; 151 mg per dose) or 2.5ml of isotonic saline on three occasions at twenty-minute intervals.

Objectives:

Primary:

Does nebulised magnesium sulphate used as an adjunct to nebulised salbutamol and ipratropium bromide for one hour in children with acute severe asthma result in a clinical improvement in the asthma severity score (ASS) when compared to nebulised salbutamol, ipratropium bromide and placebo?

Secondary:

Does nebulised magnesium sulphate used as an adjunct to nebulised salbutamol and ipratropium bromide for one hour in children with acute severe asthma, when compared to nebulised salbutamol, ipratropium bromide and placebo, have an effect on:

a) Clinical outcomes in terms of additional treatment/management whilst in hospital and length of stay in hospital;

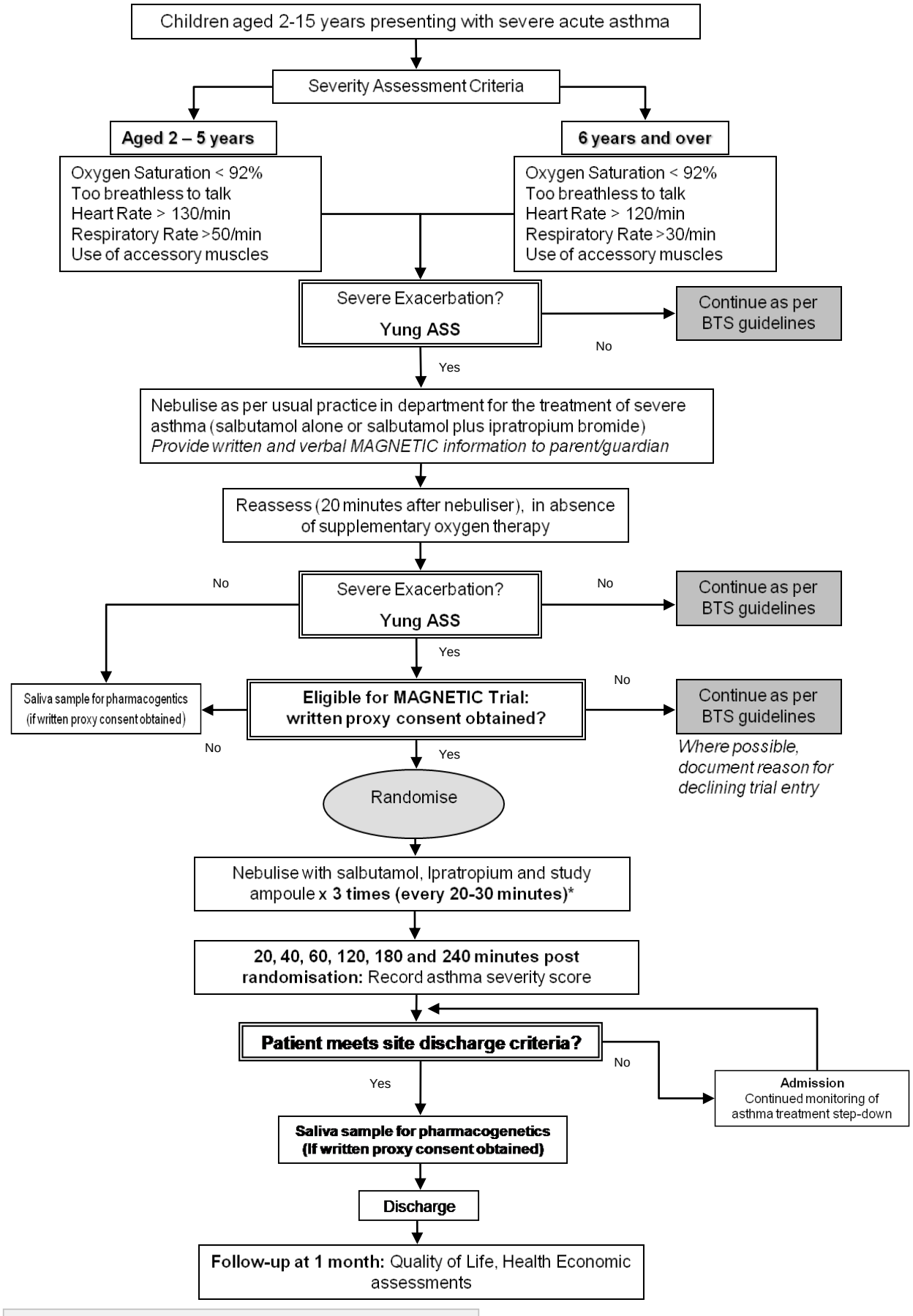
b) Patient outcomes in terms of quality of life, time off school and healthcare resource usage over the following month;

c) Parent outcomes in terms of time off work over the following month;

d) Overall cost to the NHS and society.

Protocol Summary - continued

Schematic of Study Design



2 BACKGROUND INFORMATION

2.1 Introduction

Acute asthma continues to be one of the main reasons for acute hospital admission in children and accounts for much morbidity, anxiety, stress, time off school and work for the families[17].

The Department of Health has targeted respiratory disease as an area for improved management. The British Thoracic Society and Scottish Intercollegiate Guideline Network (BTS/SIGN)[4] have developed an evidence-based guideline for the management of asthma. It offers comprehensive guidance on the acute and chronic management of asthma in children and adults, but the document highlights the paucity of good information to guide the management of a number of clinical situations. Nowhere is this more striking than in the management of acute asthma, where the recommended treatment for children (less than 16 years old) differs markedly from that for adults (16 years and older) - a reflection of the evidence base in the different age groups.

The guideline recommends that the initial management in children is inhaled ß2 agonists and ipratropium and systemic corticosteroids. Oxygen saturations of less than 92% while breathing room air at presentation is noted to be an indicator of more severe asthma, as is oxygen saturations of less than 92% at 20 minutes after inhaled ß2 agonists. For poorly responsive children over 5 years of age, clinicians are recommended to consider intravenous bronchodilator therapy - initially salbutamol followed by a continuous infusion, then intravenous aminophylline followed by infusion. There is little evidence as to the intravenous bronchodilator of choice. Furthermore, although it is recognised that intravenous magnesium sulphate is a safe treatment for acute asthma, with no side effects up to doses of 100mg/kg, it concedes that its place in management is not yet established. Magnesium sulphate does not appear to be recommended for children aged 5 years and younger. The BTS/SIGN guidelines recommend intravenous magnesium in the initial management of severe acute asthma in adults, but as there is a lack of evidence in children, it is not currently recommended as first line intravenous treatment in paediatric care[4].

The inhaled route for administering magnesium has also been examined; mainly in adult cohorts. These studies have demonstrated a good effect when magnesium is given via a nebuliser[8,11]. There are few paediatric data on the effect of nebulised magnesium sulphate[3]. The two paediatric studies, including 62 and 20 children respectively, of nebulised magnesium sulphate demonstrated equivocal results[10,12].

MAGNETIC is a randomised placebo controlled multicentre trial of the use of nebulised magnesium sulphate in severe acute asthma in childhood in patients who show a poor response to maximal conventional aerosol treatment.

2.2 Rationale

The use of magnesium for acute asthma was first described in 1936, and since then there has been increasing evidence for its use in adults with asthma. In vitro studies demonstrate an inhibitory effect of magnesium on contraction of bronchial smooth muscle, and the release of acetylcholine in cholinergic nerve terminals, and of histamine from mast cells. The recent acute asthma and magnesium study group has demonstrated its efficacy in severe acute asthma in adults[18]. In a multicentre randomised control study of 248 adults with acute asthma and a forced expiratory volume (FEV1) below 30% predicted, intravenous administration of 2mg of magnesium sulphate as an adjunct to the standard therapy resulted in significant benefit in FEV1 of nearly 5% compared to placebo. The effect appeared greatest in those with the most severe asthma, with a difference of 10% in FEV1 between magnesium and placebo treated groups. Intravenous administration of magnesium requires careful monitoring because peripheral vasodilatation and systolic hypotension can occur in association with flushing, nausea and venous phlebitis at the site of infusion. Consequently interest has grown in the use of nebulised magnesium in acute asthma. Magnesium

does not appear to act as a bronchodilator in stable asthma, but in acute exacerbations nebulised magnesium appears to have a bronchodilator response similar in magnitude to salbutamol[11]. Initial therapeutic trials of nebulised magnesium administered as an adjunct to nebulised salbutamol gave conflicting results. In a small study of 35 individuals, Nannini demonstrated a significantly greater improvement in peak expiratory flow rate at 20 minutes after administration in patients receiving nebulised magnesium in addition to nebulised salbutamol, compared to nebulised isotonic saline and salbutamol[13]. In contrast, Bessmertny could show no such benefit in 74 adults with moderately severe asthma[1]. A recent report in adults with a severe acute asthma with an FEV1 of less than 30% of predicted, thirty minutes after initial administration of salbutamol via a nebuliser, demonstrated a significant benefit in FEV_1 for those receiving magnesium sulphate compared to isotonic saline[8]. It is likely that this study will change the future management of acute asthma in adults in relation to nebulised magnesium sulphate.

There are only two paediatric nebulised magnesium studies and they both have methodological deficits[10,12]. However, nebulised magnesium appears to have a similar bronchodilator effect in acute asthma in childhood, although the magnitude and duration may not be as great as salbutamol when directly compared[12]. There appears to be an additive effect when inhaled magnesium is combined with salbutamol[10].

Meral examined two groups of 20 children, mean ages 10.6 and 11 years (range 8-13 years) with a severe exacerbation of asthma. In a randomised controlled study patients either received 2 ml of magnesium sulphate (280 mmol/L, 258 mOsm, ph 6.7) nebulised over 15 to 20 minutes or inhaled salbutamol (NB, no salbutamol was given in the magnesium group). Clinical score and PEFR were measured at 5, 15, 30, 60, 180, 240 and 360 minutes after treatment. Lung function at 5, 60 and 360 minutes was significantly greater in the salbutamol group[12]. This study had an unclear randomisation and blinding procedure, had a questionable outcome measure (due to the lack of reproducibility and reliability of peak expiratory flow rate [PEFR]) and unclear inclusion and exclusion criteria[6].

Mahajan examined 62 patients, aged 5-17 years with severe acute asthma, in a double blind randomised, placebo controlled study. Using FEV1 at 10 minutes and 20 minutes after treatment and admission rates as outcomes along with a clinical score, they administered 2.5 ml of isotonic magnesium (6.3% solution) with Albuterol (2.5 mg nebule) or Albuterol with normal saline. One dose of the study medication was used and they demonstrated a significant improvement in FEV1 at 10 and 20 minutes after treatment with magnesium[10]. This study only involved mild to moderate asthma and did not include the more severe exacerbations.

A recent Cochrane review of nebulised magnesium sulphate examined six trials, including these two paediatric studies, involving 296 patients. The overall conclusions were that the use of nebulised inhaled magnesium sulphate in addition to ß2 agonists in the treatment of an acute asthma exacerbation appears to have benefits with respect to improved pulmonary function. The benefit was significantly greater in more severe asthma exacerbations, but there were insufficient data, particularly in children. Most importantly there were no adverse events reported and so the other important conclusion was that nebulised magnesium treatment was safe[3].

2.3 Objectives

Primary Objective:
Does nebulised magnesium sulphate used as an adjunct to nebulised salbutamol and ipratropium bromide for one hour in children with severe asthma result in a clinical improvement when compared to nebulised salbutamol, ipratropium bromide and placebo?

Secondary Objective:
Does nebulised magnesium used as an adjunct to nebulised salbutamol and ipratropium bromide for one hour in children with severe asthma, when compared to nebulised salbutamol, ipratropium bromide and placebo, have an effect on:

a. Clinical outcomes in terms of additional treatment/management whilst in hospital, and length of stay in hospital.
b. Patient outcomes in terms of quality of life, time off school and healthcare resource usage over the following month
c. Parent outcomes in terms of time off work over the following month
d. Overall cost to the NHS and society

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

A Cochrane review[3] summarised the 6 published randomised controlled studies of nebulised magnesium in acute asthma involving 296 patients. Four studies compared nebulised magnesium sulphate with β_2-agonist versus β_2-agonist alone - the isotonic magnesium sulphate solution was administered together with salbutamol in the same nebuliser solution in three studies, and after salbutamol nebulisation in the other study. A total of three doses over one hour was administered in two studies, and a single dose in the other two studies. Two studies compared $MgSO_4$ alone versus β_2-agonist alone – one study compared a single dose of each, while the other compared 4 doses of each.

All 6 studies reported no serious adverse events in either arm. The risk of serious adverse events was low in both the studies comparing $MgSO_4$ to β_2-agonists (RD: 0.00; 95% CI: -0.11 to 0.11) or those comparing $MgSO_4$ with β_2-agonist to β_2-agonist alone (RD: 0.00; 95% CI: -0.03 to 0.03). The risk of less severe adverse events was low and appeared to be less likely in patients treated with $MgSO_4$ - either alone (RD: -0.17; 95% CI: -0.41 to 0.06) or in combination with β_2 agonists (RD: -0.09; 95% CI: -0.24 to 0.06).

A literature review (refer to investigators brochure for methodology) of the adverse effects of inhaled magnesium in children undertaken by the University of Liverpool identified 2 studies not included in the Cochrane review, containing at most 18 further children. There were no reported adverse events (table 1).

In the pilot study (EudraCT number: 2004-003825-29), 2 children (both of whom received magnesium sulphate) had mild adverse events. One child had transient facial flushing and although asymptomatic, a blood pressure reading appeared low. The blood pressure was immediately re-measured and was then normal. Another child had transient tingling of the fingers.

2.4.2 Known Potential Benefits

In a small study of 35 adult individuals, Nannini demonstrated a significantly greater improvement in peak expiratory flow rate at 20 minutes after administration in adult patients receiving nebulised magnesium in addition to nebulised salbutamol[13].

The Cochrane review[3] summarised the 6 published randomised controlled studies of nebulised magnesium in acute asthma involving 296 patients. There was heterogeneity between trials, but overall, there was a non significant improvement in pulmonary function between patients whose treatments included nebulised MgSO4 in addition to ß2-agonist (SMD: 0.23; 95% CI: -0.03 to 0.50; 4 studies), and hospitalizations were similar between the groups (RR: 0.69; 95% CI: 0.42 to 1.12; 3 studies). Subgroup analyses demonstrated significant differences in lung function improvements in severe asthmatics (SMD: 0.55; 95% CI: 0.12 to 0.98).

However only one study reported the effect of 3 doses of $MgSO_4$ nebulised with salbutamol in patients with severe asthma. In the study reported by Hughes three $MgSO_4$/salbutamol nebulisations were given at 30 minute intervals in adults with severe asthma, and resulted in a two-fold greater increase in FEV_1 than the same dose of salbutamol administered with isotonic saline nebuliser

solution, and this enhanced bronchodilator response was associated with a significant reduction in hospital admission rates (relative risk 0·61 [95% CI 0·37–0·99], p=0·04).

The systematic review also investigated the efficacy of nebulised magnesium in children. The findings are summarised in table 1:

Table 1: Risks and benefits identified in studies involving children included in systematic review

Study	Adverse events in MgSO4 group	Efficacy
Rolla 1987	Measured: not stated Reported: no mention of AE in results/ discussion	No difference in lung function; Improvement in airway responsiveness
Rolla 1988	Measured: not stated Reported: "no patient experienced side effects"	Inhaled doses >0.1 mmol led to improvement in bronchial hyper responsiveness
Meral 1996	Measured: "subjects were evaluated for possible adverse effects" Reported: In discussion - "No adverse reaction in either group as the heart rate and blood pressure did not change".	*PEFR*: Mg group better after 5 minutes, then back to pre-Mg measurement by 6 hours. Control group had sustained improvement at 6 hours. At 6 hours control group PEFR was better than Mg group. *Respiratory distress score*:No difference between groups
Mangat 1998	Measured:blood pressure, arrhythmia; hyporeflexia, respiratory depression Reported: (not stated whether these occurred in adults or children)- 1 transient hypotension (spontaneously resolved); no hyporeflexia	Patients treated with Nebulised MgSO4 improved in terms of bronchodilation and Fischl score. However, this effect was not significantly different to that of the group given nebulised salbutamol. Note: the study report does not report the paediatric results separately from the adult results
Mahajan 2004	Measured: tremors, headaches, nausea, vomiting, hyporeflexia Reported: "none of the patients in either group showed any side effects"	FEV1 absolute: Improvement at 10 minutes significantly better than in control group (p<0.03); at 20 minutes no difference between groups FEV1 % predicted: No difference between groups

In the pilot study (EudraCT number: 2004-003825-29), a total of 25 eligible patients were identified for inclusion into the study over a three month period. Of these, 17 gave informed consent to be randomised to receive nebulised magnesium or placebo in addition to salbutamol and ipratropium. All individuals received the treatment to which they were randomised. There were 7 patients randomised to active treatment and 10 patients randomised to placebo. There are insufficient numbers to make a comment about the efficacy of nebulised magnesium from the pilot study. There were no differences between the two groups when comparing the median ASS score after 3 nebulised treatments and the area under the curve of the Asthma Severity Score for the six time points (see appendix A for tables and plots).

3 SELECTION OF CENTRES/CLINICIANS

Each participating centre (and investigator) has been identified on the basis of:

- an institution with provision for emergency treatment of children and young people presenting with acute asthma symptoms
- having at least one lead clinician with a specific interest in, and responsibility for, supervising and managing children who present with acute exacerbations of asthma
- showing enthusiasm to participate in the study
- ensuring that sufficient time, staff and adequate facilities are available for the trial
- providing information to all supporting staff members involved with the trial or with other elements of the patient's management
- identifying that they will be able to recruit a specified target number of patients
- acknowledging and agreeing to conform to the administrative and ethical requirements and responsibilities of the study, including signing-up to Good Clinical Practice and other regulatory documentation

3.1 Centre/Clinician Inclusion Criteria

a. Positive Site Specific Assessment by LREC
b. Local R&D approval
c. Signed contract between site and sponsor
d. Receipt of evidence of completion of (a) and (b) by MCRN CTU
e. Completion and return of 'Signature and Delegation Log' to MCRN CTU.

3.2 Centre/Clinician Exclusion Criteria

a. Not meeting the inclusion criteria listed above

4 TRIAL DESIGN

A randomised, placebo controlled study of nebulised magnesium in acute severe asthma in children.

4.1 Primary Endpoint

The primary endpoint is the Asthma Severity Score (ASS) after 60 minutes of treatment.

4.2 Secondary Endpoint(s)

Clinical (during hospitalisation)

- 'stepping down' of treatment at one hour i.e. changed to having hourly treatment after the initial three, twenty-minute nebulisers
- number and frequency of additional salbutamol administrations
- length of stay in hospital
- requirement for intravenous bronchodilator treatment
- intubation and/or admission to a paediatric intensive care unit (PICU)

Patient outcomes at follow-up (1 month)

- Paediatric quality of life- PedsQL^{TM} asthma module parental report for all children and self-completion if aged over 5 years, EQ-5D
- Time off school/nursery
- Health care resource usage (e.g. GP visits, additional prescribing)

Parent outcomes at follow-up (1 month)

- Time off work (related to child's illness)

5 STUDY POPULATION

5.1 Inclusion Criteria

Severe acute asthma as defined by the BTS/ SIGN guidelines. [BTS 2003].

For children **6 years and older** severe asthma is based on at least one of the following criteria being met:

a. Oxygen saturations less than 92% while breathing room air
b. Too breathless to talk
c. Heart rate greater than 120 bpm
d. Respiratory rate greater than 30 breaths/min
e. Use of accessory neck muscles

For children aged **2-5 years of age**, severe asthma is based on at least one of the following criteria being met

a. Oxygen saturations less than 92% while breathing room air
b. Too breathless to talk
c. Heart rate greater than 130 bpm
d. Respiratory rate greater than 50 breaths/min
e. Use of accessory neck muscles

5.2 Exclusion Criteria

a. Coexisting respiratory disease such as cystic fibrosis or chronic lung disease of prematurity
b. Severe renal disease
c. Severe liver disease
d. Known to be pregnant
e. Known to have had a reaction to magnesium previously
f. Parents who are unable to give informed consent
g. Previously randomised into MAGNETIC trial
h. Patients who present with life threatening symptoms
i. Previously or currently involved with a trial of a medicinal product in the three months preceding screening

5.3 Patient Transfer and Withdrawal

5.3.1 Patient Transfers

Due to the nature of the trial, patients will have completed the clinical phase of the study after the initial hospital visit. In the event patients move from their current address during the weeks before follow up, they will be requested to inform the MCRN CTU of their change of address so that they can receive questionnaires as planned. A change of address card will be provided to facilitate this.

5.3.2 Withdrawal from Trial Intervention

Patients may be withdrawn from treatment for any of the following reasons:

a. Parent/ legal representative (or, where applicable, the patient) withdraws consent.
b. Unacceptable toxicity.
c. Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion.

Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up (see section 5.3.3). Following withdrawal from trial treatment patients will be treated according to usual local clinical practice. Details of reasons for withdrawal from the trial treatment will be recorded on the CRF.

5.3.3 Withdrawal from Trial Completely

Patients may withdraw from the trial at any stage and a withdrawal CRF should be completed. Data collected up to the time of their withdrawal from the study will be included in the analysis. If the patient explicitly states their wish not to contribute their data to the study, the MCRN CTU should be informed in writing by the responsible physician.

6 ENROLMENT AND RANDOMISATION

6.1 Screening

The start of screening will be defined as presentation at the participating site and the beginning of eligibility assessment. These assessments will be captured on the first page of the CRF. Due to the requirement to provide prompt treatment in an emergency setting, patient information and consent forms will be provided to the parent or legally acceptable representative (See Table 1: Schedule of Study Procedures) concurrently to screening assessments taking place.

Screening will include (at presentation to Accident & Emergency Department or Paediatric Assessment Unit):

- Confirmation that the patient is aged 2-15 years
- Assessment of asthma severity (based on age-specific BTS guidelines)
- Asthma Severity Score (ASS)
- Measure of blood pressure, respiration rate and oxygen saturations
- Collection of demographic information including:
    - Age of asthma onset
    - Current asthma medication
    - Duration of current exacerbation
    - Number of previous hospital admissions for asthma, including the number that resulted in admission to ICU
    - History of food allergy, hayfever and eczema

During the screening phase patients will receive an initial nebulised treatment of salbutamol or salbutamol plus ipratropium bromide (depending on current site practice). This will be recorded on the CRF. Any other medication given (such as oral steroids, or treatment given during transport to the hospital) will also be documented.

6.2 Randomisation

After completion of the screening phase, the patient will be re-assessed under BTS guidelines and the ASS completed. Blood pressure, respiration rate and oxygen saturations will also be measured. Provided they meet the inclusion criteria, and that written proxy consent has been obtained, the patient will be eligible for randomisation. The time of randomisation will be recorded on the CRF. Patients no longer meeting the criteria are excluded and will continue to be treated as per standard hospital practice. Patients who are randomised will have their contact details (name, address and telephone number) and GP details added to the CRF.

Trial treatment will begin as soon as possible after the initial nebuliser treatment has concluded and assessments have been performed. The clinician should ensure that the duration between obtaining consent, performing assessments and the start of trial treatment does not impact on the well-being of the participant. Treatment kits will be located in a locked cabinet in the department. Provisions should be made to ensure the trial medication is accessible to staff 24 hours a day. Kits will be assigned in sequential order. Details of randomised patients should be entered on the randomisation log kept in the Study Site File and on accountability logs kept with the supply of trial medication.

7 TRIAL TREATMENT/S

7.1 Introduction

This study is designed as a prospective, controlled, double-blind, multicentre, randomised clinical trial comparing the effects of magnesium sulphate versus placebo (isotonic saline) in children with severe acute asthma as defined by BTS guidelines; patients will be randomised to receive nebulised salbutamol 2.5mg (aged 2-5 years) or 5mg (aged 6 years and over) and ipratropium bromide 0.25mg mixed with either 2.5ml of isotonic magnesium sulphate (250mmol/L, tonicity 289 mOsm; 151mg per dose) or 2.5ml of isotonic saline on three occasions at 20 minute intervals.

7.2 Formulation, Packaging, Labelling, Storage and Stability

Supplies will be sourced from St Mary's Pharmaceutical Unit, Cardiff and Vale NHS Trust, who will provide labelled and blinded treatment kits following randomisation lists provided by the MCRN CTU. These will be QP released by from St Mary's Pharmaceutical Unit, Cardiff and Vale NHS Trust. Each will contain three 10ml bottles with 2.5ml magnesium sulphate solution or isotonic saline (placebo) in each bottle. Kits will have an expiry date of two years after manufacture.

Treatment kits will be received by the site pharmacy and dispensed in batches to the participating department where they will be stored in a locked cabinet at ≤25°C. Should there be a temperature excursion above 25°C, the affected kits must then only be stored in the department for a maximum period of three months from the date of the excursion at a temperature not exceeding 30°C. In the event the temperature exceeds 30°C, the affected kits must be withdrawn from use.

The cabinet will contain a calibrated maximum/minimum thermometer to monitor storage conditions. This should be checked daily and the results recorded on the log provided.

The Trial Manager will ensure sites have sufficient supplies based on recruitment projections and should be contacted regarding re-supplies.

7.2.1 Preparation, Dosage and Administration of Study Treatment/s

Patients will receive three consecutive trial treatments of 2.5ml magnesium sulphate solution or placebo at 20-30 minute intervals, interspersed with clinical assessments. Trial treatment will be directly added to a nebuliser containing salbutamol 2.5mg (2-5 years) or 5mg (6 years and over) and ipratropium bromide 0.25mg. No further preparation of the study medication is required. In the event that there is residual volume following 20 minutes of nebulisation, the remainder should be discarded so that assessments can be performed and the next trial treatment delivered as per the schedule outlined in section 8.1.

7.3 Dose Modifications

No dose modification of the study treatment is permitted and dosing will continue in the event of deterioration of the patient's condition unless cessation therapy is deemed necessary by the clinician, or if consent for the trial is withdrawn.

7.4 Accountability Procedures for Study Treatment/s

Site pharmacies will be supplied with sufficient supplies based on initial estimates of recruitment. The Trial Co-ordinator will be responsible for monitoring distribution and facilitate re-supplies where necessary. On receipt of study supplies, the site will fax a confirmation sheet back to the MCRN CTU. This will document that the correct number of treatment kits have been received. If the supplies are retained in the pharmacy, they should be subject to appropriate temperature monitoring as per individual site procedure. The kits will be dispensed to recruiting department and stored in a locked cabinet under the conditions outlined in section 7.2.
At closure of the trial, all used and unused treatment kits will be returned to the pharmacy for destruction.

7.5 Assessment of Compliance with Study Treatment/s

The CRF will record details of the compliance with the dosing schedule. In the event the treatment is not given, the reason will be documented on the CRF.

7.6 Concomitant Medications/Treatments

Additional medications used to treat exacerbation of the patient's condition or used to treat adverse events will be recorded on the concomitant medications page of the CRF. The reason for use, the drug, route of administration, dose and duration of use should be recorded.

7.6.1 Medications Permitted

After entry into the trial no other medications are permitted unless, in the opinion of the clinician, they are required to treat severe deterioration in the patient's condition or to treat adverse events.

7.6.2 Medications Not Permitted/ Precautions Required

No medications are contraindicated for use as a consequence of treatment with the study medication or comparator.

7.6.3 Data on Concomitant Medication

Concomitant medications will be record in the specified section of the CRF. The reason for use, the drug, route of administration, dose and duration of use should be noted.

7.7 Unblinding

7.7.1.1 Procedure

a. The decision to unblind a single case should be made when knowledge of an individual's allocated treatment is essential to enable treatment of serious adverse event/s.

b. Unblinding envelopes will be provided by the MCRN CTU and will contain details of the treatment allocation. These will be stored securely in an assigned place within the participating A&E department/ paediatric assessment unit.
c. Where possible, permission to unblind an individual case should be requested via the trial co-ordinator at MCRN CTU. Agreement of the Chief Investigator (Dr Colin Powell), or his agreed delegate, will then be sought.
d. If unblinding of an individual is deemed necessary, the responsible investigator will select the appropriate envelope to reveal the allocation details of an individual patient only and complete an unblinding CRF which will document:
    i. Date information needed
    ii. Detailed reason for unblinding
    iii. Identity of recipient of the unblinding information

    A copy of the unblinding CRF will be forwarded to the MCRN CTU within 24 hours.
e. The responsible investigator should ensure all necessary CRFs to time of unblinding are completed and submitted to MCRN CTU (if possible, completed *before* unblinding is performed)
f. All instances of unblinding should be recorded and reported in writing to the MCRN CTU by the local investigator, including the identity of all recipients of the unblinding information.
g. Allocation should not routinely be revealed to MCRN CTU personnel (not recorded on the unblinding CRF) unless the reason for unblinding meets the criteria as described in section 10.8.1

Accidental Unblinding

All instances of inadvertent unblinding should be recorded and reported in writing to the MCRN CTU by the local investigator. Reports to include:

1. Date of unblinding
2. Detailed explanation of circumstances
3. Recipients of the unblinding information
4. Action to prevent further occurrence

Allocation should not be routinely revealed to MCRN CTU personnel

At Trial Closure

The end of the trial will be considered as the date of the final database lock. In the event that the trial is closed prematurely by the trial steering committee, on the recommendation of the independent data and safety monitoring committee, for reasons such as clear differences between safety of trial treatments, the end of the trial will still be considered as the date of the final database lock. Upon trial closure the participating centres will return all unblinding envelopes, without breaking the seals to reveal allocation codes, to the MCRN CTU. MCRN CTU will notify local investigators in writing of unblinding information for patients under their care. A copy of this notification should be placed in the medical records and a copy retained in the site file. The local investigator is responsible for the decision as to whether participants should be informed about the treatment they received.

Individuals that have participated in a trial testing a medicinal product within the three months preceding screening will be ineligible for the MAGNETIC study. To avoid potentially confounding issues, ideally patients should not be recruited into other trials during the one month until final follow up. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the MAGNETIC trial this must first be discussed with the coordinating centre (MCRN CTU) who will contact the Chief Investigator (Dr Colin Powell).

8 ASSESSMENTS AND PROCEDURES

8.1 Schedule for Follow-up

Following randomisation, trial participants will be assessed over four hours as is usual clinical practice for this kind of episode. Follow up will continue for those patients who require admission after the initial four hours and will continue until discharge. There will be an additional, post discharge, follow-up at one month via questionnaires sent to the patient's home. Procedures should follow the timelines in table 2 and as listed below. Note that timepoints are for guidance however it is anticipated that timing of dosing and assessments may vary for some patients. The timing of the dose and timing of assessments will be recorded on the CRF.

1) Post randomisation (as soon as possible):
    a. One Vial from the treatment kit will be added to the nebuliser in conjunction with salbutamol 2.5mg or 5mg and ipratropium bromide 0.25mg and nebulised.

2) 20mins post randomisation:
    a. Conclude first nebuliser treatment
    b. Completion of ASS score (record time of assessment)
    c. Blood pressure, respiration rate and oxygen saturation
    d. Review of adverse events and concomitant medications
    e. Begin second nebuliser treatment (as for first dosing)

3) 40mins post randomisation:
    a. Conclude second nebuliser treatment
    b. Completion of ASS score (record time of assessment)
    c. Blood pressure, respiration rate and oxygen saturation
    d. Review of adverse events and concomitant medications
    e. Begin third nebuliser treatment (as for first dosing)

4) 60mins post randomisation:
    a. Conclude third nebuliser treatment
    b. Completion of ASS score (record time of assessment)
    c. Blood pressure, heart rate, respiration rate and oxygen saturation
    d. Review of adverse events and concomitant medications
    e. Treat as per usual practice

5) 120mins post randomisation:
    a. Completion of ASS score (record time of assessment)
    b. Blood pressure, respiration rate and oxygen saturation
    c. Review of adverse events and concomitant medications
    d. Treat as per usual practice

6) 180mins post randomisation:
    a. Completion of ASS score (record time of assessment)
    b. Blood pressure, respiration rate and oxygen saturation
    c. Review of adverse events and concomitant medications
    d. Treat as per usual practice

7) 240mins post randomisation:
    a. Completion of ASS score (record time of assessment)
    b. Blood pressure, respiration rate and oxygen saturation
    c. Review of adverse events and concomitant medications
    d. Treat as per usual practice

8) During admission (if applicable)
    a. Record of asthma medication (further salbutamol treatment/nebulisers/IV)
    b. Record of procedures/investigations (ventilation/surgery/other tests)
    c. Review of adverse events and concomitant medication

9) Before discharge:
    a. Review of adverse events and concomitant medications
    b. Saliva sample for pharmacogenetic substudy (provided written consent is obtained)
    c. Completion of study outcomes

10) 1 month follow up by post:
    a. Parents receive PedsQL asthma module to complete and return
    b. Children over 5 receive age-specific PedsQL asthma module to complete and return
    c. Parents receive the EQ-5D questionnaire to complete (on patient's behalf) and return
    d. Parents receive a trial specific health care resource utilisation questionnaire to complete and return

Table 2: Schedule of Study Procedures

Procedures		Screening	Randomisation*	20 minutes post Randomisation	40 minutes post Randomisation	60 minutes post Randomisation	120 minutes post Randomisation	180 minutes post Randomisation	240 minutes post Randomisation	During Admission##	Before discharge	1 month follow-up	Premature Discontinuation
Signed Consent Form			X										
Assessment of Eligibility Criteria		X	X										
Yung's Asthma Severity Score		X	X	X	X	X	X	X	X				X
Assignment to study treatment			X										
Review of Medical History		X	X										
Review of Concomitant Medications		X	X	X	X	X	X	X	X	X	X		X
Study Intervention**			X	X	X								
Blood pressure, SaO_2, respiration rate		X	X	X	X	X	X	X	X				
Saliva sample for pharmacogentic substudy#		(X)									(X)		
PedsQL™ Asthma Module												X	
EQ-5D												X	
Health Economics Questionnaires												X	
Physical Exam	Complete	X											X
	Symptom-Directed		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		
Assessment of Adverse Events				X	X	X	X	X	X	X	X		X

Patients not randomised to the trial will be asked to consent to the pharmacogenetic sub-study following screening. Randomised patients will be asked to consent to the sub study following scheduled follow up but before they are discharged.

X – Activities required

(X) – As indicated/appropriate.

*At randomisation, all procedures should be done before study intervention.

**Study Intervention – A maximum of 3 doses administered at 20-30 minute intervals. Trial treatment is administered in conjunction with nebulised salbutamol and ipratropium bromide.

If appropriate

8.2 Procedures for Assessing Efficacy

The ASS will be assessed using the most validated score, the Yung ASS[2,5,19] which comprises three clinical signs; wheezing, accessory muscle use and heart rate (Appendix A). The score has been validated as a measure of asthma severity in children, has been demonstrated to be reproducible and reliable[2] with good inter-observer agreement and correlates well with oxygen saturations and FEV_1[19]. This score is clinically easy to use and involves standard assessments, used routinely by medical and nursing staff while managing acute asthma. The ASS assessment should be carried out by a clinician, or by a nurse who in the opinion of the PI is appropriately trained to make the necessary observations, and who is trained in the use of a stethoscope to detect and assess respiratory wheeze. These individuals will be identified on the delegation of responsibilities log completed at each site. The assessor will also initial the CRF to document who performed the assessment.

8.3 Procedures for Assessing Safety

Patient status will be monitored for four hours. Accordingly, oxygen saturation, respiratory rate and blood pressure will be recorded every 20 minutes during the treatment period and details recorded on the CRF. Follow up checks will be performed at 2, 3 and 4 hours following the final study treatment. Other checks may be performed as part of routine medical treatment but will not be recorded on the CRF unless associated with an AE.

8.4 Other Assessments

8.4.1 Quality of Life and Health Economics

Parents will be asked to complete the EuroQol EQ-5D (on their child's behalf) and a questionnaire based around health economic aspects at the one month follow-up (as explained below). Parents and children also will be asked to complete the asthma module of the PedsQL™ Quality of life questionnaire at one month. The PedsQL™ is available in specific age ranges (2-4, 5-7, 8-12 and 13-18 years) and comprises of two reports (parental completion and child completion) for all age ranges apart from 2-4 years. For children aged 2-4 years, only a parental report will be completed. The 1 month follow-up questionnaire distribution will be centrally coordinated by the MCRN CTU and will be designed to maximise response rates. Non-responders will be followed up by sending a reminder letter approximately one week after the initial questionnaires. Should there be no response, they will then contacted by telephone and repeat questionnaires sent if necessary.

A prospective economic evaluation will be conducted alongside the trial with the view to estimating the cost-effectiveness of nebulised magnesium sulphate in the management of severe acute asthma in children. Data will be collected on the health services resources used in the treatment of each child during the time horizon covered by the randomised controlled trial. Data collection forms will record the duration and intensity of care provided to each child, based on standard criteria for level of care, as well as complications experienced. Details of the resources associated with salient clinical events will be recorded. Current UK unit costs will be applied to each resource item to value total resource use in each arm of the trial. A per diem cost for each level of inpatient, outpatient and day care will be calculated by the health economics researcher from detailed questionnaires completed by NHS finance departments, giving cost data and apportioning these to different categories of patient using a 'top-down' methodology. The unit costs of clinical events that are unique to this trial will be derived from the hospital accounts of the trial participating centres, although primary research that uses established accounting methods may also be required. An

incremental cost-effectiveness analysis will be performed and will be expressed as the incremental cost per quality-adjusted life year (QALY) gained. The economic evaluation will be informed, in part, by data collated by economic questionnaires completed by the parents at 4 weeks post-randomisation. These economic questionnaires will detail the use of hospital and community health services by each child following the initial hospital contact, and will provide EuroQol EQ-5D data completed by the parents[7]. Given the methodological limitations surrounding preference-based outcomes measurement in young children[15] it will be necessary to map disease specific outcomes in children aged less than 7 years onto multi-attribute utility measures, such as the EQ-5D[7].

8.5 Substudies

8.5.1 Pharmacogenetic substudy

Research question
Do β_2 adrenoceptor or muscarinic receptor polymorphisms explain the differences in response to therapy in acute severe asthma in children?

β_2 adrenoceptor gene (ADRB2) and asthma
The β_2 adrenoceptor gene (ADRB2) is located on chromosome 5q31, a region linked to asthma, allergic phenotypes and bronchial hyperresponsiveness. Single nucleotide polymorphisms occur in various positions within the gene, but those that appear to have the greatest effect on receptor function are at amino acid positions 16, 27, 34 and 164 (reviewed 1). Polymorphisms within the 5' leader cistron and the 3' untranslated region are also potential modifiers[20]. However the majority of studies have concentrated on the most common variations at positions 16 and 27 (Gly16ARArg and Gln27Glu). Although in vitro the Ile164 variant has reduced coupling to adenyl cyclase resulting in shorter duration of receptor activation, its functional effect is limited by its very low frequency in most populations. There is no difference in ligand binding or basal activation of adenyl cylcase between different polymorphisms at codon 16 or 27, but compared to the Arg16 variant, the Gly16 variant shows increased agonist promoted down-regulation of receptor expression[21, 22].

There appears to be no consistent pattern in β_2 adrenoceptor polymorphisms in the incidence, persistence or severity of asthma. Previous meta-analyses of the association between asthma susceptibility and ADRB2 polymorphisms have given conflicting results, although a recent study combining previous meta-analyses with data from the 1958 British Birth Cohort study reported no association[23, 24]. Similarly there is conflicting evidence of the effect of ADRB2 polymorphisms on the persistence of symptoms or asthma severity. In a recent cross-sectional survey of 546 Scottish children the risk of an asthma exacerbation was greater in those homozygous for Arg16 compared to those homozygous for Gly16[25].

Short acting β_2 agonists (SABAs) are the treatment of choice in acute asthma – often administered at high doses via either a metered dose inhaler and spacer or by nebuliser. In the past SABAs were often administered on a regular basis as maintenance therapy. In contrast long acting β_2 agonists (LABAs) have no role in acute severe asthma, but are increasingly used as maintenance therapy in combination with inhaled steroids.

Retrospective analyses had suggested that individuals homozygous for Arg16 using regular Salbutamol had significantly more exacerbations of asthma, and were significantly more likely to need rescue corticosteroids. In the BARGE (beta adrenergic response by genotype) study patients were recruited on the basis of their ADRB2 genotype, and randomised to receive regular Salbutamol or placebo. During a run in period with minimal Salbutamol use, peak expiratory flow rates (PEFR) were significantly higher in those homozygous for Arg16 compared to those homozygous for Gly16. However when receiving regular four times per day Salbutamol the PEFR of those homozygous for Arg16 decreased significantly, while the peak expiratory flow rate of those homozygous for Gly16 improved significantly. In contrast a number of large

studies (almost all pharmaceutical industry sponsored) report no consistent associations between ADRB2 polymorphisms and asthma outcomes in those receiving regular LABAs.

Muscarinic receptor gene (CHRM1, CHRM2 and CHRM3) and asthma
There are limited data on M2 and M3 polymorphisms in asthma[26]

Pharmacogenetics of magnesium in asthma
We are unaware of published data on the pharmacogenetics of response to magnesium in asthma. The mode of action of magnesium particularly in severe asthma is unclear, but is possibly due to increased β_2 receptor affinity. In asthmatic patients magnesium infusion resulting in an increase in serum magnesium concentration is associated with a significant leftward shift of the dose-response curve to inhaled salbutamol, but no change in the maximum response[27].
Thus there is evidence to suggest that the role of magnesium in severe asthma is via modulation of the β_2 receptor, and it could be hypothesised that this action reverses the recognised down regulation of the receptor by regular β_2 agonists.

The aim of the substudy will be to examine the polymorphisms described above to see if they are associated with:
(i) Whether children respond to the initial nebuliser prior to randomisation and improve sufficiently from the severity of their exacerbation to not fulfil the entry criteria, or whether they remain severe enough to be recruited into the study and receive treatment plus or minus the study treatment.
(ii) The asthma symptom score profile in children who are randomised to nebulised magnesium sulphate as part of the study.

Analysing the clinical details and their clinical response and comparing their polymorphisms may answer the research question: do β_2 adrenoceptor or muscarinic receptor polymorphisms explain the differences in response to therapy in acute severe asthma in children.

8.6 Loss to Follow-up

Contact will be attempted by telephone if patients do not return questionnaires at follow up. Patients will be asked to inform the CTU of changes of address between the hospital visit and contact for the follow up. A change of address card will be given to parents to facilitate this. If there is no response following a phone call and repeat sending of questionnaires, the patient's GP may be contacted in an effort to locate them.

8.7 Trial Closure

The trial may be closed prematurely by the trial steering committee, on the recommendation of the independent data and safety monitoring committee, for reasons such as clear differences between safety of trial treatments. In the event all patients have been recruited and followed up or premature discontinuation, the end of the trial will be considered as the date of the final database lock.

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

A separate and full statistical analysis plan (SAP) will be developed prior to the analysis of the trial. The SAP will be agreed by the trial steering committee before being sent to the independent data and safety monitoring committee for comment and approval.

9.2 Method of Randomisation

Randomisation lists will be generated in STATA using simple block randomisation with random variable block length and a 1:1 ratio of treatment allocation. Randomisation will be stratified by centre.

9.3 Outcome Measures

9.3.1 Primary

The primary endpoint is the Asthma Severity Score (ASS) after 60 minutes of treatment.

9.3.2 Secondary

Clinical (during hospitalisation)

- 'stepping down' of treatment at one hour
- number and frequency of additional salbutamol administrations
- length of stay in hospital
- requirement for intravenous bronchodilator treatment
- intubation and/or admission to a paediatric intensive care unit (PICU)

Patient and parental outcomes at follow-up (1 month)

- Paediatric quality of life (PedsQL^{TM} asthma module parental report for all children and self-completion if aged over 5 years, EQ-5D)
- Time off school/nursery
- Health care resource usage (e.g. GP visits, additional prescribing)
- Time off work (related to child's illness)

9.4 Sample Size

In order to detect a difference between the two groups at 60 minutes post treatment of 0.5 points on the asthma severity score at a 5% significance level with 80% power, 500 children are required. This assumes an SD =1.95 based on a similar population in Australia [Yung 1996]. The SD was estimated from the Cardiff pilot study (EudraCT number: 2004-003825-29) to be 1.7. The target of 500 children will stand. ASS can range from 0 to 9. A difference of 0.5 is deemed to be the minimum worthwhile clinically important difference to be detected. It is a relatively small difference given the low cost and perceived good safety profile of the intervention.

This sample size will also show an increase in the number of children being 'stepped down' in terms of medication after one hour of treatment from 50% to 63% with 80% power at a 5% significance level. A study examining the changes in severity after one hour of treatment in acute asthma (adults and children) has demonstrated that 50% of subjects with severe acute asthma will have improved sufficiently to be reassigned as having a moderate attack after an hour of treatment with nebulised salbutamol and ipratropium bromide every twenty minutes over an hour[9].

9.5 Interim Monitoring and Analyses

MAGNETIC will be monitored by an Independent Data and Safety Monitoring Committee (IDSMC) (see section 16.3). The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. Missing data will be monitored and strategies developed to minimise its occurrence.

An initial analysis of trial data for IDSMC review is planned for 2-3 months after the first patient is randomised (anticipated to include approximately 30 patients), to assess recruitment rates, undertake an internal pilot estimation of the standard deviation of the ASS primary outcome and consider any safety issues. The estimate of the common standard deviation used in the sample size calculation will be checked. This blinded internal pilot is not deemed to have any significant impact on the final analysis. If the standard deviation is smaller than that used in the sample size calculation, suggesting that fewer patients are required than initially proposed, then no action will be taken and the size of the study will remain as planned. If the standard deviation is larger than assumed suggesting the need for more patients then on the advice of the Independent Data and Safety Monitoring Committee, the Trial Steering Committee will aim to increase recruitment and consider implications for funding and existing resources.

Subsequent timing of the next analysis of the data will be determined on the basis of recruitment rates at the initial IDSMC meeting although it is anticipated that this will be approximately after a further 6-9 months (aiming to be halfway through the accrual period). The IDSMC may request additional interim analyses if triggered by a concern regarding Sudden Unexpected Serious Adverse Reactions (SUSARs). Each member of the IDSMC will receive details of SUSARs as they occur. All interim analysis results will be confidential to the IDSMC members and will not be for review by the Trial Management Group (except the statistical team preparing the IDSMC report).

The IDSMC will be asked to consider patient safety, particularly any Suspected Unexpected Serious Adverse Reactions (SUSARs) leading to death, alongside treatment efficacy when making their recommendation regarding continuation, amendment or discontinuation of the trial. Importantly, statistical considerations alone are not adequate for data monitoring due to the over-emphasis placed on the p-value resulting from hypothesis tests. Clinical judgment is essential to the process to account for unexpected adverse events and balance issues of safety and efficacy in light of any new external information. The decision to stop recruitment will depend on whether the results will be convincing to the medical community.

In order to estimate the effect of nebulised magnesium sulphate for the primary efficacy outcome at each interim and final analysis, the Haybittle-Peto approach will be employed for one interim analysis, planned after approximately 250 children have been randomised, with 99.9% confidence intervals calculated for the effect estimate. The final analysis will be undertaken after the final child has completed follow-up (500 randomised in total) and 95% confidence intervals will be calculated. This method has been chosen to ensure that interim efficacy results would have to be extreme before early termination is recommended in order to be convincing to the clinical community. The method also minimises controversy regarding interpretation of the results from estimation and hypothesis testing at the final analysis. No inflation factor needs to be applied to the sample size using this approach.

9.6 Analysis Plan

A full statistical analysis plan will be written prior to the conduct of any comparative analysis of the treatment arms. The primary analysis will be intention to treat and will compare the two groups of patients in terms of their ASS scores over the first hour of treatment. The sample size calculation is based on a comparison at 60 minutes, however all longitudinal ASS data collected will be used in a secondary analysis, with a resulting increase in power. The two groups will also be compared with respect to the proportion of patients who were 'stepped down' in terms of treatment at one hour. The proportion of patients who required a 'stepping up' of medication at one hour, progression to intravenous treatment, intubation and/or admittance to HDU/PICU will be compared between the two groups. Paediatric Quality of Life at one month will also be compared between the two groups. The analysis set for safety will include any patient receiving at least one dose of a study drug. Patients will be included in the treatment group they actually received.

A formal test of a treatment-covariate interaction will be conducted for the effect of age (2-5 years and 6 and over). Exploratory analysis will be conducted as to the impact on any treatment effect of other factors such as gender or presenting clinical signs.

As much information as possible will be collected about the reasons for missing outcome data and this will be used to inform any imputation approaches employed in the analysis.

9.6.1 Health Economic Analysis

A non-parametric bootstrap estimation will be used to derive 95% confidence intervals for mean cost differences between the trial groups and to calculate 95% confidence intervals for incremental cost effectiveness ratios. A series of simple and probabilistic sensitivity analyses will be undertaken to explore the implications of uncertainty on the incremental cost-effectiveness ratios and to consider the broader issue of the generalisability of the study results. Sub-group analysis will be performed in order to assess the heterogeneity of the cost-effectiveness results across age sub-groups. In addition, cost-effectiveness acceptability curves will be constructed using the net benefits approach.

10 PHARMACOVIGILANCE

10.1 Terms and Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions:

Adverse Event (AE)
Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)
Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR)
An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the investigators brochure.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)
Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect
- is an other important medical event that may jeopardise the subject***

*'life-threatening' in the definition of 'serious' refers to an event in which the patient 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.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Notes on Adverse Event Inclusions and Exclusions

10.2.1 Include

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptom present at baseline that worsens following the administration of the study/trial treatment
- Signs and symptoms of magnesium sulphate administration (as indicated in section 2.4.1) including;
    - Transient facial flushing
    - Transient hypotension
    - Finger tingling

- Any other adverse event, whether related to the study medication or not, which does not meet the criteria in 10.2.2

10.2.2 Do Not Include

- Medical or surgical procedures- the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication without signs or symptoms
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

10.2.3 Reporting of Pregnancy

No pregnancy testing is planned as part of the study procedures. Patients who are known to be pregnant will be excluded from the study.

10.3 Notes Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.
Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories.

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.4 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in table 2.
If any doubt about the causality exists the local investigator should inform the MCRN CTU who will notify the Chief Investigator. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both opinions.

Table 2: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of

	other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost Certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.5 Expectedness

An AE whose causal relationship to the study drug is assessed by the investigator as "possible", "probable", or "almost certainly" is an Adverse Drug Reaction.
All events judged by the investigator to be possibly, probably, or almost certainly related to the IMP, graded as serious and **unexpected** (see section 10.2.1) should be reported as a SUSAR.

10.6 Follow-up After Adverse Events

All adverse events should be followed up until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.
When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: recovering; recovered with sequelae (specifying with additional narrative); ongoing; fatal; unknown.

10.7 Reporting Procedures

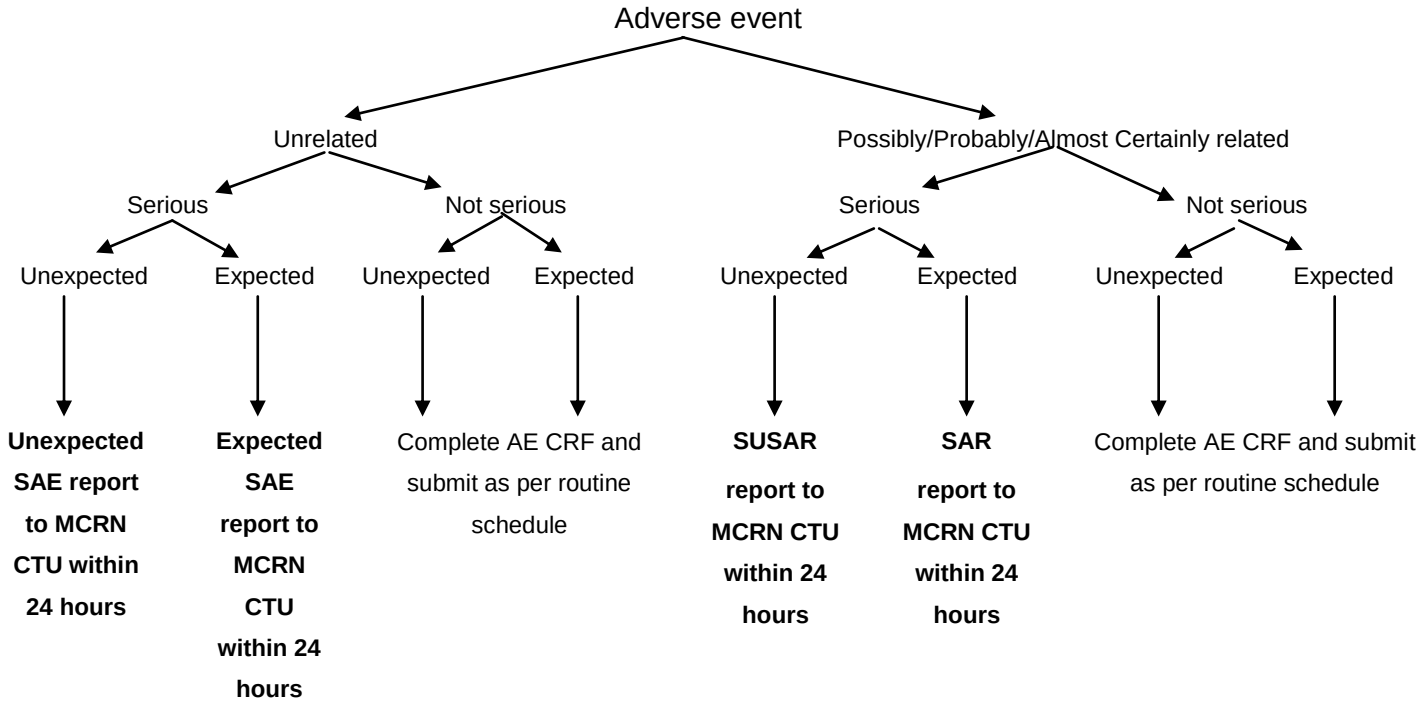
All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the MCRN CTU in the first instance. A flowchart is given below to aid in determining reporting requirements. Adverse event recording should begin as soon as a patient receives the first dose of study medication. Reporting of new AEs will cease at discharge and all AEs not resolved will be documented as 'ongoing'.

10.7.1 Non serious ARs/AEs

All such events, whether expected or not, should be recorded in the CRF.

10.7.2 Serious ARs/AEs/SUSARs

SARs, SAEs and SUSARs should be reported within 24 hours of the local site becoming aware of the event. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign to indicate they have assessed the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.
The MCRN CTU will notify the MHRA and main REC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required by their Research & and Development Office.



10.8 Responsibilities – Investigator

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.
All SAEs must be reported immediately by the investigator to the MCRN CTU on an SAE form unless the SAE is specified in the protocol/investigator's brochure as not requiring immediate reporting. All other adverse events should be reported on the regular progress/follow-up reports.

Minimum information required for reporting:

- Study identifier
- Study centre
- Patient number
- A description of the event
- Date of onset
- Current status in trial
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

i. The SAE form should be completed by the responsible investigator i.e. the consultant named on the 'signature list and delegation of responsibilities log' who is responsible for the patient's care. The investigator should assess the SAE for the likelihood that it is a response to an investigational medicine. In the absence of the responsible investigator the form should be completed and signed by a designated member of the site trial team and faxed to the MCRN CTU immediately. The responsible investigator should check the SAE form, make changes as appropriate, sign and then re-fax to the MCRN CTU as soon as possible. The initial report shall be followed by detailed, written reports.
ii. Send the SAE form by fax (within 24 hours or next working day) to the MCRN CTU:

Fax Number: 0151 282 4721

iii. The responsible investigator must notify their R&D department of the event (as per standard local procedure).

iv. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.
v. Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and faxing to the MCRN CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.
vi. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

10.8.1 Maintenance of Blinding

Systems for SUSAR and SAR reporting should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. Unblinding clinicians may be unavoidable if the information is necessary for the medical management of particular patients. The safety of patients in the trial always takes priority. In each report, seriousness, causality and expectedness should be evaluated for all of the trial treatments. Cases that are considered serious, unexpected and possibly, probably or almost certainly related to one of the trial therapies (i.e. possible SUSARs) would have to be unblinded at the MCRN CTU prior to reporting to the MHRA.

10.9 Responsibilities – MCRN CTU

The MCRN CTU is undertaking duties delegated by the trial sponsor, Cardiff University, and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA and main research ethics committees) and trial IDSMC as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the MCRN CTU is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the MCRN CTU first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion.

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:
    a. A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;
    b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
    c. A major safety finding from a newly completed animal study (such as carcinogenicity).
    d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;
- Recommendations of the Data and Safety Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at the MCRN CTU will liaise with the Chief Investigator (or designated other specified in the protocol) who will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to regulatory authorities, MREC and trial IDSMC. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The MCRN CTU will also send an annual safety report containing a list of all SARs to the MHRA, MREC and trial IDSMC. Copies of the report will be sent to the Principal Investigators at all institutions participating in the trial

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996).
We consider the specific ethical issues relating to participation in this trial to be:

- Limited time for consideration of trial entry; this trial is exploring the effects of nebulised magnesium in acute severe asthma in children, a condition requiring prompt intervention in accident and emergency departments or high dependency units. Due to the very nature of the condition and intervention being investigated, parents are required to be informed about the trial and make a decision regarding entry within 30 minutes of beginning standard treatment. Recruiting investigators will be clinicians/nurse specialists experienced at imparting important information to parents in situations of extreme stress. Parents will be made aware of alternative treatments and of their right to withdraw the child from the trial at any time without the child or family being subject to any resulting detriment.
- Informed consent in a paediatric population. The parent or legal representative of the child will have an interview with the investigator, or a designated member of the investigating team, during which opportunity will be given to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted. They will be provided with written information and contact details of the local study personnel should they require additional information. Simplified written information will be available for children aged 5-8 years, 5-10 years and for those aged 11-15 years and assent will be obtained when possible. The simplified sheets are broken into age groups as a guide only, and the researcher/clinician may provide the most appropriate version at their discretion, taking into account individual child and circumstances (consulting the parents if appropriate).

11.2 Ethical Approval

The trial protocol and all substantial amendments will be submitted for review by the North West Multi-centre Research Ethics Committee (MREC) but must undergo site specific assessment (SSA) by completing section C of the REC application form and submitting all sections of this form to the Local Research Ethics Committee (LREC). A copy of local Research & Development (R&D) approval and of the PISC and Consent form on local headed paper should be forwarded to the MCRN CTU before patients are entered. The CTU should receive notification of positive SSA for each new centre via the MREC: usually this will be through the CI as they should be the main MREC applicant.

Proxy consent from the parent or legally acceptable representative should be obtained prior to each patient participating in the trial, after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. Age and stage-of-development specific patient information and consent leaflets should also be implemented and patient assent obtained where appropriate. The right of the parent/ legal representative to refuse consent for the minor to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis. Similarly, the parent/legal representative of the patient remains free to withdraw the patient at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing the further treatment of the minor.

11.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients participating in trials coordinated through the MCRN CTU. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki

Due to the nature of the study and the requirement to provide prompt treatment in an emergency setting, there will be a short window available for obtaining consent in the A+E department/Paediatric Assessment Unit. Paediatric asthma clinics at participating centres will be provided with copies of the patient information sheet to present to parents and children to inform them the trial is taking place, and that in the event they present in hospital with a severe asthma attack, they may be asked for consent. Not all children eligible to take part will receive this information before they attend the emergency department and are approached to take part. However, it will serve to inform a proportion of the potential study population, who will perhaps develop a more considered perspective in regards to participation through having prior knowledge of the trial. A poster/flyer has been designed to increase awareness of the study and will available for placement at appropriate places around the study site. Such places may include paediatric clinics, wards/units and the accident and emergency departments. Approval will also be sought from appropriate Primary Care Trusts to display the poster and to provide patient information in GP and outreach centres within the locality of participating sites.

Parents/legal representatives will be provided with an MREC approved information sheet during the initial screening period and children who are deemed to be of suitable maturity will also receive a simplified MREC approved information sheet. Upon reviewing the documents, the investigator will explain the research study to the patient and their parent/legal representative and answer any questions that may arise. They will also explain the requirement to use information collected at admission, as this provides evidence to the eligibility of the patient. This includes ASS, BTS guideline severity assessments and demographic information collected pre-randomisation that would have otherwise been gathered as part of standard practice.

Consent will also be sought for permission to provide the MCRN CTU with the name and address of the family so that they can be contacted for the one month follow-up.

The parent/legal representative of the minor will sign the informed consent document. If capable, the patient should sign and personally date a separate IEC-approved assent form, describing (in simplified terms) the details of the trial intervention/product, trial procedures and risks. Assent forms signed by the minor do not substitute for the consent form signed by the patient's legally acceptable representative. A copy of the informed consent document will be given to the patient and their legally acceptable representative for their records.

The parent or legal representative may, without the minor being subject to any resulting detriment, withdraw the minor from the trial at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

11.3.1 Informed Consent for Pharmacogenetic Substudy

Informed consent to take a saliva sample for use in the pharmacogenetic substudy will take place at two possible timepoints:
a) At the conclusion of the screening phase, for patients who are not randomised into the main study because:

i. Severity/eligibility criteria were not met before or after the initial nebuliser, or
ii. Consent was not obtained for the main study

b) At conclusion of the follow up (240mins after randomisation), but before the patient is discharged.
Parents/legal guardians and patients will be provided with IEC-approved information sheets specifically designed for the sub-study. These will be presented to parents at the earliest opportunity as to provide parents and patients with adequate time to consider the information and ask any questions.

Discussion of objectives and potential inconveniences of participating in the sub-study are to be provided to patients by staff with experience with minors. Parental consent and, if appropriate, patient assent, will be obtained **prior** to collection of the saliva sample. Both the research practitioner taking consent and the parent or legally acceptable representative must personally sign and date the form. If capable, the patient should assent and sign and personally date a separate IEC-approved assent form. The parent or legal representative should also sign and date the assent form. Assent forms do not substitute for the consent form signed by the patient's legally acceptable representative.

The original copy of the signed consent/assent forms will be retained in the Study File and must be made available for inspection. A copy will be returned to the MCRN CTU and one will also be put in the child's notes. A further copy of the signed consent/assent forms will be given to the child's legal representative.

11.4 Study Discontinuation

In the event that the study is discontinued, children will be reverted to usual standard clinical care. Patients withdrawing early from trial treatment will also be reverted to normal standard care but will not be unblinded unless protocol unblinding criteria are fulfilled (see Section 7.7).

12 REGULATORY APPROVAL

This trial will be registered with the MHRA and granted a Clinical Trial Authorisation (CTA). The CTA reference is **2007-006227-12**. All substantial amendments will be submitted to the MREC as well as the MHRA.

13 TRIAL MONITORING

Trial monitoring is carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial. A risk assessment is performed for each trial co-ordinated by the MCRN CTU to determine the level and type of monitoring required for specific hazards. The type of trial monitoring should be specific to the individual trial and can take the form of on-site visits or central monitoring.

13.1 Risk Assessment

In accordance with the MCRN CTU (SOP TM005) this trial has undergone a risk assessment, completed in partnership between the University of Liverpool, MCRN CTU, trial sponsor and Chief Investigator. In conducting this risk assessment, the contributors considered potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.
The outcome of the risk assessment is expressed as a percentage, assigned according to the following categories:
Score ≤ 33% = Low risk
Score ≥34 to ≤ 67% = Moderate risk
Score ≥ 68 to ≤ 100% = High risk
The outcome of the MAGNETIC trial risk assessment was a score of **16.0%** therefore it has been judged to be a **low risk** clinical trial. This level of risk has determined the approach to trial monitoring described in this section and additionally in section 16.

13.2 Source Documents

Source data*: All information in original records and certified copies of original records of 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 (original records or certified copies). (ICH E6, 1.51).*
Source documents*: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).*
In order to resolve possible discrepancies between information appearing in the CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF. The following data recorded in the CRF should be consistent and verifiable with source data in source documents *other* than the CRF (e.g. medical record, laboratory reports and nurses' notes).

The following parameters that will be documented in the CRF are not source data:

- Relevant medical history and diagnosis (medical notes are source documents)
- Physical examinations (medical notes are source documents).

Therefore, for data where no prior record exists and which is recorded directly in the CRF, e.g. Asthma severity score assessments, oxygen saturation; the CRF will be considered the **source document**, unless otherwise indicated by the investigator. All such exemptions should be identified prior to the clinical phase of the trial. In addition to the above, date(s) of conducting informed consent process including date of provision of patient information, registration number, randomisation number and the fact that the patient is participating in a clinical trial including treatment arms of magnesium and placebo therapy should be added to the patient's medical record chronologically, i.e. when treatment is allocated to the patient. Further, study treatment allocation should also be noted in the patient's medical record after unblinding of the study.

13.3 Data Capture Methods

13.3.1 Case Report Forms

The case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. CRF pages will be provided in triplicate on NCR paper and when complete, should be split into three collated sets. Originals should be sent to the MCRN CTU and the copies securely retained at site

13.4 Data Management at MCRN CTU

Data stored at MCRN CTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Data queries will be generated as required and query forms will be sent to delegated individuals at study sites. They will provide responses and return copies of the completed data query forms to MCRN CTU, where the appropriate corrections will be made on the study database.

13.5 Central and Clinical Site Monitoring

13.5.1 Central Monitoring

The MCRN CTU is to receive a copy of the PIC within a week of randomisation. If consent forms are not forwarded regularly by a participating centre, the trial coordinator will conduct a site visit to check the presence of a signed PIC in the casenotes of all randomised patients.

Data submitted to the database will be centrally monitored by the CTU to ensure as far as possible that CRF data collected are consistent with adherence to the trial protocol. Data will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Discrepancies that have been raised will be queried. The MACRO data management system will automatically keep a log of what data has been changed, the time of each change, and the person who changed it.

The trial coordinator will review rates of recruitment, missing outcome data, SAEs, ADRs, study withdrawals and losses to follow-up across sites, and remedial action taken as necessary. If heterogeneity in reporting is noted across centres then the trial co-ordinator will arrange site visits to undertake source data verification.

Standardised paper Case Report Forms (CRFs) should be sent to the MCRN CTU promptly. The trial coordinator will conduct data entry checks and use automated validation checks at data entry. A site visit will be conducted if inconsistencies, unresolved queries, missing data are noted at a given site.

Monthly recruitment reports will be provided by the trial coordinator, monitoring reasons cited for consent refusal and querying reasons for slow recruitment. The TMG is charged with providing solutions to problems where possible.

The trial coordinator will keep a central protocol deviation log which will be updated with all deviations reported from trial sites. If the trial coordinator identifies significant and/or persistent non-compliance on the part of the PI, this will be documented in the monitoring report and the MCRN CTU team will discuss any further action required. A site visit will be conducted if primary and secondary measures are consistently missing from a given site. The trial coordinator will be in

regular contact with the PIs in order to monitor the impact that the study may have on the running of the service.

13.5.2 Site Monitoring

Site monitoring may be deemed to be necessary as a result of central data checks. In order to perform their role effectively, a member of the MCRN CTU staff (usually the trial coordinator) may need direct access to primary data, e.g. patient records, laboratory reports, appointment books, etc. Since this affects the patient's confidentiality, this fact is included in the Patient Information Sheet and Informed Consent Form.

13.5.3 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.
Case report forms will be labelled with the patient's name, address and unique trial registration and/or randomisation number.
Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.
The MCRN CTU will be undertaking activities requiring the transfer of identifiable data:

1. The MCRN CTU will be responsible for issuing Quality of Life (QoL) and health economic questionnaires to trial participants following discharge from hospital and therefore will be required to receive name and address details.
2. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participants' signed informed consent/assent forms being supplied to the MCRN CTU by recruiting centres, which requires that name data will be transferred to the MCRN CTU.

This transfer of identifiable data is disclosed in the PIC. The MCRN CTU will preserve the confidentiality of participants taking part in the study and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

13.5.4 Quality Assurance and Quality Control of Data

QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled.

This trial has undergone a risk assessment, the outcome of which indicates it to be a low risk trial. As such, site visits will be conducted and source data verification performed if indicated to be required as a result of central statistical monitoring processes.

To this end:

- The Principal Investigator, Research Nurse and designated Pharmacist from each centre will attend the trial launch meeting or site visit, coordinated by MCRN CTU in conjunction with the Chief investigator, Dr Colin Powell, which will incorporate elements of trial- specific training necessary to fulfil the requirements of the protocol
- The Trial Coordinator is to verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended trial specific training
- The internal QA process of the MCRN CTU involves routine audit of certain activities across all trials, including random checking of adherence to informed consent procedure (monitoring receipt of signed consent forms)
- The Trial Coordinator and Trial Statistician are to check safety reporting rates between centres

- The Trial Coordinator and Trial Statistician are to monitor screening, recruitment, treatment and study withdrawal rates between centres
- The Trial Coordinator is to monitor the quality of data entry by performing routine consistency checks and follow-up data queries until resolved
- Independent oversight of the trial will be provided by the Data and Safety Monitoring Committee and independent members of the Trial Steering Committee

13.6 Records Retention

The PI at each investigational site must make arrangements to store the essential trial documents, including the Investigator Site File, until the MCRN CTU informs the investigator that the documents are no longer to be retained, or for a maximum of 15 years, whichever is soonest.
In addition, the PI is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).
The PI is required to ensure the continued storage of the documents, even if they leave the clinic/practice or retire before the end of the required storage period. Delegation should be documented in writing.
The MCRN CTU undertakes to store originally completed CRFs and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the PI only.

14 INDEMNITY

The Sponsor, Cardiff University, has insurance coverage for liabilities relating to harm caused by negligence in the design or management of the trial. The Sponsor does not provide cover for liabilities relating to non-negligent harm. Clinical negligence is covered by the standard NHS Indemnity provisions.

15 FINANCIAL ARRANGEMENTS

This study is funded by the Health Technology Assessment programme (HTA) of the Department of Health. Contractual agreements will be in place between sponsor and collaborating sites that will incorporate financial arrangements.

15.1 Financial Support for Collaborating Sites

A sum of £200 per patient randomised will be reimbursed to participating sites. This is to be paid quarterly in arrears and is dependent upon receipt of completed CRFs for each patient randomised.

16 TRIAL COMMITTEES

16.1 Trial Management Group (TMG)

The Trial Management Group (TMG) will comprise Dr Colin Powell, Dr Iollo Doull, Professor Paula Williamson, Dr Kerry Hood, Dr Stavros Petrou, Mr John Lowe and Ms Angela Boland who will be responsible for the day-to-day running and management of the trial and will meet (via teleconference or videoconference) initially every month during trial setup and subsequently every 3 months once recruitment is underway.

16.2 Trial Steering Committee (TSC)

The Trial Steering Committee will consist of an independent chairperson, Professor Ian Russell and additional independent members; Dr Colin Gelder, Dr Bob Dinwiddie and Mrs Sue Sibert along with members of the TMG detailed above. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision concerning recommendations to the sponsor and funder about the continuation of the trial lies with the TSC.

16.3 Independent Data and Safety Monitoring Committee (IDSMC)

The Independent Data and Safety Monitoring Committee (IDSMC) consists of Professor David Jones, Professor of Medical Statistics; Dr Peter Weller, Consultant in Respiratory Medicine and Dr Ian Balfour-Lynn, Consultant Paediatrician. IDSMC members will comply with a trial-specific IDSMC charter according to ICH GCP guidelines.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the trial opening for recruitment, but will have corresponded in order to approve the protocol prior to REC submission. The IDSMC will then define the frequency of subsequent meetings (at least annually) at their first meeting. Details of the interim analysis and monitoring are provided in section 9.

The IDSMC may recommend to the Trial Steering Committee that the trial be stopped or amended if sufficient evidence emerges that nebulised magnesium sulphate is clearly indicated or contra-indicated. Analyses will be reported to IDSMC members who will consider the data in a clinical context accounting for other emerging worldwide evidence and overall clinical relevance.

17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible after the close of the trial. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.
The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) and the CONSORT guidelines[61] will be respected. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.
BMJ guidance on authorship and contributorship (see http://bmj.com/advice/3.html) will be used to acknowledge the level and nature of contribution of key individuals in publications arising from the trial. The publication strategy shall lie under the jurisdiction of the Trial Steering Committee.

18 PROTOCOL AMENDMENTS

18.1 Version 6.1 (18/01/2010)

Amendments from version 6.0 (23/07/2009) to version 6.1 (18/01/2010)

Appendix C Appendix C (list of participating sites) has been removed. The list of participating sites will now be maintained as a separate, version controlled document.

Amendments from version 5.0 (19/09/2008) to version 6.0 (23/07/2009)

Pg 21 **7.2 Formulation, Packaging, Labelling, Storage and Stability:** This section has been amended to update the procedure for storing the trial medication once dispensed from site pharmacies
Pg 21 **7.2.1 Preparation, dosage and administration of study treatment/s:** This section has been updated to clarify the procedure for disposal of residual nebuliser volume
Pg 22 **7.4 Accountability procedures for study treatment/s:** This section has been amended to update the procedure for storage of the trial medication
Pg 30 **11.3 Informed consent process:** The section has been updated to indicate that approvals for placement/distribution of study information in primary care settings may be sought.
Pg 36 **10.9 Responsibilities- MCRN CTU:** This section has been updated to confirm that all SAEs will also be reported to the trial IDSMC
Pg 43 **13.4 Data Monitoring at MCRN CTU:** The process for data querying as been clarified
Pg 57 **Appendix C:** Change of Investigator- Fairfield General Hospital
Pg 60 **Appendix C:** Addition of participating site- City General Hospital, UHNS
Pg 61 **Appendix C:** Change of Investigator- Royal London Hospital
Pg 63 **Appendix C:** Addition of participating site- University Hospital Lewisham

Amendments from version 4.0 (18/04/2008) to version 5.0 (19/09/2008)

Pg 21 **7.2 Formulation, Packaging, Labelling, Storage and Stability:** The details of the manufacturing and QP release units have been amended to St Mary's Pharmaceutical Unit, Cardiff and Vale NHS Trust.
Pg 20 **6.2 Randomisation:** This section has been amended to remove details of stratification of the randomisation in to two age groups.
Pg29 **9.2 Method of Randomisation:** This section has been amended to remove details of stratification by age. The randomisation will be stratified by centre only.

Amendments from version 3.0 (03/03/2008) to version 4.0 (18/04/2008)

Pg 11 **The flow chart** has been updated to clarify that follow up will continue if patients are admitted to hospital following the initial 4 hour phase.
Pg 24-25 **8.1 Schedule for follow up:** This section has been amended to clarify that data will be collected in the event patients are admitted to hospital. **Table 2** has been updated to clarify that adverse events and concomitant medication monitoring will continue in the event of admission.
Pg 58 **Change in Principal Investigator at Leighton Hospital:** The principal Investigator at Leighton Hospital has been changed to Dr Julie Ellison, Consultant Paediatrician.

Pg 62 **Addition of study site:** Singleton Hospital, Swansea.

Amendments from version 2.0 (18/01/2008) to version 3.0 (03/03/2008)

Pg 20 **6. 1 Screening**: Blood pressure, oxygen saturations and respiratory rate will be recording at screening.
6.2 Randomisation: Blood pressure, oxygen saturations and respiratory rate will be recorded prior to randomisation.
Pg 24 **8.1 Schedule for follow-up:** Blood pressure, oxygen saturations and respiratory rate will be recorded at 20, 40, 60, 120, 180 and 240 minutes following randomisation
Pg 25 **Table 2:** Blood pressure, oxygen saturations and respiratory rate will be recorded at screening, prior to randomisation, and at 20, 40, 60, 120, 180 and 240 minutes following randomisation
Pg 26 **8.3 Procedures for assessing safety:** Clarification that blood pressure will also be measured at 20, 40, 60, 120, 180 and 240 minutes following randomisation

Amendments from version 1.0 (23/11/2007) to Version 2.0 (18/01/2008)

Pg 21 The role of Stockport Pharmaceuticals and QCNW in IMP manufacture and QP release has been clarified.
Pg 22 The role of the site pharmacies at trial close (return, accountability and destruction) has been clarified.
Pg 38 Age ranges for simplified patient information have been redefined
Pg 39 Reference to the distribution of the flyer/poster has been added
Pg 56 Change of Principal Investigator at Wythenshawe Hospital, South Manchester University Hospitals NHS Foundation Trust.
Pg 60 Change of Principal Investigator at Queens Medical Centre, Nottingham University Hospitals NHS Trust

19 REFERENCES

1. Bessmertny O, DiGregorio RV, Cohen H, Becker E, Looney D, Golden J, Kohl L, Johnson T. A randomized clinical trial of nebulised magnesium sulphate in addition to albuterol in the treatment of acute mild-to-moderate asthma exacerbations in adults. *Annals of Emergency Medicine* 2002**;39(6)**585-591.

2. Bishop J. Evaluation of the properties and reliability of the clinical severity scale for acute asthma in children. *J Clinical Epidemiology 1*992; **45**: 71-76.

3. Blitz M. Inhaled magnesium sulphate in the treatment of acute asthma (a review). *Cochrane Database* 2005(3).

4. British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. *Thorax* 2003; **58 (Supplement)**: 1-94.

5. Conway S T. Admission to hospital with asthma. *Arch Dis Child* 1985**; 60**: 636-9.

6. Costello J, Howes M. Nebulised magnesium in asthma. *Emergency Medicine Journal* 10.1136/emj.2004.017939.

7. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**: 199-208.

8. Hughes RJ*.* The use of isotonic nebulised magnesium as an adjuvant to salbutamol*. Lancet 2003;**361**:2114-2117.*

9. Kelly AM, Kerr D, Powell CVE, Kerr D. Is severity assessment after one hour of treatment better for predicting the need for admission in acute asthma? *Respir Med* 2004**; 98:**777-81.

10. Mahajan P, Haritos D, Rosenberg N and Thomas R. Comparison of nebulised magnesium sulphate plus albuterol plus saline in children with exacerbations of mild to moderate asthma. *J Emer Med* 2004;**27(1):**21-25.

11. Mangat H S. Nebulised magnesium sulphate versus nebulised Salbutamol in acute bronchial asthma: A clinical trial. *Eur Resp J* 1998; **12:** 341-4.

12. Meral A. Inhalation therapy with MgSO4. *Turk J Pediatr* 1996;**38 :**169-75.

13. Nannini LJ, Pendino JC, Corna RA, Mannarino S, Quispe R. Magnesium sulphate as a vehicle for nebulised salbutamol in acute asthma. *Am J Med* 2000; **108(3):**193-197.

14. Pabon H Safety and efficacy of magnesium sulphate infusions in children with status asthmaticus. *Pediatr Emerg Care* 1994; **10:** 200-203.

15. Petrou S. Methodological issues raised by preference-based approaches to measuring the health status of children. *Health Economics* 2003; **12(8):** 697-702.

16. Scarfone R J. A randomised trial of magnesium in the emergency treatment of children with asthma. *Amn Emerg Med* 2000; **36**:572-8.

17. Sennhauser FH The burden of asthma in children *Paed Resp Rev* 2005; **6:**2-7.

18. Silverman R A. Intravenous sulphate in the treatment of acute severe asthma. A multi-centre randomised controlled trial. *Chest* 2002; **122**:489-97.

19. Yung M. Evaluation of an asthma severity score. *JPCH* 1996; **32:**261-264.

20. Hall IP, Sayers I. Pharmacogenetics and asthma: false hope or new dawn? *Eur Respir J* 2007; **29**(6):1239-45.

21. Green SA, Cole G, Jacinto M, Innis M, Liggett SB. A polymorphism of the human beta 2-adrenergic receptor within the fourth transmembrane domain alters ligand binding and functional properties of the receptor. *J Biol Chem* 1993; **268**(31):23116-21.

22. Green SA, Turki J, Innis M, Liggett SB. Amino-terminal polymorphisms of the human beta 2-adrenergic receptor impart distinct agonist-promoted regulatory properties. *Biochemistry* 1994; **33**(32):9414-9.

23. Thakkinstian A, McEvoy M, Minelli C, Gibson P, Hancox B, Duffy D, et al. Systematic review and meta-analysis of the association between {beta} 2-adrenoceptor polymorphisms and asthma: a HuGE review. *Am J Epidemiol* 2005; **162**(3):201-11.

24. Hall IP, Blakey JD, Al Balushi KA, Wheatley A, Sayers I, Pembrey ME, et al. Beta2-adrenoceptor polymorphisms and asthma from childhood to middle age in the British 1958 birth cohort: a genetic association study. *Lancet* 2006; **368**(9537):771-9.

25. Palmer CN, Lipworth BJ, Lee S, Ismail T, Macgregor DF, Mukhopadhyay S. Arginine-16 beta2 adrenoceptor genotype predisposes to exacerbations in young asthmatics taking regular salmeterol. *Thorax* 2006; **61**(11):940-4.

26. Fenech A, Hall IP. Pharmacogenetics of asthma. *Br J Clin Pharmacol* 2002; **53**(1):3-15.

27. Durlach J, Pages N, Bac P, Bara M, Guiet-Bara A. Beta-2 mimetics and magnesium: true or false friends? *Magnes Res* 2003; **16**(3):218-33.

20 APPENDICES

20.1 APPENDIX A: Pilot Data Summary

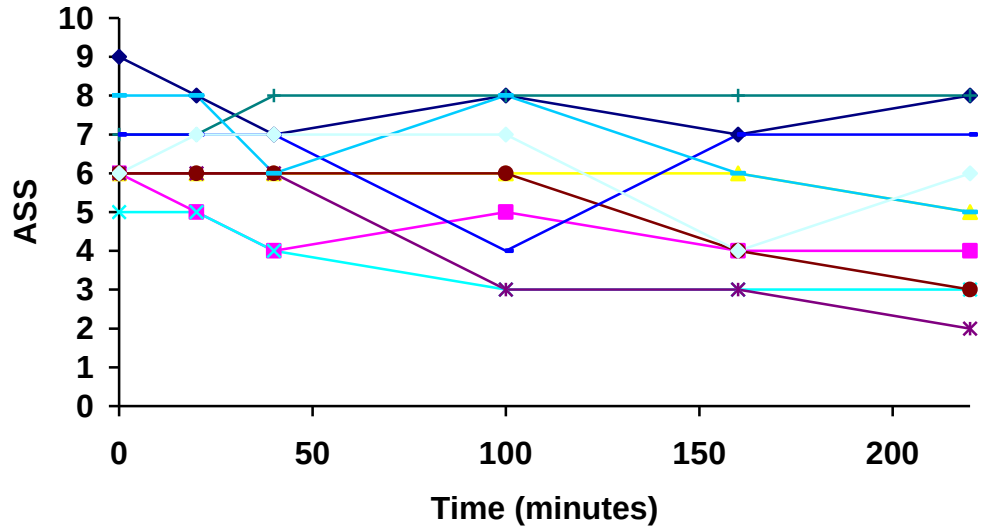
Pilot Table 1: Baseline characteristics

	Active	Placebo	Total included	Not included
Gender (% male)	2 (29%)	6 (60%)	8 (47%)	3 (38%)
Age (median, min, max))	6 (4, 13)	4 (2, 12)	5 (2, 13)	6.5 (2, 12)
Duration (days) Median (min, max)	1 (1, 7)	1 (0, 3)	1 (0, 7)	1 (1, 1)
Baseline ASS scores (median (min, max)	7 (4, 8)	6 (5, 9)	6 (4, 9)	7 (4, 8)
Score on each ASS component (median (min, max)				
Wheeze	2 (0, 2)	2 (0, 3)	2 (0, 3)	2 (1, 2)
Accessory muscle use	2 (1, 3)	2 (1, 3)	2 (1, 3)	2.5 (2, 3)
Heart rate	2 (2, 3)	3, (2, 3)	3 (2, 3)	3 (1, 3)
Baseline Oxygen saturations	92 (88, 93)	91 (85, 92)	91 (85, 93)	90 (87, 91)

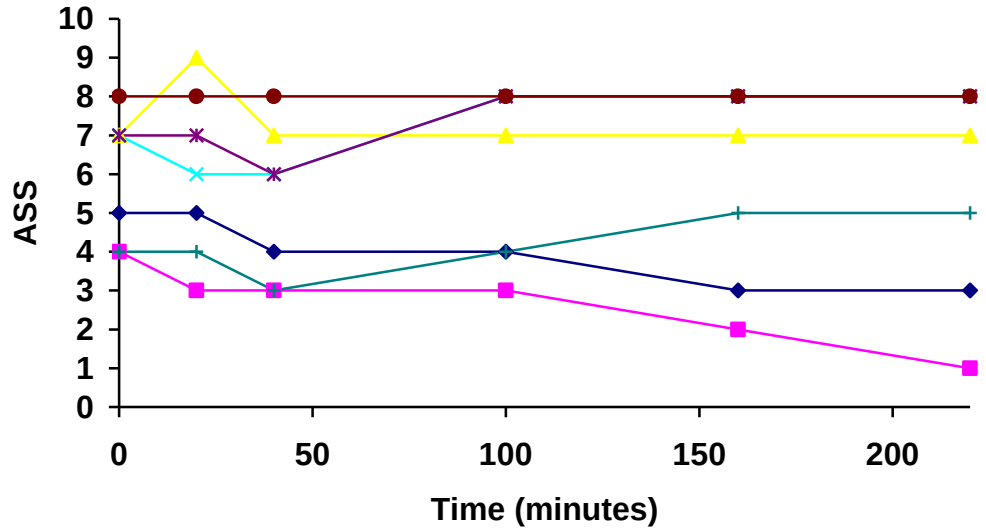
Pilot Table 2: Outcome by group

	Active N = 7	Placebo N = 10
ASS after one hour of treatment (median, min, max)	6 (3,8)	6 (4,8)
AUC of ASS (median, min, max)	1530 (690, 1760)	1355 (840, 1710)
Adverse reactions (n, %) see above	2 (29%)	0 (0%)

Pilot Figure 1: Individual participant ASS scores over time (placebo)



Pilot Figure 2: Individual participant ASS scores over time (active)



20.2 APPENDIX B: Yung Asthma Severity Score

Wheeze		Accessory muscle use		Heart rate	
None	☐ 0	None	☐ 0	< 80/min	☐ 0
Expiratory	☐ 1	+	☐ 1	81 – 110/ min	☐ 1
Expiratory + inspiratory	☐ 2	++	☐ 2	111 – 140/min	☐ 2
Heard without stethoscope	☐ 3	+++	☐ 3	> 140/min	☐ 3

The Yung ASS is scored by attributing scores of 0-3 for each component. The final score is then calculated by taking the sum of these components.

Worked example:

Wheeze		Accessory muscle use		Heart rate	
None	☐	None	☐	< 80/min	☐
Expiratory	✓ **1**	+	☐	81 – 110/ min	☐
Expiratory + inspiratory	☐	++	✓ **2**	111 – 140/min	☐
Heard without stethoscope	☐	+++	☐	> 140/min	✓ **3**

Overall score for this patient: (1+2+3) = **6**