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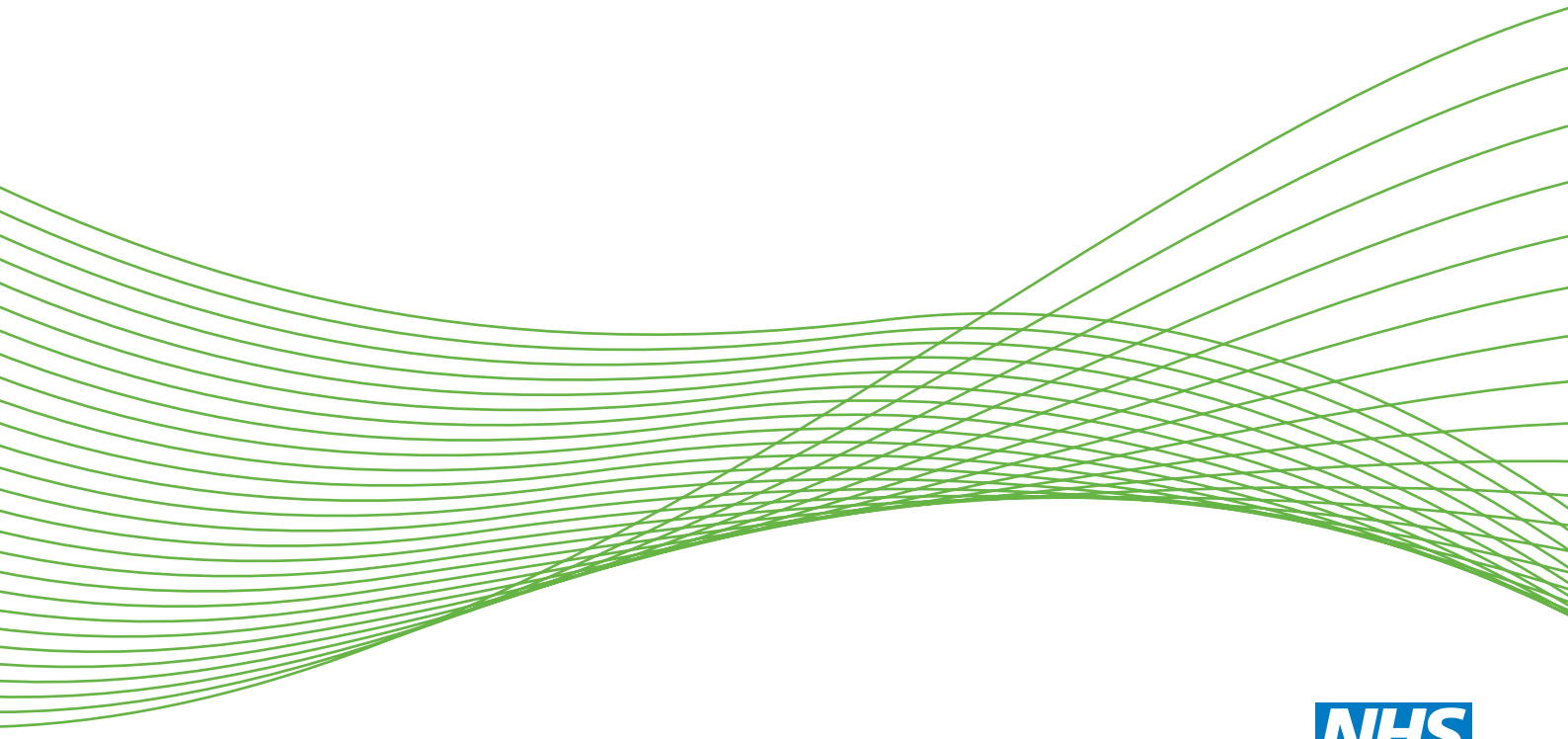

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Abstract

MAGNEsium Trial In Children (MAGNETIC): a randomised, placebo-controlled trial and economic evaluation of nebulised magnesium sulphate in acute severe asthma in children

CVE Powell,[1]* R Kolamunnage-Dona,[2] J Lowe,[2] A Boland,[3] S Petrou,[4] I Doull,[5] K Hood[1] and PR Williamson[2] on behalf of the MAGNETIC study group

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Background: There are few data on the role of nebulised magnesium sulphate ($MgSO_4$) in the management of acute asthma in children. Those studies that have been published are underpowered, and use different methods, interventions and comparisons. Thus, no firm conclusions can be drawn.

Objectives: Does the use of nebulised $MgSO_4$, when given as an adjunct to standard therapy in acute severe asthma in children, result in a clinical improvement when compared with standard treatment alone?

Design: Patients were randomised to receive three doses of $MgSO_4$ or placebo, each combined with salbutamol and ipratropium bromide, for 1 hour. The Yung Asthma Severity Score (ASS) was measured at baseline, randomisation, and at 20, 40, 60 (T60), 120, 180 and 240 minutes after randomisation.

Setting: Emergency departments and children's assessment units at 30 hospitals in the UK.

Participants: Children aged 2–15 years with acute severe asthma.

Interventions: Patients were randomised to receive nebulised salbutamol 2.5 mg (ages 2–5 years) or 5 mg (ages $\geq$ 6 years) and ipratropium bromide 0.25 mg mixed with either 2.5 ml of isotonic $MgSO_4$ (250 mmol/l, tonicity 289 mOsm; 151 mg per dose) or 2.5 ml of isotonic saline on three occasions at approximately 20-minute intervals.

Main outcome measures: The primary outcome measure was the ASS after 1 hour of treatment. Secondary measures included 'stepping down' of treatment at 1 hour, number and frequency of additional salbutamol administrations, length of stay in hospital, requirement for intravenous bronchodilator treatment, and intubation and/or admission to a paediatric intensive care unit. Data on paediatric quality of life, time off school/nursery, health-care resource usage and time off work were collected 1 month after randomisation.

Results: A total of 508 children were recruited into the study; 252 received $MgSO_4$ and 256 received placebo along with the standard treatment. There were no differences in baseline characteristics. There was a small, but statistically significant difference in ASS at T60 in those children who received nebulised $MgSO_4$ {0.25 [95% confidence interval (CI) 0.02 to 0.48]; $p = 0.034$} and this difference was sustained for up to 240 minutes [0.20 (95% CI 0.01 to 0.40), $p = 0.042$]. The clinical significance of this gain is uncertain. Assessing treatment–covariate interactions, there is evidence of a larger effect in those children

with more severe asthma exacerbations ($p = 0.034$) and those with a shorter duration of symptoms ($p = 0.049$). There were no significant differences in the secondary outcomes measured. Adverse events (AEs) were reported in 19% of children in the magnesium group and 20% in the placebo group. There were no clinically significant serious AEs in either group. The results of the base-case economic analyses are accompanied by considerable uncertainty, but suggest that, from an NHS and Personal Social Services perspective, the addition of magnesium to standard treatment may be cost-effective compared with standard treatment only. The results of economic evaluation show that the probability of magnesium being cost-effective is over 60% at cost-effectiveness thresholds of £1000 per unit decrement in ASS and £20,000 per quality-adjusted life-year (QALY) gained, respectively; it is noted that for some parameter variations this probability is much lower, reflecting the labile nature of the cost-effectiveness ratio in light of the small differences in benefits and costs shown in the trial and the relation between the main outcome measure (ASS) and preference based measures of quality of life used in cost–utility analysis (European Quality of Life-5 Dimensions; EQ-5D).

Conclusions: This study supports the use of nebulised isotonic $MgSO_4$ at the dose of 151 mg given three times in the first hour of treatment as an adjuvant to standard treatment when a child presents with an acute episode of severe asthma. No harm is done by adding magnesium to salbutamol and ipratropium bromide, and in some individuals it may be clinically helpful. The response is likely to be more marked in those children with more severe attacks and with a shorter duration of exacerbation. Although the study was not powered to demonstrate this fully, the data certainly support the hypotheses that nebulised magnesium has a greater clinical effect in children who have more severe exacerbation with shorter duration of symptoms.

Trial registration: Current Controlled Trials ISRCTN81456894.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

List of abbreviations

A&E	accident and emergency
AE	adverse event
AIC	Akaike information criterion
ANCOVA	analysis of covariance
ASS	Asthma Severity Score
AUC	area under the curve
BNF	*British National Formulary*
b.p.m.	beats per minute
BTS	British Thoracic Society
CAU	children's assessment unit
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CTU	Clinical Trials Unit (refers to MCRN CTU)
CUA	cost–utility analysis
ED	emergency department
EQ-5D	European Quality of Life-5 Dimensions
FEV_1	forced expiratory volume in 1 second
GLM	generalised linear model
GM	general paediatric ward
GP	general practitioner
HDU	high-dependency unit
ICER	incremental cost-effectiveness ratio
IDSMC	Independent Data and Safety Monitoring Committee
IMP	Investigational Medicinal Product
IQR	interquartile range
ITT	intention to treat
LOS	length of stay
LRN	local research network
MCAR	missing completely at random
MDI	metered dose inhaler
MCRN	Medicines for Children Research Network
MCRN CTU	Medicines for Children Clinical Trials Unit
MICE	Multiple Imputation by Chained Equations
$MgSO_4$	magnesium sulphate
MREC	Multicentre Research Ethics Committee
RMSE	root-mean-squared error
NICE	National Institute for Health and Care Excellence
OLS	ordinary least squares
PAU	paediatric assessment unit
PedsQL™	Paediatric Quality of Life Inventory
PEFR	peak expiratory flow rate
PICU	paediatric intensive care unit
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RD	risk difference
ROAA	rapid-onset acute asthma
ROC	receiver operating characteristic
RR	relative risk

SAE	serious adverse event
SaO_2	the saturation level of oxygen in haemoglobin, as measured in arterial blood
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SIGN	Scottish Intercollegiate Guideline Network
SMD	standard mean difference
SOAA	slow-onset acute asthma
SUSAR	suspected unexpected serious adverse reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

Scientific summary

Background

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

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) 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, for which the recommended treatment for children (< 16 years old) differs markedly from that for adults (≥ 16 years) – a reflection of the evidence base in the different age groups.

The guideline recommends that the initial management in children is inhaled β_2-agonists and ipratropium (Atrovent®, Boehringer Ingelheim) and systemic corticosteroids. Oxygen saturation of < 92% while breathing room air at presentation is noted to be an indicator of more severe asthma, as is oxygen saturation of < 92% at 20 minutes after inhaled β_2-agonists. For poorly responsive children of > 5 years of age, it is recommended that clinicians 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 ($MgSO_4$) is a safe treatment for acute asthma, with no side effects up to doses of 100 mg/kg, the guideline concedes that its place in management is not yet established. $MgSO_4$ does not appear to be recommended for children aged ≤ 5 years. 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.

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. There are few paediatric data on the effect of nebulised $MgSO_4$. The two paediatric studies of nebulised $MgSO_4$, one involving 20 children (Meral A. Inhalation therapy with $MgSO_4$. *Turk J Pediatr* 1996;**38**:169–75) and the other 62 children (Mahajan P, Haritos D, Rosenberg N, Thomas R. Comparison of nebulised magnesium sulphate plus salbutamol plus saline in children with exacerbations of mild to moderate asthma. *J Emerg Med* 2004;**27**:21–5), demonstrated equivocal results MAGNETIC is a randomised, placebo-controlled multicentre trial of the use of nebulised $MgSO_4$ in severe acute asthma in childhood in patients who show a poor response to maximal conventional aerosol treatment.

Objectives

The main objective was to determine whether the use of nebulised $MgSO_4$, when given as an adjunct to standard therapy for 1 hour in acute severe asthma in children, results in a clinical improvement compared with standard treatment alone.

Methods

Population

Children aged 2–15 years suffering from acute severe asthma exacerbations as defined by the BTS guidelines.

Setting

Emergency departments (EDs) and paediatric assessment units (PAUs) at 30 hospitals in the UK.

Inclusion criteria

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

For children aged ≥ 6 years, a diagnosis of severe asthma requires at least one of the following criteria to be met:

(a) oxygen saturations of < 92% while breathing room air
(b) too breathless to talk
(c) heart rate of > 120 beats per minute (b.p.m.)
(d) respiratory rate of > 30 breaths per minute
(e) use of accessory neck muscles.

For children aged 2–5 years, a diagnosis of severe asthma requires at least one of the following criteria to be met:

(a) oxygen saturations of < 92% while breathing room air
(b) too breathless to talk
(c) heart rate of > 130 b.p.m.
(d) respiratory rate of > 50 breaths per minute
(e) use of accessory neck muscles.

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 pregnancy.
(e) Known previous reaction to magnesium.
(f) Inability to give informed consent.
(g) Previous randomisation into the MAGNETIC trial.
(h) Life-threatening symptoms.
(i) Current or previous (in the 3 months preceding screening) involvement with a trial of a medicinal product.

Patients were identified on presentation to EDs/PAUs and assessed against the study inclusion criteria. The Yung Asthma Severity Score (ASS) was also recorded. Patients meeting one or more of the criteria were then given an initial nebulisation of salbutamol/salbutamol plus ipratropium (variation allowed as per hospital practice) and informed proxy consent obtained following consultation with a trained member of the study team. After the initial nebuliser, patients no longer meeting one or more of the inclusion criteria were excluded.

Interventions

At randomisation, eligible patients were allocated to receive either 2.5 ml of isotonic $MgSO_4$ (250 mmol/l, tonicity 289 mOsm; 151 mg per dose) or 2.5 ml of isotonic saline via nebuliser on three occasions at approximately 20-minute intervals. Each nebuliser also contained salbutamol 2.5 mg (children aged 2–5 years) or 5 mg (children aged ≥ 6 years) and ipratropium bromide 0.25 mg in both the active and placebo groups.

The ASS was recorded after each nebuliser administration [at approximately 20, 40 and 60 (T60) minutes post randomisation] and for the following 3 hours (approximately 120, 180 and 240 minutes post randomisation). Adverse events (AEs) were assessed at each assessment point. Patients were followed up until discharge from hospital to collect secondary outcome data items.

Following discharge from hospital, parents and patients (if aged > 5 years) were asked to complete a set of postal questionnaires, collecting data for the quality-of-life (QoL) and health economic measures. The 1-month follow-up postal questionnaire collected QoL [Paediatric Quality of Life Inventory (PedsQL™ Asthma Module) and European Quality of Life-5 Dimensions (EQ-5D) questionnaires] and health economics (NHS and non-NHS) data from discharge to 1 month post randomisation.

Results

In total, 508 children with acute severe asthma exacerbations were recruited into the study; 252 were randomised to receiving $MgSO_4$ and 256 received placebo along with the standard treatment. There were no differences in baseline characteristics. There was a statistically significant difference in ASS at T60 in those children who received nebulised magnesium {0.25 [95% confidence interval (CI) 0.02 to 0.48]; $p = 0.034$} and this difference was sustained for up to 240 minutes [0.20 (95% CI 0.01 to 0.40); $p = 0.042$]. These differences are likely to be of minimal clinical significance. Assessing treatment–covariate interactions, there is evidence of a larger effect in those children with more severe asthma exacerbations ($p = 0.034$) and those with a shorter duration of symptoms ($p = 0.049$). These differences are likely to be clinically relevant. There were no significant differences in secondary outcomes measured. AEs were reported in 19% of children in the magnesium group and 20% in the placebo group. There were no clinically significant serious AEs in either group. The probability of magnesium being cost-effective is over 60% at cost-effectiveness thresholds of £1000 per unit decrement in ASS and £20,000 per quality-adjusted life-year (QALY) gained, respectively.

Conclusions

In the authors' opinion, there are sufficient data in this study to support the use of nebulised isotonic $MgSO_4$ a the dose of 151 mg given three times in the first hour of treatment as an adjunct to standard treatment, though the clinical significance of the treatment effect shown remains uncertain. The response is likely to be more marked in those children with more severe attacks and with a shorter duration of exacerbation.

Implications for health care

This is the largest study of nebulised $MgSO_4$ in children to date. These data will add further evidence that may help to improve and strengthen the recommendations of national and international guidelines for the management of acute asthma in childhood. The results of the base-case economic analyses suggest that, from an NHS and Personal Social Services perspective, the addition of magnesium to standard treatment is likely to be cost-effective compared with standard treatment only. The results of both sets of analyses (cost-effectiveness analysis and cost–utility analysis), show that the probability of magnesium being cost-effective is > 60% at cost-effectiveness thresholds of £1000 per unit decrement in

ASS and £20,000 per QALY gained, respectively. The cost-effectiveness of adding this treatment to the standard treatment regimen has been demonstrated.

Recommendations for research

Further studies of dose–response relationship at different ages and frequency of administration during an attack are required. The effect on secondary outcomes, such as need for intravenous bronchodilators and paediatric intensive care unit admissions and length of stay with different nebulised magnesium treatment regimen (dose and frequency), needs further exploration. The concept of different phenotypes and severity for which the use of nebulised magnesium can be tailored to the features of the exacerbation needs further exploration.

Currently, three further analyses are planned using these data:

1. exploration of the relationship between ASS and the BTS definition of acute severe asthma
2. assessment of the value of the area under the curve analysis of ASSs
3. examination of the concept of acute phenotypes of asthma in children and the response to treatment.

It may be that these data are sufficient to recommend that nebulised magnesium is added to standard treatment, particularly in those who have a severe attack and those with a short history. Further studies of dose–response pharmacokinetics and frequency of doses, nebuliser use, compatibility studies and animal models to clarify the mechanisms of magnesium use are also to be considered.

Trial registration

This trial is registered as ISRCTN81456894.

Funding

This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 17, No. 45. See the HTA programme website for further project information.

Chapter 1 Introduction

Background

Acute asthma continues to be one of the main reasons for acute hospital admission in children, and accounts for much morbidity, anxiety, stress, and time off school and work for the families of children with asthma.[1] The Department of Health has targeted respiratory disease as an area for improved management.[2] The British Thoracic Society and Scottish Intercollegiate Guideline Network (BTS/SIGN)[3] 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, for which the recommended treatment for children (< 16 years old) differs markedly from that for adults (≥ 16 years) in those who are unresponsive to initial standard treatment – a reflection of the evidence base in the different age groups.

The guideline recommends that the initial management in children is inhaled β_2-agonists and ipratropium and systemic corticosteroids. This is similar to the initial management in adults. Oxygen saturation of < 92% while breathing room air at presentation is noted to be an indicator of more severe asthma, as is oxygen saturation of < 92% at 20 minutes after inhaled β_2-agonists. For children of > 5 years of age who do not respond to initial treatment, it is recommended that clinicians consider intravenous bronchodilator therapy – initially, salbutamol followed by a continuous infusion, then intravenous aminophylline followed by infusion. There is little evidence for an intravenous bronchodilator of choice. Furthermore, although the guideline recognises that intravenous magnesium sulphate ($MgSO_4$) is a safe treatment for patients with acute asthma, with no side effects up to doses of 100 mg/kg, it concedes that its place in management is not yet established. $MgSO_4$ is not recommended for children aged ≤ 5 years. The BTS guidelines[3] recommend intravenous $MgSO_4$ 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.[3] There are no current paediatric recommendations concerning nebulised $MgSO_4$.

There is clear evidence that $MgSO_4$ has bronchodilator effects in acute asthma.[4] The BTS guidelines state that experience suggests that intravenous and the nebulised routes are both safe ways of administering $MgSO_4$ in adults. Further trial results are awaited in adults.[5] A single dose of intravenous $MgSO_4$ of a dose of 1.2–2 g in an infusion over 20 minutes is safe and effective improving lung function in adults with acute severe asthma. Safety and efficacy at higher dosages in adults have not been assessed. There is some concern about higher doses causing muscle weakness and respiratory failure. Nebulised $MgSO_4$ in doses of 135–1152 mg in combination with β_2-agonists shows a trend towards reduction in the number of hospital admissions and is mentioned as a possible treatment in adults.[6,7] In marked contrast with the paediatric recommendations, intravenous aminophylline and intravenous β_2-agonists have limited use in adults, with recommendations that these interventions are reserved for ventilated patients and those in extremis.[3] The final recommendation from BTS/SIGN[3] is that more studies are needed regarding the route, frequency and dose in adults for $MgSO_4$. The recommendations from the Cochrane review of 2005[6] and the 2007 systematic review by Mohammed and Goodacre[4] are that more studies are needed in both adults and children to identify exactly how $MgSO_4$ (intravenous or inhaled) should be used.

Rationale

Mechanisms

The use of $MgSO_4$ for acute asthma was first described in 1936, and since then there has been increasing evidence for its use in adults and children with asthma.[3] There are a number of proposed mechanisms

for its actions. In vitro studies demonstrate an inhibitory effect of $MgSO_4$ on contraction of bronchial smooth muscle, and the release of acetylcholine in cholinergic nerve terminals and of histamine from mast cells.[6] There is evidence that $MgSO_4$ may act as an anti-inflammatory agent by inhibiting the neutrophil respiratory burst in adults with asthma.[8] The main effect of $MgSO_4$ is that it blocks the calcium ion influx to the smooth muscles of the respiratory system[9] and bronchodilatation occurs.

Clinical evidence for magnesium sulphate as a bronchodilator

Intravenous magnesium sulphate

The Acute Asthma and Magnesium Study Group has demonstrated the efficacy of intravenous $MgSO_4$ in severe acute asthma in adults.[10] In a multicentre randomised placebo-controlled trial of 248 adults with acute asthma and a forced expiratory volume in 1 second (FEV_1) of < 30% predicted, intravenous administration of 2 mg of $MgSO_4$ as an adjunct to the standard therapy resulted in significant benefit in FEV_1 of nearly 5%. The effect appeared greatest in those with the most severe asthma, with a difference of 10% in FEV_1 between $MgSO_4$- and placebo-treated groups, thus the recommendations set out in the BTS guidelines.[3] A Cochrane review of intravenous treatment with $MgSO_4$[11] supports this evidence and recommendation. Intravenous administration of $MgSO_4$ 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 $MgSO_4$ in acute asthma.

Nebulised magnesium sulphate

Nebulised $MgSO_4$ does not appear to act as a bronchodilator in subjects with stable chronic asthma.[12,13] However, in acute exacerbations in subjects between the age of 12 and 60 years with moderate to severe acute asthma, the response to nebulised $MgSO_4$ appears to be of similar magnitude as the response to salbutamol, as defined by changes in peak expiratory flow rate (PEFR).[14]

Initial therapeutic trials of nebulised $MgSO_4$ administered as an adjunct to nebulised salbutamol gave conflicting results in adults. In a small study of 35 adults, Nannini *et al.* demonstrated a significantly greater improvement in PEFR at 20 minutes after administration in patients receiving nebulised $MgSO_4$ in addition to nebulised salbutamol than with nebulised isotonic saline and salbutamol.[15] A report in adults with severe acute asthma with an FEV_1 of < 30% of that predicted, 30 minutes after initial administration of salbutamol via a nebuliser, demonstrated a significant benefit in FEV_1 for those receiving $MgSO_4$ compared with isotonic saline.[16] In contrast, Bessmertny *et al.* could show no evidence of benefit in 74 adults with moderately severe asthma.[17]

The most recent Cochrane review of nebulised $MgSO_4$ examined only six randomised controlled trials (RCTs) involving a total of 296 patients.[6] Four studies[15–18] compared nebulised $MgSO_4$ plus a β_2-agonist with a β_2-agonist plus placebo, and two studies[14,19] compared $MgSO_4$ with a β_2-agonist alone. Three[15–17] of the six studies[14–19] involved adults exclusively: those by Bessmertny *et al.* (18–65 years),[17] Hughes (16–65 years)[16] and Nannini *et al.* (> 18 years).[15] Of the remaining three studies,[14,18,19] one included a mix of adult and paediatric patients aged 12–60 years[14] and there were two paediatric studies[18,19] that included patients aged 5–17 years.

The two paediatric studies[18,19] that used nebulised $MgSO_4$ both have methodological deficits. However, the results of the studies show that nebulised $MgSO_4$ 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.[19] There appears to be an additive effect when inhaled $MgSO_4$ is combined with salbutamol.[18]

Meral[19] examined two groups of 20 children with mean ages of 10.6 years and 11 years (range 8–13 years) with a severe exacerbation of asthma. In a RCT, patients received either 2 ml of $MgSO_4$ (280 mmol/l, tonicity 258 mOsm, pH 6.7) nebulised over 15–20 minutes or inhaled salbutamol (note: no salbutamol was given in the $MgSO_4$ 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.[19] This study[19] had an unclear randomisation and blinding procedure, had a questionable outcome measure (owing to the lack of reproducibility and reliability of PEFR) and unclear inclusion and exclusion criteria.[20]

Mahajan *et al.*[18] included 62 patients, aged 5–17 years, with severe acute asthma in a double-blind, randomised, placebo-controlled trial. Using FEV_1 at 10 and 20 minutes after treatment and admission rates as outcomes along with a clinical score, they administered 2.5 ml of isotonic $MgSO_4$ (6.3% solution) with salbutamol (2.5-mg nebule) or salbutamol with normal saline. One dose of the study medication was used and they demonstrated a significant improvement in FEV_1 at 10 and 20 minutes after treatment with $MgSO_4$ and salbutamol combined.[18]

The overall conclusions from this review were that the use of nebulised inhaled $MgSO_4$ in addition to β_2-agonists in the treatment of an acute asthma exacerbation appears to have benefits with respect to improved pulmonary function [standard mean difference (SMD) 0.23 [95% confidence interval (CI) – 0.03 to 0.50]; four studies].[6] The benefit was significantly greater in more severe asthma exacerbations [SMD 0.55 (95% CI 0.12 to 0.98)] but overall there were insufficient data, particularly in children, to make firm recommendations. Most importantly, there were no adverse events (AEs) reported and so the other important conclusion was that nebulised $MgSO_4$ treatment was safe.[5] Thus, conclusions regarding treatment with nebulised $MgSO_4$ were difficult to draw.

Mohammed and Goodacre[4] completed a systematic review in 2007 and identified three more studies involving nebulised $MgSO_4$. There were no new exclusively paediatric publications. There was one new adult study by Kokturk *et al.*[21] in 2005 (18–60 years) and two studies[22,23] including mixed populations of adults and adolescents: Aggarwal *et al.*[22] (13–60 years) and Drobina *et al.*[23] (12–60 years). These three studies[21–23] contributed a further 236 patients bringing the overall total to 532.

Kokturk *et al.*[21] examined 26 patients (18- to 60-year-olds) in a randomised, single-blinded trial. They examined PEFR up to 240 minutes post randomisation and admissions as their main outcomes of interest. They examined moderate to severe exacerbations and compared $MgSO_4$ (2.5 ml of 6.3%) and salbutamol (2.5 ml) with saline as placebo and salbutamol. This small study[21] suggested there is no benefit to be gained from adding $MgSO_4$ to salbutamol in terms of PEFR or number of hospital admissions.

Aggarwal *et al.*[22] went on to study 100 patients (aged 13–60 years). The mean age of the patients studied was 46 years in both the intervention and the control group, which would suggest that the study was unlikely to have contained many adolescents. The authors examined PEFR up to 120 minutes post randomisation and admissions as the main outcomes and looked at severe to life-threatening acute asthma. They compared nebulised salbutamol (1 ml) with nebulised $MgSO_4$ (1 ml of 500 mg), three doses in 1 hour, with saline and distilled water as placebo. The patients were randomised using a random number table and the study was double-blind. The investigators found no difference in outcomes between the two groups and concluded that there is no therapeutic benefit to be gained from adding $MgSO_4$ to the standard treatment regimen.[22] Drobina *et al.*[23] (findings published in abstract only) examined 110 patients (12–60 years) with mild to severe asthma, again using PEFR and admissions as the primary outcomes. The intervention group received 150 mg of $MgSO_4$ (0.3 ml of 50% $MgSO_4$) added to each nebulised dose of medication. The control group received nebulised treatments of salbutamol 0.5% (5 mg/ml) combined with 0.5 mg of ipratropium bromide 0.02% inhalation solution. This study showed no evidence of an effect of adding $MgSO_4$ on the above outcomes.[23]

These further three studies[21–23] with 236 patients thus found no evidence of an effect. Based on these findings, along with those of the other six studies, the reviewers concluded, that, in adolescents and adults, there is only weak evidence that the use of nebulised $MgSO_4$ has an effect on respiratory function [SMD 0.17 (95% CI – 0.02 to 0.36); $p = 0.09$] or hospital admission [relative risk (RR) 0.68 (95% CI 0.46 to 1.02); $p = 0.06$]. These effects were clearly weaker that the results from the 2005 Cochrane review.[6] The reviewers felt able to draw an overall conclusion of the paediatric evidence based on the two paediatric

studies. They concluded that there was no evidence of a significant effect of the addition of $MgSO_4$ to standard treatment on respiratory function [SMD – 0.26 (95% CI – 1.49 to 0.98); $p = 0.69$] or hospital admission [RR 2.0 (95% CI 0.19 to 20.93); $p = 0.56$]. This conclusion did not differ significantly from the results of the Cochrane review in 2005.[6] Assessment of the risk of outcome reporting bias in the latest systematic review[4] led to a sensitivity analysis adjusting for the suspected bias; the results[24] suggested that the conclusions of the review were robust to this problem.

Risks and benefits

Risks

All six studies[14–19] reported in the Cochrane review reported no serious adverse events (SAEs) in either arm.[6] The risk of SAEs was low in the studies comparing (1) $MgSO_4$ with β_2-agonists [risk difference (RD) 0.00 (95% CI – 0.11 to 0.11)] and (2) $MgSO_4$ with a β_2-agonist to a β_2-agonist alone (RD 0.00; 95% CI – 0.03 to 0.03). The risk of SAEs was low and appeared to be even lower 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). In the three extra papers in the Mohammed review,[4] Aggarwal *et al.*[22] and Kokturk *et al.*[21] reported no significant AEs and Drobina *et al.*[23] made no comment (see *Appendix 1*, *Table 38*).

A systematic review (not published) of the adverse effects of inhaled $MgSO_4$ in children was undertaken by the University of Liverpool for this study and identified two studies,[25,26] not included in the Cochrane review,[6] containing at most 18 further children. There were no reported AEs (see *Table 1*). These extra studies were not RCTs of $MgSO_4$ during an acute asthma attack but they did report the effects of administering nebulised $MgSO_4$, thus AEs could be examined.[25,26]

In the MAGNET pilot study (Ashtekar *et al.*;[27] EudraCT no. 2004-003825-29), a total of 25 eligible patients were identified for inclusion into the study over a 3-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. Seven patients who were randomised to active treatment and 10 patients to placebo. MAGNET[27] found that there were no differences between the two groups when comparing the median Asthma Severity Score (ASS)[28–30] after three nebulised treatments and the area under the curve (AUC) analysis of the ASS for the six time points.[27] There were insufficient numbers to make a significant comment about the efficacy of nebulised $MgSO_4$ from the pilot study, the main aim of which was to test recruitment, administration and outcome assessment feasibility.

Two children (both of whom received $MgSO_4$) had mild AEs. One child had transient facial flushing and, although asymptomatic, a blood pressure reading appeared low. The blood pressure was immediately remeasured and was then normal. Another child had transient tingling of the fingers.[27]

Benefits

As described in detail above, five studies[14–16,18–19] showed a benefit to using nebulised $MgSO_4$ in some preparation, whereas four studies[17,21–23] showed no benefit. There was heterogeneity between trials regarding study design, dose given, intervention comparison, primary outcomes and exclusion criteria (see *Appendix 1*, *Tables 37–39*), There was a non-statistically significant improvement in pulmonary function between patients whose treatments included nebulised $MgSO_4$ in addition to β_2-agonists [SMD 0.23 (95% CI – 0.03 to 0.50), four studies] and hospitalisations were similar between the groups [RR 0.69 (95% CI 0.42 to 1.12), three studies]. Subgroup analyses demonstrated statistically significant differences in lung function improvements with nebulised $MgSO_4$ in addition to a β_2-agonist in patients with severe exacerbations of their asthma [SMD 0.55 (95% CI 0.12 to 0.98)].

However, only one study[16] reported the effect of three doses of $MgSO_4$ nebulised with salbutamol in patients with severe asthma. In the study reported by Hughes,[16] three nebulised treatments of $MgSO_4$ mixed with salbutamol were given at 30-minute intervals to adults with severe asthma, and resulted in a

twofold greater increase in FEV_1 than the same dose of salbutamol administered with isotonic saline nebuliser solution; this enhanced bronchodilator response was associated with a significant reduction in hospital admission rates [RR 0.61 (95% CI 0.37 to 0.99), $p = 0.04$]. Only one study[23] had used nebulised ipratropium bromide as well as salbutamol as standard treatment,[23] which is certainly the current recommendation from the BTS for children and for adults.[3]

The University of Liverpool systematic review also investigated the efficacy of nebulised $MgSO_4$ in children. The findings are summarised in *Table 1*.

At the beginning of recruitment to MAGNETIC, this was the current published evidence. We have currently completed a further update of the Cochrane review[6] using the Cochrane review methodology, and this has now been published.[32] At the time of this report there were a total of 16 published studies of randomised controlled study design in acute asthma, with a total of 838 patients (439 subjects who had completed an intervention with $MgSO_4$ and 399 who were control subjects in studies). The seven studies[27,33–38] published since Mohammed 2007, or earlier studies not included in Mohammed's systematic review, are three studies involving adults exclusively;[33–35] one study including adults and paediatric patients;[36] two studies that enrolled children[27,37] and, one study[38] in which the age of participants was not stated. The data from these studies will be discussed in *Chapter 5* of this report. The features of these 16 studies[14–19,21–23,27,33–38] are presented in *Appendix 1* in three tables but they are clearly heterogeneous in study design, population examined, intervention administered and outcomes measured.

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

Study	AEs in $MgSO_4$ group	Efficacy
Rolla 1987[25]	Measured: not stated	No difference in lung function
	Reported: no mention of AE in results/discussion	Improvement in airway responsiveness
Rolla 1988[26]	Measured: not stated	Inhaled doses of > 0.1 mmol led to improvement in bronchial hyper-responsiveness
	Reported: 'no patient experienced side effects'	
Meral 1996[19]	Measured: 'subjects were evaluated for possible adverse effects'	PEFR: $MgSO_4$ 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 magnesium group. Respiratory distress score: no difference between groups
	Reported: in discussion – 'No adverse reaction in either group as the heart rate and blood pressure did not change'	
Mangat 1998[14]	Measured: blood pressure, arrhythmia; hyporeflexia, respiratory depression	Patients treated with nebulised $MgSO_4$ improved in terms of bronchodilatation and Fischl score.[31] However, this effect was not significantly different to that of the group given nebulised salbutamol
	Reported: (not stated whether these occurred in adults or children) – one transient hypotension (spontaneously resolved); no hyporeflexia	Note: the study report does not report the paediatric results separately from the adult results
Mahajan 2004[18]	Measured: tremors, headaches, nausea, vomiting, hyporeflexia	FEV_1 absolute: improvement at 10 minutes significantly better than in control group ($p < 0.03$); at 20 minutes no difference between groups
	Reported: 'none of the patients in either group showed any side effects'	FEV_1% predicted: no difference between groups

Thus there is a need for a large study examining the addition of nebulised $MgSO_4$ in children with acute severe asthma compared with standard treatment in a placebo-controlled double-blind randomised manner. MAGNETIC is a randomised placebo-controlled multicentre trial of the use of nebulised $MgSO_4$ in severe acute asthma in childhood in patients who show a poor response to maximal conventional aerosol treatment.

Objective

Primary objective

Does nebulised $MgSO_4$, used as an adjunct to nebulised salbutamol and ipratropium bromide for 1 hour in children with severe asthma, result in a clinical improvement compared with nebulised salbutamol, ipratropium bromide and placebo?

Secondary objectives

Does nebulised $MgSO_4$, used as an adjunct to nebulised salbutamol and ipratropium bromide for 1 hour in children with severe asthma, compared with nebulised salbutamol, ipratropium bromide and placebo, have an effect on:

(a) clinical outcomes in terms of additional treatment/management while in hospital, and length of stay (LOS) in hospital
(b) patient outcomes in terms of quality of life (QoL), time off school and health-care resource usage over the following month
(c) parent outcomes in terms of time off work over the following month
(d) costs *and* cost-effectiveness for the NHS and Personal Social Services and, more broadly, for society?

Chapter 2 Methods

Objective

The objective of the MAGNETIC trial was to assess whether the addition of magnesium to standard treatment for acute severe asthma in children resulted in a clinical improvement compared with standard treatment alone.

Design

This was designed as a prospective, controlled, double-blind, multicentre RCT comparing the effects of nebulised $MgSO_4$ with placebo for children presenting to secondary care with an acute severe asthma exacerbation.

Participants

Using the Medicines for Children Research Network (MCRN), 30 centres were identified. The network now covers most regions in England. Adding the Northern Ireland Research Network, the Scottish MCRN and the one site in Wales (Cardiff), we established (via an initial feasibility study) that each centre would be likely to able to recruit sufficient patients with severe acute asthma for the numbers required for the study. These centres all received patients with acute asthma into their unit's unscheduled care service and this may be in the form of a visit to emergency department (ED) or a children's assessment unit (CAU) or both. The patient inclusion and exclusion criteria for the MAGNETIC trial were as follows.

Inclusion criteria

Potential participants for the study could be between the ages of 2 years and 16 years. They could have had a previous history and diagnosis of asthma and be on treatment but could also be patients who have presented for the first time with acute asthma as per BTS/SIGN definitions.[3] Subjects could be recruited in either an ED or a CAU in secondary care. The main clinical definition for inclusion was severe acute asthma as defined by the BTS/SIGN guidelines.[3]

For children of ≥ 6 years, severe acute asthma is based on at least one of the following criteria being met:

(a) oxygen saturations of $< 92\%$ while breathing room air
(b) too breathless to talk
(c) heart rate of > 120 beats per minute (b.p.m.)
(d) respiratory rate of > 30 breaths per minute
(e) use of accessory neck muscles.

For children aged 2–5 years, severe acute asthma is based on at least one of the following criteria being met:

(a) oxygen saturations of $< 92\%$ while breathing room air
(b) too breathless to talk
(c) heart rate of > 130 b.p.m.
(d) respiratory rate of > 50 breaths per minute
(e) use of accessory neck muscles.

Exclusion criteria

(a) Co-existing respiratory disease, such as cystic fibrosis or chronic lung disease of prematurity.
(b) Severe renal disease.
(c) Severe liver disease.
(d) Known pregnancy.
(e) Known previous reaction to magnesium.
(f) Inability to give informed consent.
(g) Previous randomisation into the MAGNETIC trial.
(h) Life-threatening symptoms.
(i) Current or previous (in the 3 months preceding screening) involvement with a trial of a medicinal product.

Interventions

Patients were randomised to receive nebulised salbutamol 2.5 mg (aged 2–5 years) or 5 mg (aged ≥ 6 years) and ipratropium bromide 0.25 mg mixed with either 2.5 ml of isotonic $MgSO_4$ (250 mmol/l, tonicity 289 mOsm; 151 mg per dose) or 2.5 ml of isotonic saline on three occasions at approximately 20-minute intervals. There is currently no specific agreed dose of $MgSO_4$ for use in children.[4] The $MgSO_4$ dose for this study was chosen based on the doses described in the published paper by Hughes in 2003,[16] as they were shown to be effective and safe in acute asthma in an adult population.[16] The magnesium solution needs to be isotonic as hypertonic and hypotonic solutions may cause bronchoconstriction.[16] The doses used in the published paediatric studies were both isotonic [Meral,[19] 2 ml of isotonic $MgSO_4$ (280 mmol/l, tonicity 258 mOsm, 116 mg/dose); Mahajan *et al.*,[18] 2.5 ml of isotonic (6.3%) $MgSO_4$, 145 mg/dose)]. The frequency of the dosing was based on the three doses of bronchodilators (salbutamol and ipratropium) in the first hour of treatment as recommended by BTS,[3] with the $MgSO_4$ or placebo added. Use of various doses is described in the clinical effectiveness literature (see *Appendix 1* and discussion in *Chapter 5*).

Study procedures

Patients were identified on presentation to EDs or CAUs and assessed against the study inclusion criteria. If they fulfilled the severity criteria as defined by the BTS definition,[3] the Yung ASS was recorded.[30] Patients were then given a nebuliser containing salbutamol and/or ipratropium bromide (variations allowed; as per site routine clinical practice) and parents/guardians were then approached and asked for their informed consent.

Following this initial nebuliser the patient was re-assessed against the inclusion criteria and the ASS recorded again. Patients were eligible for randomisation provided at least one of the inclusion criteria of the severe asthma BTS definition[3] were met and informed consent had been obtained from the parent and if appropriate assent from the child.

Patients were randomised to receive either 2.5 ml of isotonic $MgSO_4$ (250 mmol/l, tonicity 289 mOsm; 151 mg per dose) or 2.5 ml of isotonic saline via nebuliser on three occasions at approximately 20-minute intervals. Each nebuliser also contained salbutamol 2.5 mg (children aged 2–5 years) or 5 mg (children aged ≥ 6 years) and ipratropium bromide 0.25 mg in both the active and placebo groups. It was planned that as soon as they were randomised then the treatment would start.

The ASS was measured at approximately 20 (T20, after first treatment nebuliser), 40 (T40, after second treatment nebuliser), 60 (T60, after third treatment nebuliser), 120, 180 and 240 minutes post randomisation. AEs, concomitant medication, oxygen saturation, respiratory rate and blood pressure were also recorded at these assessment points.

Following the conclusion of 4-hour follow-up, AEs were monitored and data collection continued until discharge from hospital to assess secondary outcome measures. Parents and patients (if aged ≥ 5years) were contacted by the research team and asked to complete postal questionnaires 1 month after their hospital visit in order to collect health-related QoL and health economics data. The schedule of study procedures is shown in *Table 2*, see below.

Procedures for assessment

Efficacy

Asthma severity was assessed using a validated score, the Yung ASS,[28–30] which comprises three clinical signs: wheezing, accessory muscle use and heart rate. Each component has a minimal score of zero and a maximum of 3. The total score is a sum of each component, giving a minimum score of zero and a maximum of 9. The score has been validated as a measure of asthma severity in children including the younger age group, has been demonstrated to be reproducible and reliable,[29] with good interobserver agreement, and correlates well with oxygen saturation and FEV_1.[30] This score is clinically easy to use and involves some of the standard assessments, used routinely by medical and nursing staff while managing children with acute asthma. The ASS assessment was carried out by a clinician or by a nurse who was appropriately trained to make the necessary observations in the opinion of the principal investigator for that site.

Safety

Patient status was monitored for 4 hours post randomisation. Oxygen saturation, respiratory rate and blood pressure were recorded twice during screening, approximately 20, 40 and 60 minutes post randomisation, and follow-up checks at 120, 180 and 240 minutes post randomisation. The research team were prompted to check for AEs at each assessment point, by reviewing physiological parameters such as blood pressure and asking about known side effects, for example facial flushing. AEs were followed up until discharge from hospital.

Health economics and quality of life

The case report form (CRF) used by the clinical team at each site recorded each child's NHS resource use from randomisation to discharge from hospital. The 1-month follow-up postal questionnaire collected QoL [Paediatric Quality of Life Inventory (PedsQL™) Asthma Module and European Quality of Life-5 Dimensions (EQ-5D) questionnaires] and health economics (NHS and non-NHS) data from discharge to 1 month post randomisation (see *Appendices 2* and *9*).

Outcomes

There are many and varied primary outcomes to choose from in acute asthma studies.[39] There are no agreed core outcomes for use in acute asthma studies in ether adult or paediatric studies, and so there is huge variation in the primary and secondary outcomes reported.[4,6] In the nebulised $MgSO_4$ literature, numerous and varied outcomes (see *Appendix 1*, *Table 38*) are reported. Measurements of lung function in children recorded during an acute attack or in those in whom lung function has never previously been measured are too unreliable to use accurately.[40] Thus, an ASS appears to be a clinically relevant score to use in children to avoid the need for measuring lung function. The main problem is there are over 20 asthma severity scores[39,41,42] all with different qualities. We chose the most validated and easiest to use – the Yung ASS.[30] The choice of the ASS is discussed further in *Chapter 5*. As there was evidence that the response to inhaled $MgSO_4$ is within the first hour of treatment[4,7,19] we decided to measure the primary outcome as the ASS at 60 minutes post treatment (T60) and then hourly up to 240 (T240) minutes post treatment to establish if there is a sustained effect. We also measured respiratory rate, heart rate, oxygen saturation in air and blood pressure as objective measurements. There are a number of secondary outcomes that we collected based on the most common secondary outcomes measured in acute asthma studies.[39] 'Stepping down' of treatment at 1 hour describes the decision to change from nebulisers to

TABLE 2 Schedule of study procedures

Procedures		Screening	Randomisation[a]	Minutes post randomisation: 20	40	60	120	180	240	During admission	Before discharge	1-month follow-up	Premature discontinuation
Signed consent form			✗										
Assessment of eligibility criteria		✗	✗										
Yung ASS		✗	✗	✗	✗	✗	✗	✗	✗				
Assignment to study treatment			✗										
Review of medical history		✗	✗										
Review of concomitant medications		✗	✗	✗	✗	✗	✗	✗	✗	✗	✗		✗
Study intervention[b]			✗	✗	✗								
Blood pressure, SaO_2, respiration rate		✗	✗	✗	✗	✗	✗	✗	✗				
PedsQL™ Asthma Module												✗	
EQ-5D												✗	
Health economics questionnaires												✗	
Physical examination	Complete	✗											✗
	Symptom-directed		(✗)	(✗)	(✗)	(✗)	(✗)	(✗)	(✗)	(✗)	(✗)		
Assessment of AEs				✗	✗	✗	✗	✗	✗	✗	✗		✗

✗, activities required; (✗), activities as indicated/appropriate; PedsQL™; EQ-5D, European Quality of Life-5 Dimensions; SaO_2, the saturation level of oxygen in haemoglobin, as measured in arterial blood.

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

b Study intervention: a maximum of three doses administered at 20- to 30-minute intervals. Trial treatment is administered in conjunction with nebulised salbutamol and ipratropium bromide.

spacers, a proxy for the treating clinician making a judgement that the child is getting better having presented with severe exacerbation. In a study of 36 EDs in Australia including 720 patients with acute asthma, 50% of those with acute asthma who presented as a severe exacerbation improved sufficiently to be classified as to be moderate at 1 hour after treatment was started, thus potentially able to change from nebulisers to spacers.[43]

Primary outcome

The primary end point was the ASS after 60 minutes of treatment. It was defined as ASS at T60.

Secondary outcomes

Clinical (during hospitalisation):

- 'stepping down' of treatment at 1 hour (the 'stepping down' of treatment at 1 hour is defined by the change to metered dose inhaler (MDI)/spacer combination only or no further treatment until discharge)
- number and frequency of additional salbutamol administrations
- LOS 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 QoL (PedsQL™ Asthma Module parental report for all children and self-completion if aged > 5 years, EQ-5D)
- time off school/nursery for the child
- health-care resource usage [e.g. general practitioner (GP) visits, additional prescribing]
- time off work (related to child's illness).

Sample size calculation

In order to detect a difference between the two treatment groups at T60 of 0.5 points on the ASS at a 5% significance level with 80% power, 500 children were required to participate in the trial. This assumes a standard deviation (SD) = 1.95 based on a similar population in Australia.[30] The SD was estimated from the Cardiff pilot study (EudraCT no. 2004–003825–29) to be 1.7. We took the larger SD estimate in order to be conservative. The ASS can range from zero to 9. A difference of 0.5 was deemed by the research and Trial Management Group (TMG) members to be the minimum worthwhile clinically important difference to be detected. This sample size will also be sufficient to identify an increase in the number of children being 'stepped down' in terms of medication after 1 hour of treatment from 50–63% with 80% power at a 5% significance level. Sample size calculations were undertaken using nQuery Advisor software (Statistical Solutions, Saugus, MA, USA), version 4.[44]

Randomisation and blinding

Randomisation lists were generated in Stata Statistical Software (StataCorp LP, College Station, TX, USA), release 9, using block randomisation with random variable blocks length 2 and 4 and a 1 : 1 ratio of treatment allocation. Randomisation was stratified by centre. Treatment packs were identical in appearance and numbered in sequential order in the format XXXYYY (X = site code, Y = sequential number beginning with 001). Each pack contained three vials of 2.5 ml of $MgSO_4$ or placebo, manufactured and quality controlled and QP released by St Mary's Pharmaceutical Unit, Cardiff, UK [MA (IMP) 35929] (IMP, Investigational Medicinal Product). Centres used their own stock of salbutamol and ipratropium bromide.

Data management

The data were recorded on standardised CRFs designed collaboratively by the TMG. These were returned to the MCRN CTU and the data entered on to a validated electronic study database [InferMed MACRO version 3 (InferMed, London)] by trained staff. Confirmation of patient recruitment was by receipt of a fully signed consent form. Each CRF was checked for adherence to the trial protocol and for missing and/or erroneous values. Discrepancies were queried with study sites to obtain the correct data or obtain reasons, where possible, for missing data/errors. Data entry accuracy checks were performed on 100% of primary outcome data, 'LOS', 'admission to PICU/intubation' and 'need for IV treatment'. Checks were performed by a member of staff independent from the trial. Levels of missing data were monitored throughout and strategies developed to minimise occurrence; however; as much information as possible were collected about the reasons for missing data.

Statistical methods

Internal pilot

To ensure the appropriateness of the SD used in the sample size calculation it was planned to undertake an internal pilot after the first 30 children had been randomised and completed follow-up. This blinded internal pilot was not deemed to have any significant impact on the final analysis and no between-group comparisons were made. If the SD had been found to be smaller than that used in the sample size calculation, suggesting that fewer patients were required than initially proposed, then no action would be taken and the size of the study would remain as planned. If the SD was found to be larger than assumed, suggesting the need for more patients, then, on the advice of the Independent Data and Safety Monitoring Committee (IDSMC), the Trial Steering Committee (TSC) would have aimed to increase recruitment and consider implications for funding and existing resources.

Interim analysis

To estimate the effect of nebulised $MgSO_4$ for the primary efficacy outcome, a single interim analysis adopting the Haybittle–Peto[45] approach was planned after approximately 250 children had been randomised, with 99.9% CIs calculated for the effect estimate. This method was chosen to ensure that interim efficacy results would have to be extreme before early termination would be 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, and no inflation factor needs to be applied to the sample size using this approach.

Study statistical analysis plan

All analyses were conducted according to the statistical analysis plan (SAP) (see *Appendix 3*), which provides a detailed and comprehensive description of the main, pre-planned analyses for the study. Analyses were performed with standard statistical software (SAS version 9.3, SAS Institute Inc., Cary, NC, USA) apart from joint modelling (undertaken as a sensitivity analysis for examining the effect of missing primary outcome data) that was undertaken using the R language, version 2.15.2 (The R Foundation for Statistical Computing, Vienna, Austria) (http://cran.r-project.org/). The software for joint modelling (JoineR library; 2.13.0 version, the R Foundation for Statistical Computing, Vienna, Austina) has been validated through simulations in variety of settings representing different correlation patterns between longitudinal and survival processes. The main features of the SAP are summarised below.

The CONSORT (Consolidated Standards of Reporting Trials) flow diagram is used to summarise representativeness of the study sample and patient throughput in the trial. It was planned to collect screening data, and hence efforts were regularly made to encourage the return of screening logs.

Baseline characteristics are presented by treatment group and overall, with continuous variables summarised in terms of means (SD) or medians [interquartile range (IQR)] depending on the degree of skewness,

and categorical variables presented in terms of numbers (%) per category. The intention-to-treat (ITT) principle is used with a two sided *p*-value of 0.05 (5% level) for statistical significance and 95% CIs for the relative treatment effect reported throughout.

The primary outcome is presented with means and SDs at T60 for each treatment group. Analysis of covariance (ANCOVA) is used to present results adjusted for baseline ASS value. The reasons for missing primary outcome data are provided with the results of the sensitivity analyses which are used to investigate the robustness of the primary outcome results to missing data (see *Appendix 5*). The chief investigator classified the information on the reason for missing ASS data and was blind to the treatment group allocation. Key baseline characteristics for those with observed ASS at T60 are compared between treatment groups, and differences in key baseline characteristics between patients with observed and missing ASS at T60 are also investigated (see *Appendix 5*) to assess whether missingness affects the randomisation balance and plausibility of the missing completely at random (MCAR) assumption. Sensitivity analysis was also performed to examine a centre effect (see *Appendix 6*).

All continuous secondary outcomes that were non-normally distributed are summarised in terms of medians and IQR for each treatment group, and compared using the Mann–Whitney *U*-test. When a secondary outcome is categorical, the two treatment groups are compared using a chi-squared test.

The chief investigator classified information on the reason for PICU admission/intubation in terms of whether it was likely to be related to trial treatment, queries regarding whether children had stepped down at 1 hour, and AEs and SAEs, blind to treatment group allocation. A statistical test comparing the percentage of children suffering an AE in each arm has not been performed for two reasons: (1) this analysis would assume the AEs are of equal importance; and (2) no hypotheses on AEs were set out upfront before the blind had been broken.

Protocol amendments

Protocol amendments are summarised in *Appendix 4*. In summary, the main amendments following those made to obtain Multicentre Research Ethics Committee (MREC) and Medicines and Healthcare products Regulatory Agency (MHRA) approval were to include additional principal investigators and participating centres. No major changes to the study procedures were made during the trial.

Health economics analysis plan

The economic evaluation aimed to assess the cost-effectiveness of nebulised $MgSO_4$ in the management of severe acute asthma in children based on the data collected within the MAGNETIC trial.

Treating children with asthma is likely to have at least two economic research aspects, which both relate to clinical effectiveness. The first is the short-term side effects and relief from primary symptoms and direct consequences of the condition on costs and health-related QoL. The second is the medium- and long-term effects in terms of reduced disability and any medium- and long-term adverse reactions from treatment. This study focused on the short- and medium-term costs and consequences of nebulised $MgSO_4$ in the management of severe acute asthma in children. The study protocol had allowed for extrapolation of costs and consequences over a longer time horizon if the results had demonstrated a difference in medium-term outcomes. This longer-term modelling would have been based on the natural history of the disease and additional evidence from the literature in the event that the trial yielded significant benefits for $MgSO_4$.

The primary analysis (base case) took the perspective of the NHS and Personal Social Services[46] and, consequently, the costs incurred by children's families or education services were excluded from the base-case analysis. A sensitivity analysis took a wider societal perspective that included broader

economic costs, including costs incurred by children's families at the time of treatment and during the 4 weeks thereafter.

Two main analyses of incremental cost-effectiveness were conducted. The first analysis comprised a cost-effectiveness analysis (CEA) calculating the incremental cost per unit change in ASS after 60 minutes of treatment, whereas the second comprised a cost–utility analysis (CUA) calculating the incremental cost per quality-adjusted life-year (QALY) gained through treatment.

Collection of resource-use data

Data were collected about all significant health service and broader societal resource inputs over the 1-month time horizon of the study (i.e. over the period between randomisation and 1 month post randomisation). These data were obtained through two principal means. First, the study CRFs captured all resource use related to the child's primary hospital attendance(s) including diagnosis and treatment as well as transfers between wards and hospitals. Specifically, individualised resource use was estimated for the resources associated with the primary ED/CAU attendance, admissions to inpatient wards [classified as PICU, high-dependency unit (HDU), general paediatric ward (GM)], duration of intubation during the hospital admission(s), duration of mechanical ventilation during the hospital admission(s), surgical procedures performed during the hospital admission(s), tests or investigations performed during the hospital admission(s), additional bronchodilator medication, concomitant medications, and resources associated with AEs. Duration of resource use for significant resource items during the ED/CAU attendance and hospital admission(s) was recorded. Second, economic questionnaires were posted to the main parent of each child approximately 1 month post randomisation. The questionnaires recorded the children's resource use during the period between completion of ED/CUA or hospital discharge and 1 month post randomisation (see *Appendix 9*). The data collected in the postal questionnaires recorded direct non-medical costs borne by parents and carers as a result of attending hospital with the child during their ED/CAU and/or hospital admission(s). These direct non-medical costs covered travel costs, child care costs, expenses incurred while in hospital, and other direct non-medical expenses. The parent-completed questionnaires also recorded the children's use of prescribed inhalers, other prescribed medicines, privately purchased over-the-counter medications, and non-hospital community health and social services, as well as their hospital outpatient attendances and hospital re-admissions (by type of ward). Finally, the parent-completed questionnaires recorded direct non-medical costs borne by parents and carers, as well as their self-reported lost earnings, as a result of the child's asthma during the period between completion of ED/CAU or hospital discharge and 1 month post randomisation. The 1-month economic questionnaire had been piloted among members of the lay panels of the MCRN to ascertain its acceptability, comprehension and reliability, and reminder letters were sent to parents to increase the response and completion rates. All resource-use data were entered directly from the postal questionnaires into the MACRO trial database, with in-built safeguards against inconsistent entries, and then verified by dual coding.

Valuation of resource-use cost data

Unit costs for resources used by children who participated in the study were obtained from a variety of primary and secondary sources, with the majority obtained from secondary sources. All unit costs used followed recent guidelines on costing health and social care services as part of an economic evaluation.[46,47] Where necessary, secondary information was obtained from ad hoc studies reported in the literature. Unit costs of hospital and community health-care costs were largely derived from national sources and took account of the cost of the health professionals' qualifications.[48] Some costs were valued using the NHS Reference Costs (2009–10), a catalogue of costs compiled by the Department of Health in England.[49] Drug costs were obtained from the *British National Formulary* (BNF).[50] Costs for individual preparations were used as well as costs for chemical entities, i.e. drugs were grouped by chemical entity and unit costs for these chemical entities were calculated (Prescription Cost Analysis 2010).[49] The values attached to direct non-medical costs borne by parents and carers and their lost earnings were those provided by the parents completing the 1-month economic questionnaire. Lost earnings were not valued if annual or compassionate leave was taken as a result of the child's health state. All costs were expressed in pounds sterling and valued at 2009–10 prices. None of the costs were inflated or deflated for use in the economic

evaluation. For the base-case analyses, unit costs were combined with resource volumes to obtain a net cost per child covering all categories of hospital and community health and social services. In one of several sensitivity analyses, these costs were supplemented with the range of costs incurred by family members and carers in the course of treatment and follow-up (societal perspective adopted). Further details on the methods used to value resource use are provided in *Appendix 2*.

Calculation of utilities and quality-adjusted life-years

Parents of children aged ≥ 5 years were asked to describe their children's QoL at 1 month after participation in the MAGNETIC trial using the proxy version of the EuroQol EQ-5D instrument.[51] The EQ-5D is the generic, multiattribute, preference-based measure preferred by National Institute for Health and Care Excellence (NICE) for broader cost-effectiveness comparative purposes.[46] The EQ-5D consists of two principal measurement components. The first is a descriptive system, which defines health-related QoL in terms of five dimensions: 'mobility', 'self care', 'usual activities', 'pain/discomfort' and 'anxiety/depression'. Responses in each dimension are divided into three ordinal levels coded: (1) no problems; (2) some or moderate problems; and (3) severe or extreme problems. A total of 243 health states are generated by the EQ-5D descriptive system. For the purposes of this study, the York A1 tariff was applied to each set of responses to the descriptive system to generate an EQ-5D utility score at 1 month for each child.[52] The York A1 tariff set was derived from a survey of the adult UK population ($n = 3337$), which used the time trade-off valuation method to estimate utility scores for a subset of 45 EQ-5D health states, with the remainder of the EQ-5D health states subsequently valued through the estimation of a multivariate model.[52] Resulting utility scores range from scores −0.59 to 1.0, with '0' representing death and '1' representing full health. Utilities values of < 0 indicate health states worse than death. The second measurement component of the EQ-5D, the vertical visual analogue scale ranging from 100 (best imaginable health state) to 0 (worst imaginable health state), was not included in MAGNETIC.

There is limited evidence of the psychometric properties of the EQ-5D in young children.[53] Consequently, analyses were conducted to 'map' or 'cross-walk' responses to the PedsQL™ Asthma Module on to EQ-5D utility scores. These mapping models were developed on the basis of data collected for 5- to 16-year-old children for whom both EQ-5D and PedsQL™ responses were available; the resulting mapping algorithms were used to estimate EQ-5D utility scores for 2- to 4-year-old children in MAGNETIC for whom the validated toddler module of the PedsQL™ Asthma Scales had been completed. A number of models were used to develop these mapping algorithms in keeping with current methodological guidance for mapping between non-preference-based and preference-based measures of health status.[54,55]

Model 1: ordinary least squares using PedsQL™ total score

It was assumed that there was a linear relationship between the PedsQL™ total score and the EQ-5D utility score with a high score on the PedsQL™ correlated with a high score on the EQ-5D measure and vice versa. An ordinary least squares (OLS) model was used to examine the existence of such a relationship between the PedsQL™ total score and the EQ-5D utility score. The dependent variable, the EQ-5D utility score, was measured on its natural scale (i.e. −0.594 to 1). The PedsQL™ total score was measured on a (0–100) scale. Covariates for age and gender were also included in the model.

Model 2: ordinary least squares using the PedsQL™ subscales

A simple model that includes the PedsQL™ total score may not be able to explain the variation between PedsQL™ and EQ-5D responses, as the relationship between the two may be more complex. The PedsQL™ total score can be broken down into four subscales: asthma symptoms, treatment problems, worry and communication; using information from these subscales may result in a model that provides a better fit. The simple OLS model can therefore be improved by using the four subscales of the PedsQL™ as independent variables in place of the PedsQL™ total score. As in model 1, the dependent variable (EQ-5D utility score) was measured on its natural scale and the PedsQL™ subscale scores were each measured on a (0–100) scale. Covariates for age and gender were also included in the model. We explored whether multicollinearity was present in our mapping model 2, which included PedsQL™ subscale scores and age and gender as explanatory variables. The mean variance inflation factor in this model was estimated at 1.72, well

below the threshold value of 10 that is normally indicative of multicollinearity. Moreover, there is a now a wealth of evidence in the published literature confirming the four-factor conceptually derived measurement model for the PedsQL™ scales (www.pedsql.org).

Model 3: ordinary least squares using the PedsQL™ subscales with squared terms and interactions

A multiple OLS regression model was used to examine the relationship between the EQ-5D utility score and the four PedsQL™ subscale scores, squared subscale scores and interaction terms derived using the product of subscale scores. The dependent variable (EQ-5D utility score) was measured on its natural scale and the PedsQL™ subscale scores were measured on a (0–100) scale. The model was defined as:

$$y_i = a + \beta x_{ij} + \theta r_{ij} + \delta z_{ij} + \varepsilon_{ij} \quad (1)$$

where $i = 1, 2, \ldots, n$ represents individual respondents, $j = 1, 2, \ldots,$ and m represents the four different subscales. The dependent variable, y, represents the EQ-5D utility score, x represents the vector of PedsQL™ subscales, r represents the vector of squared terms, z represents the vector of interaction terms and ε_{ij} represents the error term. This is an additive model that imposes no restrictions on the relationship between dimensions. The squared terms are designed to pick up non-linearities in the relationship between dimension scores and the EQ-5D utility score. The interaction terms are considered important as the dimensions are not additive. Covariates for age and gender were also included in this model.

The best-fitting model of the three was identified on the basis of the highest explanatory power in terms of the lowest Akaike information criterion (AIC) statistic. This model was used to make the EQ-5D predictions for the 2- to 4-year-old children in MAGNETIC. The accuracy of the predictions were tested by carrying out a within sample validation and the root-mean-squared error (RMSE) (a recommended measure of predictive ability) was calculated for each model.[54]

Baseline utility data were not collected because trial participants were enrolled in ED/CUA with minimal data collection and concomitant concerns surrounding family intrusions at such a sensitive time. To estimate QALYs, it was necessary to impute baseline utility data based on secondary evidence. A physician panel made up of two respiratory nurses and a consultant mapped the ASS scores on to EQ-5D health states from which baseline utility scores were estimated. In the base-case analysis, ASS scores of 1–3 were mapped on to an EQ-5D health state of 11111; ASS scores of 4–6 were mapped on to an EQ-5D health state of 22222; and ASS scores of 7–9 were mapped on to an EQ-5D health state of 33333. These mappings were varied as part of the sensitivity analyses (see *Chapter 4* for details).

The number of QALYs accrued over the 1-month follow-up period was calculated using linear interpolation between the baseline and follow-up utility score. It is likely that children return to the EQ-5D health state reported at 1 month earlier than that time; however, it is acknowledged that this depends in part on the number of asthma attacks that have occurred since treatment. Consequently, the base-case analysis assumed that the EQ-5D health state had been achieved immediately following hospital discharge, while a sensitivity analysis applied linear interpolation of the utility scores over the follow-up period. In order to account for potential baseline imbalances between the trial groups, adjustments were made to the QALY estimates by simply subtracting each child's baseline utility value from their on-treatment utilities before calculating QALYs. This method effectively indexes the utilities relative to baseline.

Missing data

Multiple imputation was used to impute missing data and avoid biases associated with complete case analysis.[56] Missing data was a particular issue for costs and utility scores collected at the 1-month follow-up. The MICE (Multiple Imputation by Chained Equations) algorithm within R statistical software version 2.13 (R Development Core Team) was used to impute missing data for the following variables: total health and social care costs based on data combined from the CRFs and from parental questionnaires; total societal costs based on data combined from the CRFs and from parental questionnaires; QALY estimates

based on linear interpolation, assuming that the health gain was achieved immediately following hospital discharge; and QALY estimates based on linear interpolation assuming that the health gain was achieved linearly over the follow-up period. Age, sex and treatment allocation were included as explanatory variables in the imputation models. Costs up to completion of ED/CUA attendance or hospital discharge were included as an additional explanatory variable in the models that imputed values for total health and social care costs and total societal costs over the 1-month time horizon. The 'match' option within 'ice' was used for utilities and costs as this algorithm is less dependent on assumptions of normality than default options. Five imputed data sets were generated.

Cost-effectiveness analytic models

As described above, the primary clinical outcome measure for the study was ASS at T60. Assessment severity score data were collected both before (as part of screening) and during the trial (prior to randomisation and at T20, T40, T60 and when necessary thereafter). The assessment severity score at T60 was the primary clinical outcome pre-specified in the protocol and this was also used in the CEA. In the CEA, the incremental cost-effectiveness ratio (ICER) was calculated as the difference in average costs (ΔC) divided by the difference in average effects (ΔE) and expressed as the incremental cost per unit change in ASS at T60. A separate CUA was performed, the results of which were expressed in terms of incremental cost per QALY gained. The time horizon for the measurement and valuation of costs and health outcomes within the CEA covered the period between randomisation and discharge from the ED/CUA or the hospital where the child was admitted to an inpatient ward immediately following ED/CUA attendance. The time horizon for the measurement and valuation of costs and health outcomes within the CUA covered the period between randomisation and 1 month post randomisation. No discounting of costs or benefits was applied as the time horizon was < 12 months.

Independent-sample *t*-tests were used to test for differences in resource use, costs, utility scores and QALYs between treatment groups. All statistical tests were two-tailed. Multiple regression was used to estimate the differences in total cost between the magnesium and placebo groups and to adjust for potential confounders, including the covariates incorporated into the main clinical analyses. For the generalised linear model (GLM) on costs, a gamma distribution and identity link function was selected in preference to alternative distributional forms and link functions on the basis of its low AIC statistic.

The five imputed data sets generated through multiple imputation were bootstrapped separately in Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA, USA) and the results were subsequently combined[56] to calculate standard errors (SEs) around mean costs and effects that incorporate uncertainty around imputed values as well as sampling variation. SEs were used to calculate 95% CIs around total and incremental costs, incremental effects and QALYs based on Student's *t*-distribution. Cost-effectiveness acceptability curves (CEACs) showing the probability that magnesium is cost-effective relative to placebo at a range of ceiling ratios were generated, based on the proportion of bootstrap replicates (across all five imputed data sets) with positive incremental net benefits.[57,58] For the purposes of the CEA, incremental net benefit was defined as the unit reduction in ASS multiplied by the cost-effectiveness threshold for this clinical outcome minus the incremental cost, where the ceiling ratio (or cost-effectiveness threshold) represents the maximum society is willing or able to pay for each unit reduction in ASS. For the purposes of the CUA, incremental net benefit was defined as the incremental QALY gain multiplied by the ceiling ratio minus the incremental cost, where the ceiling ratio (or threshold) represents the maximum that society is willing or able to pay for each additional QALY. Unless otherwise stated, all statements about cost-effectiveness are based on a £20,000 per QALY gained threshold. The probability that magnesium is less costly or more effective than no treatment was based on the proportion of bootstrap replicates that had negative incremental costs or positive incremental health benefits (unit reduction in ASS for the purposes of the CEA: QALYs for the purposes of the CUA), respectively.

Several sensitivity analyses were undertaken to assess the impact of areas of uncertainty surrounding components of the economic evaluation. These included the following for purposes of the CEA: (1) performing a complete case (rather than multiple imputation) analysis, which limited the CEA to the

children for whom complete information on both costs and ASS were available; (2) varying the per diem costs for inpatient stays in paediatric wards (PICU, HDU, GM); (3) assuming that part of a day spent by a child in an inpatient ward equated to a proportional period for costing purposes and that, consequently, the vacated inpatient bed would be filled immediately; (4) assuming that part of a day spent by a child in an inpatient ward equated to a full 24-hour period for costing purposes and that, consequently, the inpatient bed would not be filled until the end of that 24-hour period; and (5) varying the average cost of an ED/CUA attendance. The sensitivity analyses included the following for purposes of the CUA: (1) performing a complete case (rather than multiple imputation) analysis, which limited the CUA to the children for whom complete information on both costs and QALYs was available; (2) assuming linear interpolation of health utilities over entire follow-up period; (3) assuming baseline ASS scores mapped on to EQ-5D health states with lower utility scores than in the baseline analysis (ASS scores of 1–3 mapped on to an EQ-5D health state of 11222; ASS scores of 4–6 mapped on to an EQ-5D health state of 22333; and ASS scores of 7–9 were mapped on to an EQ-5D health state of 33333); (4) assuming baseline ASS mapped on to EQ-5D health states with higher utility scores than in the baseline analysis (ASS of 1–3 mapped on to an EQ-5D health state of 11111; ASS of 4–6 mapped on to an EQ-5D health state of 22111; and ASS of 7–9 were mapped on to an EQ-5D health state of 33222); and (5) adopting a societal perspective rather than a NHS and Personal Social Services perspective.

Chapter 3 Results

Participant flow and recruitment

Five hundred and eight children were randomised from 30 centres throughout the UK (one centre in Wales, two in Scotland, two in Northern Ireland and 25 in England).

The first child was recruited on 14 December 2008 and the last child was randomised on 21 March 2011. *Table 3* shows all of the 30 recruiting centres, the date the site was initiated, the target recruitment, the number of participants randomised, the date of the first randomisation and the date of the last randomisation. All 30 centres randomised at least one participant.

Five further centres were at different stages of opening for recruitment at the end of the study (Royal Alexander Children's Hospital, Brighton; Fairfield Hospital, Bury; Leighton Hospital, Crewe; Whiston Hospital, Prescot, Liverpool; Morriston Hospital, Swansea; Royal Hospital for Sick Children, Belfast) but did not randomise any children.

Screening data

Sites were requested to prospectively record each potentially eligible child on a screening log and return this to the Clinical Trials Unit (CTU) on a monthly basis. The log recorded the time and date of presentation, whether or not the child was screened/eligible, and whether or not he/she was then randomised. Reasons for screen failures/non-randomisation were also requested.

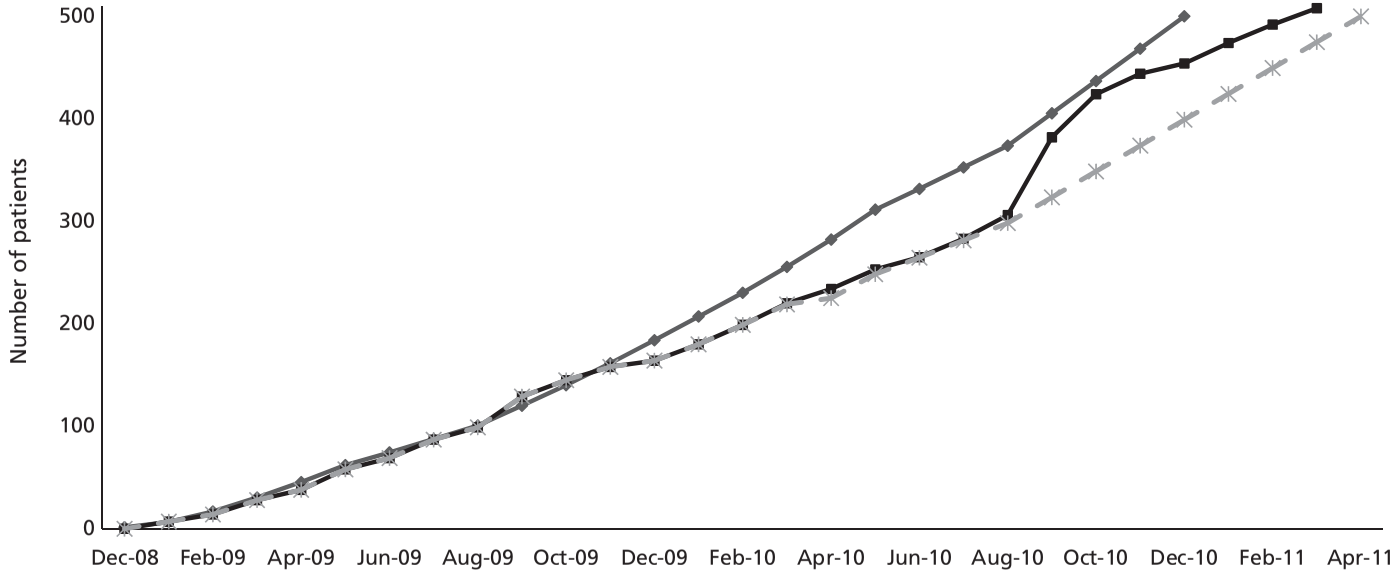
Unfortunately, few centres complied, with the majority citing that collection of this information prospectively was too onerous for staff. In instances in which the logs were received, they were often sent sporadically and were poorly completed, not recording children who were missed for trial eligibility assessment.

Efforts were regularly made to encourage return [supported on one occasion by the MRCN local research networks (LRNs)], as screening information was the primary way to objectively assess barriers to recruitment in underperforming sites. Another option given was to record the information retrospectively by review of departmental records; however, again the majority of centres stated they did not have the resources to do this on a regular basis.

Recruitment rates

The study target sample size of 500 was expected to have been achieved within a 24-month recruitment period. The actual recruitment was somewhat slower than anticipated (*Figure 1*), being achieved within 28 months. Reasons for the slower than expected recruitment include the time taken to obtain approvals and undertake training at centres (specifically, good clinical practice training, required to consent children to the trial), rotation of middle-grade medical staff responsible for obtaining consent at many centres (again a training issue), and the seasonal fluctuations in asthma presentations.

The recruitment period of the trial was extended for 5 months in August 2010, and recruitment rates improved following intervention of the MCRN LRNs who conducted a feasibility survey to identify additional recruiting centres. Throughout the trial, at different stages of the study, the LRNs ran MAGNETIC promotions to keep up the profile of the study. For example, Nottingham invested extra resources to boost recruitment in March 2010 with the theme of MAGNETIC March.



	Dec-08	Jan-09	Feb-09	Mar-09	Apr-09	May-09	Jun-09	Jul-09	Aug-09	Sep-09	Oct-09	Nov-09	Dec-09	Jan-10	Feb-10	Mar-10	Apr-10	May-10	Jun-10	Jul-10	Aug-10	Sep-10	Oct-10	Nov-10	Dec-10	Jan-11	Feb-11	Mar-11	Apr-11
Original target	1	7	17	31	46	62	74	87	101	120	140	161	184	207	230	255	282	311	332	353	374	405	437	468	500				
Actual	0	7	14	28	38	58	69	87	99	129	145	158	164	180	199	220	234	253	265	283	306	382	424	444	454	474	492	508	
Extension	0	7	14	28	38	58	69	87	99	129	145	158	164	180	199	219	225	248	265	281	298	323	349	374	399	424	450	475	500

FIGURE 1 Expected vs. actual recruitment rates.

TABLE 3 Recruitment by centre

Centre	Date site initiated	Target recruitment	No. randomised	Date of first randomisation	Date of final randomisation
St Thomas' Hospital	4 December 2008	30	26	2 January 2009	17 March 2011
Royal Devon and Exeter Hospital	4 December 2008	30	33	5 January 2009	20 March 2011
Derbyshire Children's Hospital	17 December 2008	20	21	20 February 2009	17 January 2011
Tameside General Hospital	17 December 2008	10	3	14 January 2009	27 October 2009
Leicester Royal Infirmary	9 January 2009	20	20	23 July 2009	8 July 2010
Royal Albert Edward Infirmary, Wigan	9 January 2009	18	20	2 March 2009	25 February 2011
Queens Hospital, Burton	9 January 2009	20	21	13 February 2009	14 November 2010
University Hospital of Wales	9 January 2009	25	31	5 February 2009	18 January 2011
Royal London Hospital	9 January 2009	12	11	2 April 2009	21 November 2010
Countess of Chester Hospital	21 January 2009	16	26	30 July 2009	15 March 2011
Macclesfield District General Hospital	21 January 2009	25	28	17 February 2009	5 March 2011
Royal Hospital for Sick Children, Glasgow	29 January 2009	30	22	14 April 2009	21 December 2010
Sheffield Children's Hospital	29 January 2009	20	14	28 May 2009	19 November 2010
Preston Royal Infirmary	29 January 2009	14	12	4 August 2009	6 February 2011
Bristol Royal Children's Hospital	16 April 2009	30	37	27 April 2009	15 March 2011
Queen's Medical Centre Nottingham	6 May 2009	20	20	29 June 2009	22 November 2010
Victoria Hospital Blackpool	6 May 2009	17	7	26 June 2009	1 February 2011
Ormskirk and District Hospital	12 May 2009	20	30	5 June 2009	9 June 2011
Wythenshawe Hospital	16 September 2009	10	3	15 December 2009	6 December 2010
Birmingham Children's Hospital	2 October 2009	15	14	28 November 2009	23 February 2011
University Hospital of North Staffordshire	3 November 2009	18	19	28 January 2010	9 February 2011
Craigavon Area Hospital	14 November 2009	13	9	29 January 2010	24 January 2011
Birmingham Heartlands Hospital	18 January 2010	15	4	28 March 2010	11 May 2010
Royal Aberdeen Children's Hospital	1 April 2010	16	11	8 June 2010	27 January 2011
University Hospital North Tees	30 April 2010	18	17	22 May 2010	6 March 2011
University Hospital Lewisham	30 April 2010	15	14	30 May 2010	7 March 2011
Altnagelvin Area Hospital	9 June 2010	10	14	15 August 2010	2 February 2011

continued

TABLE 3 Recruitment by centre (*continued*)

Centre	Date site initiated	Target recruitment	No. randomised	Date of first randomisation	Date of final randomisation
Southampton General Hospital	2 July 2010	10	6	29 July 2010	14 October 2010
Royal Manchester Children's Hospital	23 August 2010	10	10	27 August 2010	28 January 2011
Royal Cornwall Hospital	7 December 2010	8	5	9 February 2011	16 March 2011

The flow of children

The flow of children through the trial is represented in the CONSORT flow diagram in *Figure 2*. Five hundred and eight children were randomised: 339 patients from EDs and 169 from paediatric assessment units (PAUs), 252 to the magnesium group and 256 to the placebo group.

In total, 13 children withdrew in the magnesium group; six children discontinued the intervention (withdrew before T60 assessment) and five out of six children did not provide data for the primary outcome analysis; seven children withdrew after T60 assessment and only one child continued to provide further data following withdrawal. In total, 10 children withdrew from the placebo group; five children discontinued the intervention (withdrew before T60 assessment) and three out of five did not provide data for the primary outcome analysis; five children withdrew after T60 assessment and none continued to provide further data following withdrawal. In total, 25 children on magnesium and 13 children on placebo did not have data to contribute to the analysis of the primary outcome. Consequently, 227 children were analysed for the primary outcome in the magnesium group, and 243 children were analysed for the primary outcome in the placebo group.

Baseline comparability of randomised groups

Table 4 shows that the baseline characteristics of the 508 randomised participants were similar, with no differences deemed clinically significant.

Participants ranged in age between 1 and 15 years, with the median age similar in both the treatment groups as well as their median age at asthma onset. There were no gender differences between the groups. There were also no differences in current treatment taken for their asthma, treatment given before presentation for the acute attack or previous admissions for acute asthma.

The mean ASS at baseline was almost identical in the two treatment groups. There were no physiological differences in presentation heart rate, respiratory rate or blood pressure or oxygen therapy required at admission.

Most (69%) children were randomised between 0900 and 1700 hours. This is clearly when most of the research staff were around to recruit patients. There were three categories of duration of most recent asthma attack, with the most frequent duration being between 6 and 24 hours.

Timing of treatment administration

Each child was randomised to receive nebulised salbutamol 2.5 mg (aged 2–5 years) or 5 mg (aged $\geq$ 6 years) and ipratropium bromide 0.25 mg mixed with either 2.5 ml of isotonic $MgSO_4$ (250 mmol/l, tonicity 289 mOsm; 151 mg per dose) or 2.5 ml of isotonic saline on three occasions at 20-minute intervals. No dose modification of the study treatment was permitted and dosing was continued in the event of deterioration of the child's condition unless cessation of therapy was deemed necessary by the clinician or if consent for the trial was withdrawn.

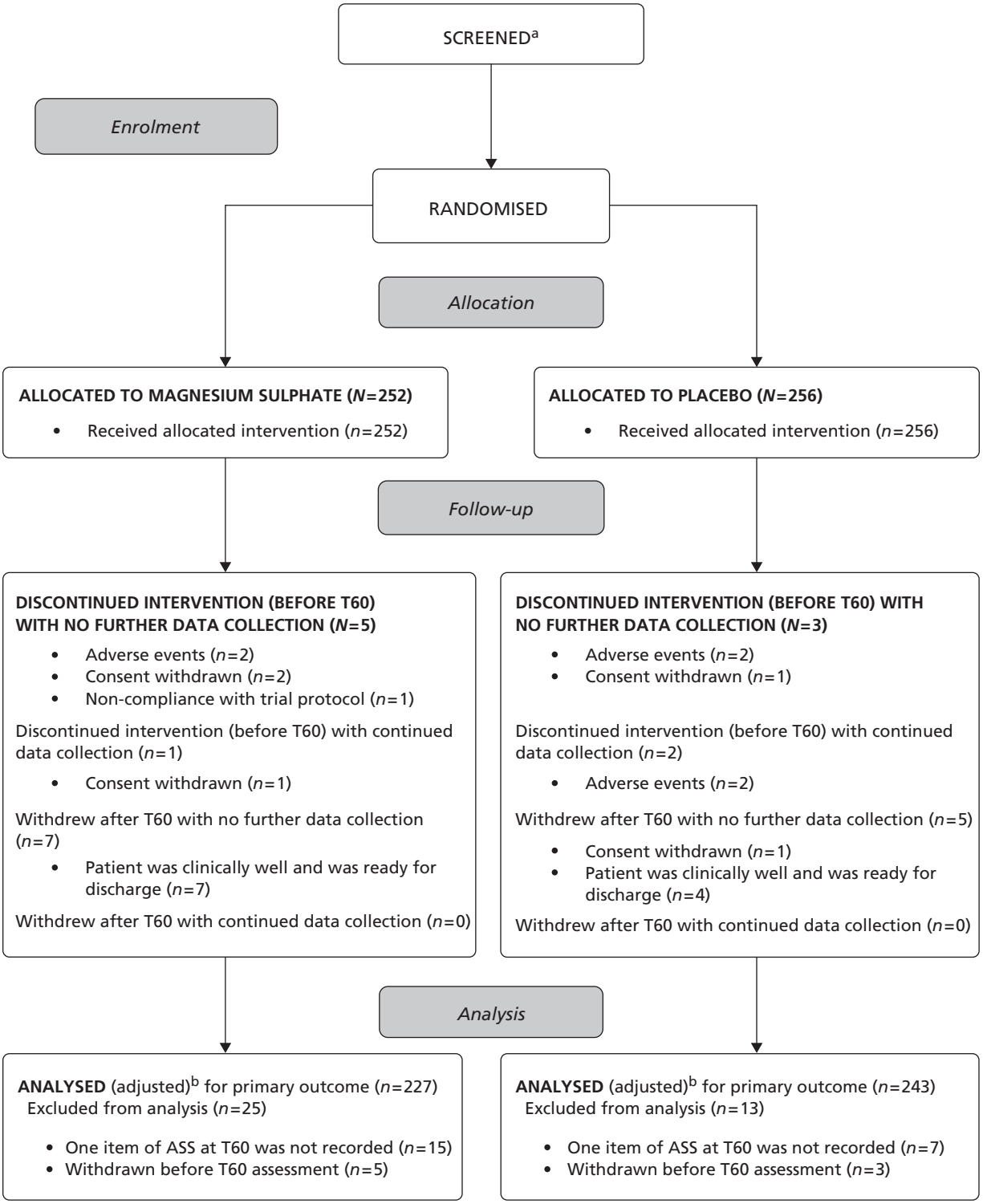


FIGURE 2 Consort flow diagram. (a) Few centres complied, with the majority citing that collection of this information prospectively was too onerous for staff. In instances where the logs were received, they were often sent sporadically and were poorly completed and not recording children who were missed. (b) Analysed unadjusted for baseline ASS.

TABLE 4 Baseline characteristics of the study population

Baseline characteristic	Magnesium (*n* = 252)	Placebo (*n* = 256)	Total (*n* = 508)
Age (years): median (IQR), range	4.0 (3.0–7.0), 2–15	4.0 (3.0–7.0), 1–15	4.0 (3.0–7.0), 1–15
Male, *n* (%)	143 (57)	150 (59)	293 (58)
Age (years) at asthma onset:	(*n* = 165)	(*n* = 168)	(*n* = 333)
Median (IQR), range	2.0 (1.0–3.0), 0–11	2.0 (1.0–3.0), 0–10	2.0 (1.0–3.0), 0–11
Undiagnosed, *n* (%)	79 (31)	76 (30)	155 (31)
Missing, *n* (%)	8 (3)	12 (5)	20 (4)
Time of day that randomisation occurred: *n* (%)			
0900–1700	181 (72)	168 (66)	349 (69)
1700–2200	49 (19)	59 (23)	108 (21)
2200–0900	22 (9)	29 (11)	51 (10)
ASS at baseline	(*n* = 248)	(*n* = 254)	(*n* = 502)
Mean (SD), range	5.7 (1.3), 2–9	5.8 (1.4), 2–9	5.7 (1.4), 2–9
Previous admissions for asthma: *n* (%)	(*n* = 250)	(*n* = 255)	(*n* = 505)
0	101 (40)	99 (39)	200 (40)
1–4	101 (40)	95 (37)	196 (39)
> 4	48 (20)	61 (24)	109 (21)
Duration of the most recent asthma attack: *n* (%)	(*n* = 251)	(*n* = 254)	(*n* = 505)
For the last few days	54 (22)	54 (21)	108 (21)
For the last 24 hours	162 (64)	162 (64)	324 (64)
For the last 6 hours or less	35 (14)	38 (15)	73 (15)
Current asthma medication: *n* (%) (can be > 1)			
Undiagnosed	79	76	155
Diagnosed	173	180	353
None	7 (2)	1 (0)	8 (1)
Short-acting β_2-agonists	196 (51)	207 (53)	403 (52)
Inhaled corticosteroids	106 (28)	109 (28)	215 (28)
Long-acting β_2-agonists	11 (3)	19 (5)	30 (4)
Long-acting β_2-agonist/steroid combination	15 (4)	14 (4)	29 (4)
Leukotriene receptor antagonists	28 (7)	28 (7)	56 (7)
Oral steroids	6 (2)	2 (0)	8 (1)
Other[a]	8 (2)	7 (2)	15 (2)
Nothing ticked (V1 CRF)[b]	5 (1)	6 (1)	11 (1)
Allergy history: *n* (%) (can be more than one)			
None/nothing ticked	118 (40)	123 (39)	241 (39)
Hay fever	38 (13)	61 (19)	99 (16)
Eczema	97 (33)	91 (29)	188 (31)
Food allergy	41 (14)	42 (13)	83 (14)

TABLE 4 Baseline characteristics of the study population (*continued*)

Baseline characteristic	Magnesium (*n* = 252)	Placebo (*n* = 256)	Total (*n* = 508)
Treatment received pre-admission:			
Steroids only	21 (8)	25 (10)	46 (9)
Nebulisers only	68 (27)	72 (28)	140 (27)
Both steroids and nebulisers	47 (19)	55 (21)	102 (20)
Yes, but neither steroids nor nebulisers	20 (8)	17 (7)	37 (7)
Not known	3 (1)	10 (4)	13 (3)
None	79 (31)	73 (29)	152 (30)
Nothing ticked (V1 CRF)	10 (4)	3 (1)	13 (3)
Other treatment missing (V1 CRF)	4 (2)	1 (0)	5 (1)
Nebuliser received before randomisation: *n* (%)	(*n* = 250)	(*n* = 254)	(*n* = 504)
Salbutamol	106 (42)	101 (40)	207 (41)
Salbutamol + ipratropium	144 (58)	150 (59)	294 (58)
Not given	0 (0)	3 (1)	3 (1)
SaO_2 (%), mean (SD), range	(*n* = 250)	(*n* = 253)	(*n* = 503)
	93.8 (3.5), 84–100	93.4 (3.4), 81–100	93.6 (3.4), 81–100
Blood pressure (mmHg), mean (SD), range	(*n* = 210)	(*n* = 211)	(*n* = 421)
Systolic	109.5 (14.1), 62–163	112.7 (12.5), 70–172	111.1 (13.4), 62–172
Diastolic	65.5 (11.6), 30–105	66.3 (12.7), 34–123	65.9 (12.2), 30–123
Respiratory rate (breaths per minute), mean (SD), range	(*n* = 247)	(*n* = 250)	(*n* = 497)
	43.2 (10.5), 20–72	42.5 (10.9), 20–70	42.9 (10.7), 20–72
Oxygen therapy, *n* (%)	(*n* = 241)	(*n* = 247)	(*n* = 488)
Yes	94 (37)	98 (38)	192 (38)
No	147 (63)	149 (62)	296 (62)

SaO_2, the saturation level of oxygen in haemoglobin, as measured in arterial blood.
a Other drugs: ipratropium bromide, desloratadine, cetrizine, erythromycin, sodium cromoglicate.
b Version 1 of the CRF did not include a category 'None' and listed only the various medications.

Table 5 shows treatment details for all randomised children. There was no clinically significant deviation in mean prescribed times between the treatment groups on any of the three occasions.

There were 246 and 250 children who received all three treatments in the magnesium and placebo groups respectively. It was expected that all three trial treatments should have been received within approximately 1 hour; however, in some cases, treatments were administered slightly late. Based on the fact that the prescription time of each treatment was reported, and not the time of the end of the third treatment, it was expected that the time between first and third treatments should be 40 minutes but an allowance of an additional 15 minutes would be tolerable. Therefore, if the above timing was > 55 minutes, this was defined as a deviation outside the acceptable window (see *Table 6*). There were 53 children who received their third treatment at > 55 minutes after randomisation. Note that this is a change to the proposed deviation outlined in the SAP, and was made prior to unblinding and any comparative analysis (see *Appendix 3* for more details).

TABLE 5 Treatment details for *all* randomised children

Treatment details	Prescribed time (minutes)								
	Magnesium			Placebo			Total		
	First[a]	Second[b]	Third[c]	First[a]	Second[b]	Third[c]	First[a]	Second[b]	Third[c]
No. treated	252	248	246	255	252	250	507	500	496
Timing of treatment									
Mean (SD)	5.3 (8.4)	23.6 (5.9)	23.7 (6.8)	6.4 (8.1)	23.1 (5.1)	23.0 (5.5)	5.8 (8.3)	23.4 (5.5)	23.3 (6.2)
Range	0–65	10–65	10–65	0–40	5–40	14–60	0–65	5–65	10–65

a Time from randomisation to prescription of first nebulised treatment.
b Time from prescription of first treatment to prescription of second treatment.
c Time from prescription of second treatment to prescription of third treatment.

TABLE 6 Protocol deviations (post randomisation)

Protocol specification	No. of deviations (%)	
	Magnesium	Placebo
Inclusion criteria – two children aged 15 and 23 months were recruited	0[a]	2 (1)
Exclusion criteria – one child was recruited twice	0[a]	2 (1)
Treatment regime		
Allocation (did not receive full trial treatment as per protocol)	7 (3)	12 (5)
Timing[b] (deviations outside acceptable timing window)	24 (10)	29 (12)
Primary outcome data (deviation in the method of assessment)	0	0
Secondary outcome data (deviation in the method of assessment)		
Clinical outcomes	0	0
Child and parental outcomes at 1-month follow-up	0	0

a Data not available for one child.
b Where the child has received fewer than three treatments, they were not included and, hence, not included in the denominator when looking at rates.

Unblinding of randomised treatments

The treatment allocation for two children was unblinded during the course of the trial (one in the magnesium group and one in the placebo group; see *Table 14*). One child (magnesium group) was unblinded to enable treatment of a SAE; however, the event was considered to be unlikely to be related to trial medication. One child (placebo group) was unblinded after resolution of a SAE as parents wished to be notified of their child's treatment allocation.

Protocol deviations

There were 14 children who did not receive nebulised treatment during screening pre-randomisation. Two children aged 15 and 23 months were recruited. One child was recruited twice. Further protocol deviations were classified in *Table 6* and summarised for each treatment group. There is no imbalance across treatment groups.

Internal pilot and interim analysis

To ensure the appropriateness of the SD used in the sample size calculation, we undertook an internal pilot after the first 36 children had been randomised and completed follow-up. The SD estimated from a sample of 26 patients with complete ASS data at T60 (ranging from 2 to 7) was 1.4. As there were 10 patients with missing ASS at T60, and these could plausibly include both extremes of the possible ASS range (0–9), this may be an underestimate of the true value, so we undertook a sensitivity analysis. Nine of the ten patients with missing ASS at T60 had T40 data and the mean value of ASS of these records was 5.56. Among those 26 patients who did have ASS at T60, 25 had T40 data and the mean value of ASS of these records was 5.32. So, on average, T40 ASS was slightly higher among those who had a missing ASS at T60 measurement. The IDSMC did not consider that the missing observations would have a substantial impact on the SD, which was lower than the value assumed for the original power calculation. The IDSMC recommended no change to the sample size based on these results.

Furthermore, a blinded interim analysis was undertaken after 262 children had been randomised. ANCOVA adjusted for baseline ASS and independent samples *t*-test were performed, and the mean differences and 99.9% CIs were reported in the closed section of the IDSMC report; blinded results as presented to the IDSMC are shown in *Table 7*.

The IDSMC noted that the difference in ASS at T60 was less than the minimum critical difference value of 0.5 on which the sample size was based. There were no substantial risk–benefit concerns, and continued recruitment and conduct of the trial was recommended.

Analysis of primary outcome

The results for the final analysis of the primary outcome are presented in *Table 8*. The mean difference in ASS at T60 between the two treatment groups, magnesium minus placebo, adjusting for baseline ASS, was –0.25 points (95% CI –0.48 to –0.02 points), i.e. magnesium appears to lower the score. However, although the difference between the treatment groups was statistically significant, the 95% CI lies above the minimum clinically important difference of 0.5 points defined prior to the trial. Diagnostic plots for the analysis of the primary outcome data are presented in *Appendix 7*. There is no evidence of violation of model assumptions.

Key baseline characteristics for those with observed ASS at T60 are presented in *Appendix 5*, *Table 40*, and show no differences between the treatment groups, which implies that the patients with missing outcomes do not affect the randomisation balance. There is no evidence of a difference in key baseline characteristics between patients with observed and missing ASS at T60 (see *Appendix 5*, *Table 41*), indicating plausibility of the MCAR assumption.

TABLE 7 Treatment means at interim analysis

Treatment I ($n = 123$)	Treatment J ($n = 115$)	Mean difference (99.9% CI)	Adjusted mean difference (99.9% CI)
4.97	4.66	–0.307[a] (–0.922 to 0.308)	–0.356 (–0.923 to 0.211)

a Treatment difference of < 0 favours treatment.

TABLE 8 Primary outcome results

			Estimate (95% CI), *p*-value	
Outcome	Magnesium ($n_m = 228$): T60 mean (SD), range	Placebo ($n_p = 244$): T60 mean (SD), range	Difference in mean: $n_m = 228$, $n_p = 244$	Adjusted difference in mean: $n_m = 227$, $n_p = 243$
ASS	4.72 (1.37), 2–9	4.95 (1.40), 2–9	–0.24 (–0.49 to 0.02), $p = 0.066$	–0.25 (–0.48 to –0.02), $p = 0.034$

The reasons for missing primary outcome data are provided in *Appendix 5* (see *Reasons for exclusion of children from primary outcome analysis*) with the results of the sensitivity analyses (see *Sensitivity analyses of missing primary outcome*). The problem of non-ignorable missing ASS data is addressed through joint modelling of the longitudinal data and the time to drop out from the study [*Appendix 5*, see *Sensitivity analysis (3)*]. Sensitivity analyses did not suggest substantially different conclusions to those above.

A sensitivity analysis to test the robustness of ignoring the centre effect in the primary analysis is presented in *Appendix 6*. Both random-effects analysis of variance and fixed-effect models indicated a significant main effect of centre but there is no evidence that the treatment effect varies by centre.

Analysis of secondary outcomes

Area under the curve for Asthma Severity Score over three time intervals

The results for the AUC analysis for ASS at 20, 40 and 60 minutes are presented in *Table 9*. *Figure 3* shows the mean longitudinal profiles for each group. All three values of ASS were available for 462 (91%) children. The mean difference in AUC between the two treatment groups was 8.1 points (95% CI –20.8 to 4.6 points) lower in the magnesium group. However, the difference between the treatment groups was not statistically significant.

Analysis of secondary efficacy clinical outcomes

There were five secondary efficacy clinical outcomes: 'stepping down' of treatment at 1 hour, number of additional salbutamol administrations, LOS in hospital, requirement for intravenous bronchodilator treatment and intubation and/or admission to a PICU. Results are shown in *Table 10*.

The 'stepping down' of treatment at 1 hour was defined by the no treatment or MDI spacer only until discharge. The proportion of child stepping down at 1 hour was slightly higher in magnesium group; however, the results did not show a statistically significant difference between the two treatment groups. We abandoned a detailed analysis of stepping down of treatment as a primary outcome, as it became apparent that the definition was not clear and varied from centre to centre.

The total number of additional salbutamol administrations was slightly lower in the magnesium group; however, the results did not show a statistically significant difference between the two treatment groups.

TABLE 9 Area under the curve for primary outcome

Outcome	Magnesium: AUC mean (SD), range	Placebo: AUC mean (SD), range	Difference in mean: estimate (95% CI), *p*-value
AUC: $n_m = 223$, $n_p = 239$	316.1 (68.4), 160–520	324.2 (70.7), 110–540	–8.1 (–20.8 to 4.6), $p = 0.210$

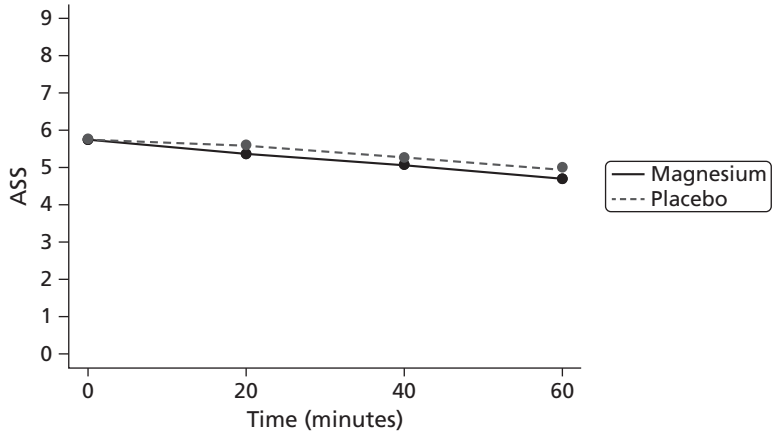


FIGURE 3 Mean longitudinal profiles.

TABLE 10 Secondary outcome results

Secondary outcome	Magnesium	Placebo	Estimate (95% CI), *p*-value
Proportion (%) stepping down treatment at 1 hour: $n_m = 248$, $n_p = 253$	82/248 (33)	76/253 (30)	0.03 (–0.05 to 0.11), $p = 0.527$
No. of additional salbutamol administrations [median (IQR)]: $n_m = 247$, $n_p = 253$	8 (4 to 14)	9 (4 to 17)	–1.0 (–2.00 to 0.00), $p = 0.236$
LOS (hours) in hospital [median (IQR)]: $n_m = 251$, $n_p = 254$	26.3 (17.4 to 44.8)	27.1 (19.2 to 47.6)	–1.8 (–4.80 to 0.70), $p = 0.166$
Proportion (%) requiring intravenous bronchodilator treatment: $n_m = 249$, $n_p = 255$	24/249 (10)	30/255 (12)	–0.02 (–0.07 to 0.03), $p = 0.527$
Proportion (%) requiring intubation and/or admission to a PICU:[a] $n_m = 251$, $n_p = 254$	22/251 (9)	15/254 (6)	0.03 (–0.02 to 0.07), $p = 0.283$

a Thirty-five children were admitted to paediatric intensive care for escalation of treatment and further closer observations owing to the severity of their asthma and lack of response to initial treatment. There was only one child who required intubation who was in the placebo group.

The LOS in hospital was defined by the time from randomisation to trial treatment to discharge from hospital. The median LOS for children in magnesium group is 26 hours, whereas that for placebo was 27 hours. The results did not show a statistically significant difference between the two treatment groups.

The proportion of children requiring of intravenous bronchodilator treatment was slightly lower in the magnesium group; however, the results did not show a statistically significant difference between the two treatment groups.

The proportion of children requiring intubation and/or admission to a PICU was slightly higher in the magnesium group; however, the results did not show a statistically significant difference between the two treatment groups. There was only one child who required intubation in the study and this child was in the placebo group.

Although children in the magnesium group showed favourable secondary outcomes compared with the placebo group, none of the differences reached statistical significance. As presented in *Appendix 6*, as there is no evidence that the treatment effect varies by centre, no sensitivity analyses for the centre-specific outcomes ('stepping down' of treatment at 1 hour, progression to intravenous treatment, intubation and/or admittance to PICU) were undertaken to account for centre characteristics. Histograms for continuous secondary outcome data are presented in *Appendix 7*.

Assessing the evidence for treatment–covariate interactions

There is evidence that the more severe the exacerbation of asthma, the more likely a better response to magnesium.[4,6,31] Our hypothesis would be that the effect of the addition of magnesium would be greater in those with more severe disease. We thus took the saturation level of oxygen in haemoglobin, as measured in arterial blood (SaO_2) level at presentation to be the best marker of severity to examine as a treatment covariate,[3] there is evidence that as magnesium acts as a smooth muscle bronchodilator and that the early response is affected by nebulised magnesium to a greater extent than the later more inflammatory response;[59] a further hypothesis would be that those with a shorter duration of attack may have a better response to treatment.

Other factors, such as age or gender, may affect the response but a number of possible interactions could be argued. Prognostic factors affecting response could thus be examined in further analysis and could not be justified at this stage.

Treatment–covariate interactions were thus investigated for two clinically important baseline covariates: duration of the most recent asthma attack and SaO_2 level. This is a change to the proposed analysis

outlined in SAP (see *Appendix 3* for more details). The models were adjusted for treatment group, baseline ASS and the baseline covariate of interest. The results are presented in *Table 11*, and predicted treatment–covariate interactions are shown graphically in *Figures 4* and *5*. Both treatment–covariate interactions are statistically significant. The model including the duration of the most recent asthma attack indicates a trend towards the effect of magnesium being greater, and clinically significant, if given within the first 6 hours of the onset of the attack. As both ASS and SaO_2 are measures of severity, we have also investigated a second model for SaO_2 level, excluding baseline ASS. Both models indicate that magnesium appears beneficial for lower SaO_2 level (more severe) but no difference for higher SaO_2 level (less severe).

Safety outcomes

Adverse effects were assessed during follow-up checks at 2, 3 and 4 hours after the final study treatment.

For the analysis of safety outcomes, all children who have received at least one dose of the study drug and were available for follow-up were included. One patient did not receive the study drug.

TABLE 11 Treatment–covariate interaction effects

Variable	Estimate (95% CI), *p*-value	
	Models with main effects only	Models with treatment–covariate interaction effects
Duration of the most recent asthma attack		
Intercept	2.62 (2.07 to 3.17), $p < 0.0001$	2.52 (1.94 to 3.10), $p < 0.0001$
Magnesium	– 0.28 (– 0.51 to – 0.04), $p = 0.020$	0.01 (– 0.48 to 0.51), $p = 0.955$
ASS at baseline	0.40 (0.32 to 0.49), $p < 0.0001$	0.40 (0.31 to 0.48), $p < 0.0001$
For the last 6 hours or less vs. for the last few days	– 0.34 (– 0.74 to 0.06), $p = 0.099$	0.03 (– 0.51 to 0.57), $p = 0.920$
For the last 24 hours vs. for the last few days	0.10 (– 0.19 to 0.39), $p = 0.490$ Marginal effect of attack duration $p = 0.040$	0.24 (– 0.16 to 0.64), $p = 0.250$
For the last 6 hours or less vs. for the last few days* magnesium		– 0.79 (– 1.58 to -0.00), $p = 0.049$
For the last 24 hours vs. for the last few days* magnesium		– 0.28 (– 0.85 to 0.30), $p = 0.346$ Marginal effect of attack duration* magnesium, $p = 0.143$
SaO_2 (model 1)		
Intercept	5.28 (2.01 to 8.56), $p = 0.002$	8.70 (4.16 to 13.24), $p < 0.001$
Magnesium	– 0.23 (– 046 to 0.01), $p = 0.055$	– 7.11 (– 13.49 to – 0.74), $p = 0.029$
ASS at baseline	0.38 (0.29 to 0.46), $p < 0.0001$	0.37 (0.28 to 0.46), $p < 0.0001$
SaO_2	– 0.03 (– 0.06 to 0.01), $p = 0.124$	– 0.06 (– 0.11 to – 0.02), $p = 0.010$
SaO_2* magnesium		0.07 (0.01 to 0.14), $p = 0.034$
SaO_2 (model 2: without ASS at baseline)		
Intercept	8.24 (4.82 to 11.66), $p < 0.0001$	12.19 (7.39 to 16.98), $p < 0.0001$
Magnesium	– 0.21 (– 0.46 to 0.04), $p = 0.095$	– 8.17 (– 14. 99 to – 1.36), $p = 0.019$
SaO_2	– 0.04 (– 0.07 to 0.00), $p = 0.058$	– 0.08 (– 0.13 to – 0.03), $p = 0.003$
SaO_2* magnesium		0.08 (0.01 to 0.16), $p = 0.022$

Note
Interaction between the two variables is signified by an asterisk.

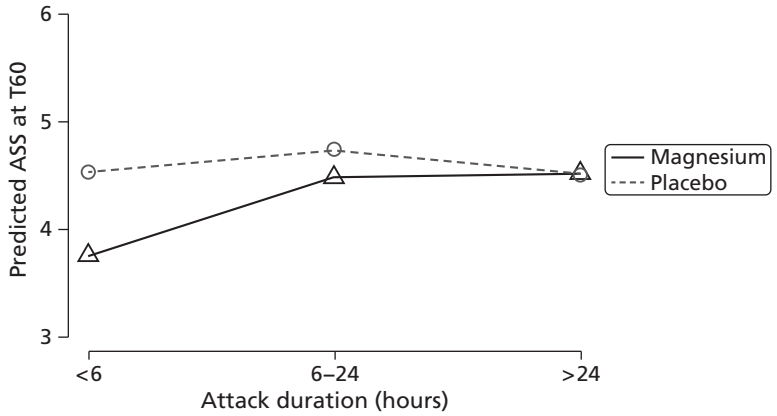


FIGURE 4 Predicted scores for treatment: duration of the most recent asthma attack interaction effect.

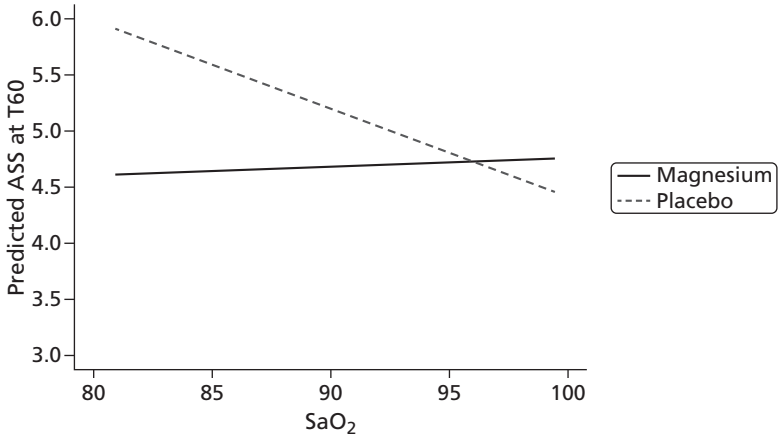


FIGURE 5 Predicted scores for treatment: SaO_2 interaction effect.

Adverse events

The number (and percentage) of children experiencing each AE is presented for each treatment arm in *Table 12*. Serious AEs were not included in this section but will be discussed in more detail in the next section. *Table 12* presents AEs categorised by severity. For each child, only the maximum severity experienced of each type of AE is displayed. There were 21 types of AEs (abdominal pain, asymptomatic hypotension, back pain, blood per rectum, chest pain, diarrhoea, dizziness, drowsiness, facial flushing, feet cramp, fever, headache, hypokalaemia, itchy face, jitteriness, nausea, sleepiness, teeth whitening, urticarial rash, vacant episode, vomiting).

A statistical test comparing the percentage of children suffering an AE in each arm has not been performed for two reasons: (1) this analysis would assume the AEs are of equal importance and (2) no hypotheses on AEs were set out upfront before the blind has been broken.

The results in *Tables 12* and *13* do not appear to suggest there are any important increases in any event in either of the treatment groups.

Serious adverse events and suspected unexpected serious adverse reactions

There were 15 SAEs (three on magnesium, 12 on placebo) but no suspected unexpected serious adverse reactions (SUSARs) during the course of the trial. The same child reported increased bronchospasm on two occasions during follow-up. One child who was admitted to PICU was subsequently admitted to hospital twice owing to worsening symptoms. Seven SAEs were deemed to be unrelated, seven unlikely to be related and one possibly related. Full details are shown in *Table 14*.

TABLE 12 Adverse events by number of participants and number of events

Event	Magnesium		Placebo		Total	
	Children [*n* = 47/252 (19%)]: *n* (%)	Events (*n* = 47)	Children [*n* = 52/255 (20%)]: *n* (%)	Events (*n* = 59)	Children [*n* = 99/507 (19%)]: *n* (%)	Events (*n* = 106)
Abdominal pain	2 (0.8)	2	2 (0.8)	2	4 (0.8)	4
Asymptomatic hypotension	1 (0.4)	1	2 (0.8)	2	3 (0.6)	3
Back pain	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1
Blood per rectum	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1
Chest pain	1 (0.4)	1	2 (0.8)	3	3 (1.2)	4
Diarrhoea	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1
Dizziness	1 (0.4)	1	0 (0.0)	0	1 (0.2)	1
Drowsiness	1 (0.4)	1	0 (0.0)	0	1 (0.2)	1
Facial flushing	2 (0.8)	2	3 (1.2)	3	5 (1.0)	5
Feet cramp	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1
Fever	8 (3.2)	8	5 (2.0)	5	13 (2.6)	13
Headache	5 (2.0)	5	1 (0.4)	1	6 (1.2)	6
Hypokalaemia	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1
Itchy face	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1
Jitteriness	1 (0.4)	1	0 (0.0)	0	1 (0.2)	1
Nausea	4 (1.6)	4	2 (0.8)	2	6 (1.2)	6
Sleep[a]	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1
Teeth whitening	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1
Urticarial rash	0 (0.0)	0	1 (0.4)	2	1 (0.2)	2
Vacant episode	0 (0.0)	0	2 (0.8)	2	2 (0.4)	2
Vomiting	21 (8.3)	21	24 (9.4)	29	45 (8.9)	50

a 'Sleep' is different from 'Drowsiness'. Drowsiness may suggest an impaired consciousness, which may be more of a concern and certainly a feature of severe asthma attack due to hypoxia.

TABLE 13 Adverse events by severity

Event	Severity[a]	No. of events			No. of children[b]		
		Magnesium	Placebo	Total	Magnesium [*n* = 47/252 (19%)]: *n* (%)	Placebo [*n* = 52/255 (20%)]: *n* (%)	Total [*n* = 99/507 (19%)]: *n* (%)
Abdominal pain	Mild	2	2	4	2 (0.8)	2 (0.8)	4 (0.8)
	Moderate	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Asymptomatic hypotension	Mild	1	1	2	1 (0.4)	1 (0.4)	2 (0.4)
	Moderate	0	1	1	0 (0.0)	1 (0.4)	1 (0.2)
Back pain	Mild	0	1	1	0 (0.0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Blood per rectum	Mild	0	1	1	0 (0.0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)

TABLE 13 Adverse events by severity (*continued*)

Event	Severity[a]	No. of events			No. of children[b]		
		Magnesium	Placebo	Total	Magnesium [*n* = 47/252 (19%)]: *n* (%)	Placebo [*n* = 52/255 (20%)]: *n* (%)	Total [*n* = 99/507 (19%)]: *n* (%)
Chest pain	Mild	1	2	3	1 (0.4)	1 (0.4)	2 (0.4)
	Moderate	0	1	1	0 (0.0)	1 (0.4)	1 (0.2)
Diarrhoea	Mild	0	1	1	0 (0.0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	Mild	1	0	1	1 (0.4)	0 (0.0)	1 (0.2)
	Moderate	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Drowsiness	Mild	1	0	1	1 (0.4)	0 (0.0)	1 (0.2)
	Moderate	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Facial flushing	Mild	2	1	3	2 (0.8)	1 (0.4)	3 (0.6)
	Moderate	0	2	2	0 (0.0)	2 (0.8)	2 (0.4)
Feet cramp	Mild	0	1	1	0 (0.0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Fever	Mild	7	5	12	7 (2.8)	5 (2.0)	12 (2.4)
	Moderate	1	0	1	1 (0.4)	0 (0.0)	1 (0.2)
Headache	Mild	5	1	6	5 (2.0)	1 (0.4)	6 (1.2)
	Moderate	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Hypokalaemia	Mild	0	1	1	0 (0.0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Itchy face	Mild	0	1	1	0 (0.0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Jitteriness	Mild	1	0	1	1 (0.4)	0 (0.0)	1 (0.2)
	Moderate	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	Mild	4	2	6	4 (1.6)	2 (0.8)	6 (1.2)
	Moderate	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Sleep	Mild	0	1	1	0 (0.0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Teeth whitening	Mild	0	1	1	0 (0.0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Urticarial rash	Mild	0	2	2	0 (0.0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Vacant episode	Mild	0	1	1	0 (0.0)	1 (0.4)	1 (0.2)
	Moderate	0	1	1	0 (0.0)	1 (0.4)	1 (0.2)
Vomiting	Mild	20	24	44	20 (7.9)	21 (8.2)	41 (8.1)
	Moderate	1	5	6	1 (0.4)	3 (1.2)	4 (0.8)

a No AE was listed as severe.
b Each child recorded once in the highest severity category.

TABLE 14 Serious adverse events

No.	Treatment allocation	Description	Seriousness	Severity	Relationship	Expectedness	Cause	Outcome	Child Status	Unblinded
1	Placebo	Low SaO_2 level (< 86%)/silent chest/cyanosis	Medically significant/important; required hospitalisation; Immediately life-threatening; prolonged existing hospitalisation	Severe	Possibly	Unexpected	Disease under study	Resolved	Withdrawn from treatment	*Yes*
2	Placebo	Child had glycosuria and high blood sugars of > 20 mmol/l	Medically significant/important	Mild	Unrelated	Unexpected	Prior or concomitant treatment	Resolved	Completed trial	No
3	Placebo	Chest infection	Prolonged existing hospitalisation	Moderate	Unrelated	Unexpected	Other illness	Resolved	Completed trial	No
4	Magnesium	Child deterioration, developing silent chest, vomiting	Required hospitalisation	Severe	Unlikely	Unexpected	Disease under study	Resolved	Withdrawn from treatment	*Yes*
5	Placebo	Increased bronchospasm	Medically significant/important; prolonged existing hospitalisation	Mild	Unlikely	Unexpected	Disease under study	Resolved	Completed trial	No
6	Placebo	Increased bronchospasm	Medically significant/important; prolonged existing hospitalisation	Moderate	Unlikely	Unexpected	Disease under study	Resolved	Completed trial	No
7	Placebo	Admission to PICU as HDU child – increased wheeze, respiratory rate and air entry	Prolonged existing hospitalisation	Moderate	Unlikely	Expected	Disease under study	Resolved	Completed trial	No
8	Magnesium	Viral pneumonia	Required hospitalisation; prolonged existing hospitalisation	Mild	Unrelated	Unexpected	Other illness	Ongoing at final follow-up	Continuing in trial	No
9	Magnesium	Admission to PICU because of clinical deterioration and nebuliser poor compliance	Prolonged existing hospitalisation	Moderate	Unlikely	Expected	Disease under study	Resolved	Completed trial	No
10	Placebo	Bronchiectasis	Medically significant/important	Mild	Unrelated	Unexpected	Other illness	Ongoing at final follow-up	Completed trial	No
11	Placebo	Admission to PICU as symptoms not improving	Prolonged existing hospitalisation	Mild	Unrelated	Unexpected	Disease under study	Resolved	Completed trial	No
12	Placebo	Re-admitted to hospital	Required hospitalisation	Mild	Unlikely	Unexpected	Disease under study	Resolved with sequelae	Continuing in trial	No
13	Placebo	Re-admitted to hospital	Required hospitalisation	Mild	Unrelated	Expected	Disease under study	Resolved with sequelae	Completed trial	No
14	Placebo	Worsening of asthma, required aminophylline	Prolonged existing hospitalisation	Moderate	Unrelated	Expected	Disease under study	Resolved	Continuing in trial	No
15	Placebo	Deterioration in asthma, requiring intravenous drugs	Medically significant/important	Moderate	Unlikely	Expected	Disease under study	Resolved	Continuing in trial	No

Withdrawals

There were a total of 20 withdrawals from the study with no further data collection; eight in the placebo group and 12 in the magnesium group. There were three further withdrawals with continued data collection: two in the placebo group and one in the magnesium group. The reasons for withdrawal are shown in *Tables 15* and *16* by time point. The number in parentheses is the number of occurrences for each reason.

TABLE 15 Withdrawals by time point, with no further data collection

Treatment allocation	Reason for withdrawal from study	T0	T20	T40	T60	T120	T180	T240
Magnesium	Child was clinically well and was ready for discharge					✗ (2)	✗ (5)	
Placebo	Child was clinically well and was ready for discharge					✗ (2)	✗ (2)	
Placebo	SAE [low SaO_2 level (< 86%)/silent chest/cyanosis]			✗				
Magnesium	AE (hypotension)			✗				
Placebo	AE (sleep)		✗					
Placebo	Mother withdrew consent (child's father not present, mother was tired, tearful and unsure)	✗						
Placebo	Self-discharged (parent felt they could provide required treatment at home)					✗		
Magnesium	Child did not like the taste of nebuliser		✗					
Magnesium	Child not tolerating nebulisers, becoming distressed		✗ (2)					
Magnesium	Non-compliance with protocol		✗					

TABLE 16 Withdrawals by time point, with continued data collection

Treatment allocation	Reason for withdrawal from study	T0	T20	T40	T60	T120	T180	T240
Magnesium	SAE (developed silent chest)			✗				
Placebo	AE (vacant episode)		✗					
Placebo	AE (vomiting)		✗					

Chapter 4 Results of economic evaluation

Analysis of resource use and costs

Table 17 provides a summary of the resource-use values for each arm of the trial; results are presented separately for the magnesium and placebo groups. There were no statistically significant differences between the trial arms in any category of resource use with the exception of number of children who had contact with community health-care services and number of children who had a full blood count analysis.

Adverse event costs represented the least costly resource category in both trial arms (£0.35 and £0.73 for the magnesium and placebo groups, respectively; *Table 18*), whereas initial hospital admissions represented the most costly resource category (£765.20 and £748.93 for the magnesium and placebo groups, respectively; *Table 19*). Statistical analysis revealed that, at the 5% level, there were no significant differences between the two trial groups in any cost category with the exception of the cost

TABLE 17 Resource use values by resource item and allocation group

Resource	Magnesium: *n* (%)		Placebo: *n* (%)		*p*-value[a]		
NHS and social care resources from randomisation to discharge [resource use based on complete case data (n = 252 for magnesium and n = 256 for placebo)]							
Initial hospital inpatient admissions	232 (92)		245 (96)		0.097		
Chest radiography	72 (29)		83 (33)		0.386		
Lung function	2 (1)		4 (2)		0.686		
Electrolytes	33 (13)		48 (19)		0.090		
Blood culture	13 (5)		21 (8)		0.214		
Full blood count	30 (12)		49 (19)		0.028		
NHS and social care resources from discharge to 4 weeks [resource use based on complete case data (n = 118 for magnesium and n = 112 for placebo)]							
Hospital re-admissions (asthma)	8 (7)		8 (7)		1.000		
Outpatient visits	20 (17)		28 (25)		0.146		
Community health service contacts	42 (36)		56 (50)		0.033		
Medications prescribed	51 (43)		51 (46)		0.791		
Inhalers prescribed	111 (94)		107 (96)		0.769		
	Magnesium		**Placebo**		**Difference**		
	Mean	**SE[a]**	**Mean**	**SE**	**Mean**	**SE**	***p*-value[b]**
Days off school (days off school based on complete case data (n = 89 for magnesium and n = 80 for placebo)							
Full days off school	2.28	0.303	2.35	0.389	−0.69	0.488	0.889
Half days off school	0.73	0.237	0.68	0.186	0.055	0.301	0.855
Total days off school	2.65	0.314	2.69	3.380	−0.414	−0.492	0.933

a The *p*-values were calculated in SPSS using the chi-squared test.

b Standard errors and *p*-values were calculated in Microsoft Excel/SPSS using two-tailed Student's *t*-tests assuming unequal variance.

TABLE 18 NHS and social service costs by cost category and allocation group

	Magnesium		Placebo		Difference		
Resource	Mean	SE[a]	Mean	SE	Mean	SE	*p*-value[a]
NHS and social care costs: from randomisation to discharge [costs (£) based on complete case data (n = 252 for magnesium and n = 256 for placebo)]							
(Initial) hospital admissions	765.20	68.40	748.93	57.60	16.26	89.42	0.856
ED/CUA attendances only	128.30	0.58	129.53	0.43	−1.23	0.72	0.880
Intervention costs	1.79	0.15	1.42	0.15	0.36	0.22	0.000
AEs costs	0.35	0.15	0.73	0.25	−0.38	0.29	0.191
Total cost of care up to discharge	896.53	68.61	881.50	57.70	15.02	89.65	0.867
NHS and social care costs: from discharge up to 4 weeks post randomisation [costs (£) based on complete case data (n = 118 for magnesium and n = 112 for placebo)]							
Hospital re-admissions costs	71.73	28.45	52.57	20.80	19.16	35.24	0.587
Outpatient attendances costs	23.22	4.98	39.98	7.56	−16.76	9.06	0.066
Community health service costs	14.95	2.35	19.23	2.25	−4.28	3.25	0.189
Medications prescribed	6.32	1.45	6.48	1.18	−0.16	1.87	0.932
Inhalers prescribed	22.03	1.90	22.56	1.90	−0.53	2.68	0.843
Total cost of care up to discharge and including 1-month data	1064.96	100.15	1118.65	110.14	−53.68	148.87	0.719
Total non-NHS costs	91.57	13.12	83.52	16.36	8.04	20.97	0.702
Total societal costs	1156.53	103.90	1202.17	115.92	−45.63	155.67	0.770

a Standard errors and *p*-values were calculated in Microsoft Excel using two-tailed Student's *t*-tests assuming unequal variance.

TABLE 19 Broader societal costs (£) by category and allocation group

	Magnesium		Placebo		Difference		
Resource	Mean	SE[a]	Mean	SE	Mean	SE	*p*-value[a]
Non-NHS costs up to 4 weeks post randomisation [costs (£) based on complete case data (n = 118 for magnesium and n = 112 for placebo)]							
Initial hospital visit: travel costs (parents)	16.89	4.07	12.07	1.30	4.83	4.27	0.261
Initial hospital visit: travel costs (others)	8.80	1.30	12.19	2.18	−3.39	2.53	0.182
Initial hospital visit: expenses (e.g. lost pay, child care, snacks)	48.43	8.42	47.29	12.81	1.14	15.33	0.941
Additional costs after discharge from hospital (e.g. travel, lost pay, child care)	16.30	5.43	9.35	3.30	6.94	6.36	0.276
Additional cost of over-the-counter medicines after discharge from hospital	1.14	0.32	2.61	0.87	−1.47	0.932	0.116

a Standard errors and *p*-values were calculated in Microsoft Excel using two-tailed Student's *t*-tests assuming unequal variance.

of the experimental intervention. *Table 19* shows the costs of non-NHS resource use for both the magnesium and placebo groups.

Mean total health service costs including magnesium during the period between randomisation and discharge from the ED or CAU, or the hospital where the child was admitted to an inpatient ward immediately following attendance, was £908 in the magnesium group, compared with £863 in the placebo group, generating a mean cost difference of £45 that was not statistically significant ($p = 0.63$) (see *Table 20*). When multiple imputation was used to impute all missing data over this time horizon, mean total health service costs were £897 in the magnesium group, compared with £882 in the placebo group, generating a mean cost difference of £15 that was not statistically significant ($p = 0.87$) (see *Table 22*). When the time horizon of the economic evaluation extended to 1 month post randomisation, mean total health and social services costs were £1056 in the magnesium group, compared with £1126 in the placebo group, generating a mean cost difference of £70 (complete case analysis) (see *Table 32*). When multiple imputation was used to impute all missing data over the 1-month time horizon, mean total health and social service costs were £1009 in the magnesium group, compared with £1014 in the placebo group, generating a mean cost difference of £5 (see *Table 34*).

Results of the cost-effectiveness analysis

Complete case analysis

The CEA evaluated the cost-effectiveness of magnesium in terms of natural units, calculating the incremental cost per unit decrement in ASS after 60 minutes of treatment. The time horizon for the CEA covered the period between randomisation and discharge from the ED or CAU, or the hospital where the child was admitted to an inpatient ward immediately following attendance. The incremental cost-effectiveness of magnesium is shown in *Table 20* for the 472 children (228 receiving magnesium and 244 receiving placebo) for whom we had complete cost and outcomes data. Within the base-case analysis, the average cost was £908 in the magnesium group, compared with £863 in the placebo group, generating a mean cost difference of £45. The costs presented in *Table 20* differ from those presented in *Table 22*, as the latter represents a multiple imputation analysis including all 508 trial participants. There was no statistically significant difference in costs between the two trial groups, with 36.6% of bootstrap replicates finding magnesium to be less costly than placebo.

In the base-case analysis, the incremental cost-effectiveness of magnesium was estimated at £189 per unit decrement in ASS. However, there was substantial stochastic uncertainty around this finding. The variability around the base-case estimates of cost-effectiveness is shown in *Figure 6*. Although the majority (54.3%) of the bootstrapped replications of the ICER fall in the north-east quadrant of the cost-effectiveness plane, some bootstrapped replications fall in the other three quadrants of the cost-effectiveness plane. As a result, a meaningful ordering of the bootstrapped replications required to make the CI surrounding the ICER interpretable is very difficult. Under these circumstances, CEACs provide an appropriate approach to representing the uncertainty surrounding the ICER. The CEAC curve for the primary clinical outcome measure is displayed in *Figure 7*. The CEAC shown in *Figure 7* indicates that the higher the value decision-makers place on an additional unit decrement in ASS after 60 minutes of treatment, the higher the probability that magnesium will be cost-effective. At the notional cost-effectiveness threshold (or ceiling ratio) of £1000 per unit decrement in ASS, the probability that use of magnesium is cost-effective is 75.1%. Although no previous research has shown how much society or the NHS may or should be willing to pay to reduce the ASS, the economic burden of impairment in children with severe asthma is likely to be significant.[60] If decision-makers are willing to pay £5000 per unit decrement in ASS, the probability that use of magnesium is cost-effective increases to 85.5%.

Mean net benefits were estimated for alternative cost-effectiveness thresholds per unit decrement in ASS (*Table 21*). Assuming that the cost-effectiveness threshold equals £1000 per unit decrement in ASS generates a mean net benefit to the health service attributable to magnesium of £170 (i.e. on average, there is a net gain to the health service in monetary terms). This is analogous to stating that if the actual

TABLE 20 Cost-effectiveness ratios for the CEA base-case analysis and sensitivity analyses: complete case analyses

Analysis[a]	Mean costs (95% CI)			Mean effects (95% CI)			ICER (£)	Probability that magnesium is			
	Magnesium (£)	Placebo (£)	Difference (£)	Magnesium (£)	Placebo (£)	Difference (£)		More effective (%)[b]	Less costly (%)[b]	Cost-effective (%)[b,c]	Cost-effective (%)[b,d]
Base case	908 (764 and 1052)	863 (752 and 975)	45 (–138 and 227)	4.72 (4.54 and 4.90)	4.95 (4.78 and 5.13)	0.24[e] (–0.02 and 0.49)	189	88.00	36.60	75.10	85.50
Higher level inpatient care valued using NHS cost for paediatric high-dependency care (£886)	813 (708 and 918)	794 (718 and 871)	18 (–111 and 148)	4.72 (4.54 and 4.90)	4.95 (4.78 and 5.13)	0.24 (–0.02 and 0.49)	78	89.50	41.90	81.50	87.80
Higher level inpatient care valued using NHS cost for paediatric intensive care (£2225)	1027 (826 and 1227)	950 (790 and 1109)	77 (–179 and 333)	4.72 (4.54 and 4.90)	4.95 (4.78 and 5.13)	0.24 (–0.02 and 0.49)	327	89.20	32.60	68.30	85.90
Exact LOS used	783 (649 and 917)	753 (651 and 855)	30 (–139 and 198)	4.72 (4.54 and 4.90)	4.95 (4.78 and 5.13)	0.24 (–0.02 and 0.49)	126	89.50	42.60	81.00	87.50
LOS rounded up to full days	1019 (867 and 1172)	964 (844 and 1084)	56 (–139 and 250)	4.72 (4.54 and 4.90)	4.95 (4.78 and 5.13)	0.24 (–0.02 and 0.49)	233	88.90	35.00	74.70	86.70
NHS reference costs used to value A&E department visit	876 (732 and 1020)	831 (719 and 942)	45 (–136 and 227)	4.72 (4.54 and 4.90)	4.95 (4.78 and 5.13)	0.24 (–0.02 and 0.49)	193	87.70	36.70	76.50	85.40
NHS reference costs used to value stay on GM ward	943 (797 and 1090)	900 (787 and 1013)	43 (–142 and 228)	4.72 (4.54 and 4.90)	4.95 (4.78 and 5.13)	0.24 (–0.02 and 0.49)	184	90.30	38.50	78.10	88.70

A&E, accident and emergency.

a Complete case analysis included: placebo $n = 244$ and magnesium $n = 228$.

b Based on 1000 bootstrap replicates of the data set.

c Magnesium was considered to be 'cost-effective' if it had positive net benefit at a £1000 cost-effectiveness threshold.

d Magnesium was considered to be 'cost-effective' if it had positive net benefit at a £5000 cost-effectiveness threshold.

e The difference in effects was inverted, i.e. negative values were given a positive sign, to reflect the fact that a decrement in ASS score is synonymous with a positive health effect.

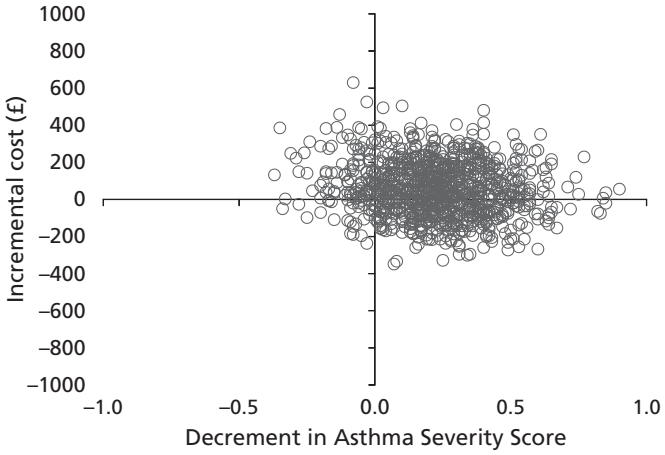


FIGURE 6 Cost-effectiveness plane for CEA base-case analysis: complete case analyses.

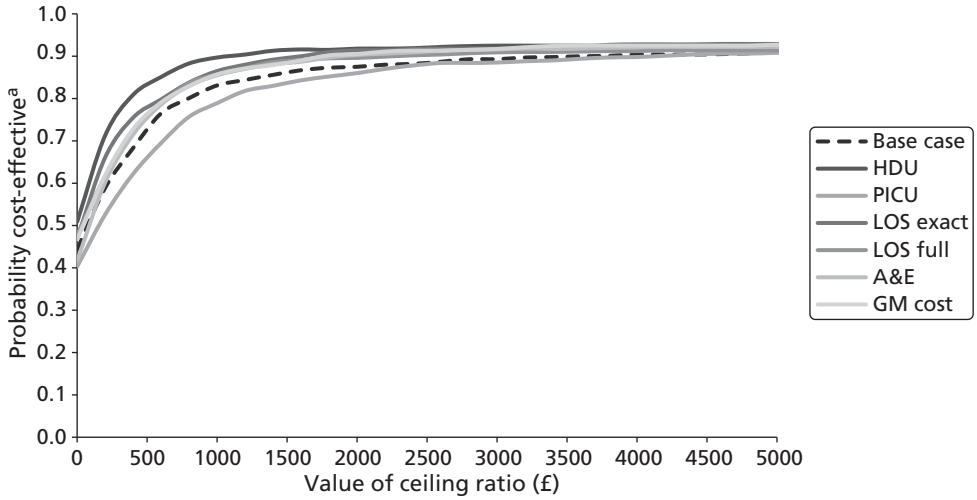


FIGURE 7 Cost-effectiveness acceptability curves for CEA base-case analyses and sensitivity analyses: complete case analyses. a, Each CEAC shows the probability that magnesium is cost-effective with changes in the amount that society is willing to pay for a unit reduction in the asthma ASS. A&E, a lower NHS reference cost applied to A&E department attendances; GM, a higher per diem cost applied to general paediatric ward care; HDU, a lower per diem cost applied to higher-level care; LOS exact, part of a day spent by a child in an inpatient ward equated to a proportional period for costing purposes; LOS full, part of a day spent by a child in an inpatient ward equated to a full 24-hour period for costing purposes; PICU, a higher per diem cost applied to higher-level care.

health benefit of magnesium, in terms of the reduction in ASS, is multiplied by an assumed willingness to pay of £1000 per unit decrement in ASS, and the net cost is subtracted, then the benefit to the NHS of adopting magnesium is, on average, positive in monetary terms. Note, however, that the 95% CI surrounding the mean net benefit (–362 to 678) includes negative values, i.e. there is a possibility of a net monetary loss associated with adopting magnesium (see *Table 20*). If the cost-effectiveness threshold is increased as high as £5000 per unit decrement in ASS, the mean net benefit increases to £1066 (95% CI –£945 to £3058).

Sensitivity analyses were conducted to determine the impact of changing particular parameter values or assumptions on the size of the ICER (see *Tables 20* and *21*; see *Figure 7*). Assuming that higher level inpatient care was valued per diem, using the NHS reference cost for paediatric high-dependency care reduced the mean cost difference between the trial arms to £18 and increased the probability that magnesium is cost-effective to 81.5% at a £1000 cost-effectiveness threshold (mean ICER £78; north-east quadrant of cost-effectiveness plane). In contrast, assuming that higher-level inpatient care was valued per diem, using the NHS reference cost for paediatric intensive care increased the mean cost difference between the trial arms to £77, and reduced the probability that magnesium is cost-effective to 68.3% at a £1000

TABLE 21 Net benefits for the CEA base-case and sensitivity analyses: complete case analyses

Analysis[a]	Mean monetary net benefit (95% CI)						
Value of threshold (£)	Base case (£)	Higher-level inpatient care valued using NHS cost for paediatric high-dependency care (£886)	Higher-level inpatient care valued using NHS cost for paediatric intensive care (£2225)	Exact LOS used (£)	LOS rounded up to full days (£)	NHS reference costs used to value A&E department visit (£)	NHS reference costs used to value stay on GM ward (£)
£0	−54 (−347 and 214)	−21 (−247 to 184)	−87 (−493 and 303)	−26 (−280 and 233)	−59 (−353 and 229)	−49 (−346 and 217)	−49 (−332 and 217)
£500	58 (−321 and 412)	102 (−223 and 391)	31 (−398 and 514)	93 (−254 and 427)	55 (−300 and 416)	65 (−307 and 421)	76 (−285 and 416)
£1000	170 (−362 and 678)	225 (−260 and 686)	149 (−391 and 779)	211 (−298 and 688)	169 (−312 and 690)	179 (−358 and 687)	201 (−295 and 693)
£1500	282 (−410 and 977)	349 (−320 and 988)	267 (−406 and 1073)	329 (−360 and 992)	282 (−363 and 1022)	293 (−403 and 957)	326 (−326 and 988)
£2000	394 (−499 and 1263)	472 (−383 and 1284)	385 (−464 and 1344)	447 (−415 and 1316)	396 (−428 and 1332)	407 (−470 and 1228)	450 (−371 and 1302)
£2500	506 (−570 and 1554)	595 (−451 and 1596)	503 (−493 and 1635)	565 (−470 and 1617)	510 (−524 and 1629)	521 (−525 and 1512)	575 (−418 and 1637)
£3000	618 (−648 and 1845)	718 (−516 and 1922)	621 (−571 and 1928)	684 (−560 and 1922)	624 (595 and 1962)	635 (−588 and 1813)	700 (−468 and 1956)
£3500	730 (−708 and 2139)	842 (−584 and 2232)	739 (−641 and 2250)	802 (−650 and 2228)	737 (−675 and 2302)	749 (−655 and 2100)	825 (−524 and 2273)
£4000	842 (−807 and 2438)	965 (−629 and 2546)	857 (−709 and 2541)	920 (−731 and 2558)	851 (−754 and 2634)	863 (−721 and 2402)	950 (−579 and 2588)
£4500	954 (−874 and 2734)	1088 (−680 and 2867)	975 (−784 and 2889)	1038 (−811 and 2888)	965 (−830 and 2949)	977 (−796 and 2726)	1075 (−634 and 2904)
£5000	1066 (−945 and 3058)	1212 (−767 and 3174)	1092 (−864 and 3184)	1156 (−98 and 3198)	1079 (−908 and 3273)	1091 (−868 and 2999)	1199 (−689 and 3228)

A&E, accident and emergency; CI, [bootstrap] confidence interval; GM, general paediatric ward.

a Complete case analysis included placebo ($n = 244$) and magnesium ($n = 228$).

Based on 1000 bootstrap replicates of the data set.

cost-effectiveness threshold (mean ICER £327; north-east quadrant). Assuming that part of a day spent by a child in an inpatient ward equated to a proportional period for costing purposes and that, consequently, the vacated inpatient bed would be filled immediately reduced the mean cost difference between the trial arms to £30, and increased the probability that magnesium is cost-effective to 81.0% at a £1000 cost-effectiveness threshold (mean ICER £126; north-east quadrant). Assuming that part of a day spent by a child in an inpatient ward equated to a full 24-hour period for costing purposes and that, consequently, the inpatient bed would not be filled until the end of that 24-hour period, and varying the average cost of an ED attendance and general medical ward admission, each had less impact on the cost-effectiveness results. CEACs generated following each sensitivity analysis are shown in *Figure 7*. Estimates of net monetary benefits for notional cost-effectiveness thresholds per unit decrement in ASS are shown in *Table 21* for each sensitivity analysis. For example, assuming that the cost-effectiveness threshold equals £1000 per unit decrement in ASS and that higher-level inpatient care was valued per diem, using the NHS reference cost for paediatric high-dependency care generates a mean net benefit to the health service attributable to magnesium of £225 (i.e. on average, there is a net gain to the health service in monetary terms).

Analyses following multiple imputation

The CEA, expressed in terms of incremental cost per unit decrement in ASS after 60 minutes of treatment, was repeated for all 508 trial participants (252 receiving magnesium and 256 receiving placebo) following multiple imputation of missing cost and outcomes data. As with the complete case analysis, the time horizon for this analysis covered the period between randomisation and discharge from the ED, or the hospital where the child was admitted to an inpatient ward immediately following attendance. The incremental cost-effectiveness of magnesium is shown in *Table 22*. Within the base-case analysis, the average cost was £897 in the magnesium group compared with £882 in the placebo group, generating a mean cost difference of £15. There was no statistically significant difference in costs between the two trial groups, with 44.9% of bootstrap replicates finding magnesium to be less costly than placebo.

In the base-case analysis, the incremental cost-effectiveness of magnesium was estimated at £52 per unit decrement in ASS (north-east quadrant of cost-effectiveness plane). However, as in the complete case analysis, substantial stochastic uncertainty surrounded this finding. This is displayed in the cost-effectiveness plane in *Figure 8*. The CEAC shown in *Figure 9* indicates that at the notional cost-effectiveness threshold of £1000 per unit decrement in ASS, the probability that use of magnesium is cost-effective is 83.1%. If decision-makers are willing to pay £5000 per unit decrement in ASS, the probability that use of magnesium is cost-effective increases to 90.8%. Mean net benefits were also estimated for alternative cost-effectiveness thresholds per unit decrement in ASS following the multiple imputation procedures (*Table 23*). Assuming that the cost-effectiveness threshold equals £1000 per unit decrement in ASS generates a mean net benefit to the health service attributable to magnesium of £266 (95% CI – £275 to £805). If the cost-effectiveness threshold is increased as high as £5000 per unit decrement in ASS, the mean net benefit increases to £1420 (95% CI – £523 to £3440).

Finally, sensitivity analyses were conducted to determine the impact of changing particular parameter values or assumptions on the ICER (see *Tables 22* and *23*; see *Figure 9*). Assuming that higher level inpatient care was valued per diem, using the NHS reference cost for paediatric high-dependency care reduced the mean cost difference between the trial arms to £1, and increased the probability that magnesium is cost-effective to 89.7% at a £1000 cost-effectiveness threshold (mean ICER – £2; south-east quadrant of cost-effectiveness plane). In contrast, assuming that higher-level inpatient care was valued per diem, using the NHS reference cost for paediatric intensive care increased the mean cost difference between the trial arms to £35 and reduced the probability that magnesium is cost-effective to 78.9% at a £1000 cost-effectiveness threshold (mean ICER £119; north-east quadrant of cost-effectiveness plane). Assuming that part of a day spent by a child in an inpatient ward equated to a proportional period for costing purposes and that, consequently, the vacated inpatient bed would be filled immediately reduced the mean cost difference between the trial arms to £4, and increased the probability that magnesium is cost-effective to 86.5% at a £1000 cost-effectiveness threshold (mean ICER £14; north-east quadrant of cost-effectiveness plane). Assuming that part of a day spent by a child in an inpatient ward equated to a full 24-hour period

TABLE 22 Incremental cost-effectiveness ratios for the CEA base-case analysis and sensitivity analyses: analyses following multiple imputation

	Mean costs (95% CI)			Mean effects (95% CI)				Probability active treatment is			
Analysis[a]	Magnesium (£)	Placebo (£)	Difference (£)	Magnesium (£)	Placebo (£)	Difference (£)	ICER (£)	More effective (%)[b]	Less costly (%)[b]	Cost-effective (%)[b,c]	Cost-effective (%)[b,d]
Base case	897 (762 to 1031)	882 (768 to 995)	15 (–161 to 191)	4.66 (4.49 to 4.83)	4.95 (4.78 to 5.12)	0.29[e] (0.05 to 0.53)	52	92.30	44.90	83.10	90.80
Higher level inpatient care valued using NHS cost for paediatric high-dependency care (£886)	802 (704 to 900)	802 (726 to 879)	–1 (–125 to 123)	4.66 (4.49 to 4.83)	4.95 (4.78 to 5.12)	0.29 (0.05 to 0.53)	–2	93.00	51.90	89.70	92.50
Higher level inpatient care valued using NHS cost for paediatric intensive care (£2225)	1015 (827 to 1202)	980 (816 to 1144)	35 (–214 to 283)	4.66 (4.49 to 4.83)	4.95 (4.78 to 5.12)	0.29 (0.05 to 0.53)	119	92.40	40.90	78.90	90.80
Exact LOS used	773 (649 to 898)	769 (666 to 873)	4 (–158 to 166)	4.66 (4.49 to 4.83)	4.95 (4.78 to 5.12)	0.29 (0.05 to 0.53)	14	93.30	47.70	86.50	92.90
LOS rounded up to full days	1005 (861 to 1148)	985 (862 to 1108)	20 (–169 to 208)	4.66 (4.49 to 4.83)	4.95 (4.78 to 5.12)	0.29 (0.05 to 0.53)	68	92.90	48.30	85.50	91.40
NHS reference costs used to value A&E department visit	865 (730 to 999)	849 (736 to 962)	16 (–159 to 192)	4.66 (4.49 to 4.83)	4.95 (4.78 to 5.12)	0.29 (0.05 to 0.53)	55	93.80	42.00	85.50	92.20
NHS reference costs used to value stay on GM ward	931 (794 to 1068)	918 (804 to 1032)	14 (–165 to 192)	4.66 (4.49 to 4.83)	4.95 (4.78 to 5.12)	0.29 (0.05 to 0.53)	47	92.90	47.50	85.70	92.70

A&E, accident and emergency; GM general paediatric ward.

a Imputed case analysis included placebo $n = 256$, magnesium $n = 252$.

b Based on 1000 bootstrap replicates of the data set.

c Magnesium was considered to be 'cost-effective' if it had positive net benefit at a £1000 cost-effectiveness threshold.

d Magnesium was considered to be 'cost-effective' if it had positive net benefit at a £5000 cost-effectiveness threshold.

e The difference in effects was inverted, i.e. negative values were given a positive sign, to reflect the fact that a decrement in ASS score is synonymous with a positive health effect.

TABLE 23 Net benefits for the CEA base case and sensitivity analyses: analyses following multiple imputation

Analysis[a]	Mean monetary net benefit (95% CI)						
Value of threshold (£)	Base case (£)	Higher-level inpatient care valued using NHS cost for paediatric high-dependency care (£886)	Higher level inpatient care valued using NHS cost for paediatric intensive care (£2225)	Exact LOS used (£)	LOS rounded up to full days (£)	NHS reference costs used to value A&E department visit (£)	NHS reference costs used to value stay on GM ward (£)
0	−23 (−310 and 249)	−1 (−200 to 191)	−42 (−441 to 366)	−3 (−284 to 260)	−12 (−318 to 285)	−26 (−312 to 251)	−13 (−307 to 261)
500	121 (−266 to 493)	142 (−162 to 413)	97 (−379 to 562)	142 (−187 to 491)	134 (−230 to 510)	120 (−250 to 473)	133 (−237 to 492)
1000	266 (−275 to 805)	284 (−189 to 693)	235 (−364 to 842)	288 (−184 to 794)	279 (−224 to 799)	266 (−266 to 763)	279 (−237 to 799)
1500	410 (−304 to 1135)	426 (−211 to 993)	374 (−350 to 1128)	434 (190 to 1112)	425 (−229 to 1014)	412 (−280 to 1066)	426 (−274 to 1135)
2000	554 (−338 to 1473)	569 (−255 to 1315)	512 (−387 to 1452)	579 (−223 to 1435)	570 (−259 to 1413)	557 (−303 to 1393)	572 (−311 to 1459)
2500	699 (−362 to 1797)	711 (−285 to 1635)	651 (−444 to 1778)	725 (−254 to 1775)	715 (−299 to 1722)	703 (−348 to 1719)	718 (−343 to 1793)
3000	843 (−400 to 2125)	853 (−311 to 1957)	790 (−485 to 2075)	871 (−287 to 2120)	861 (−325 to 2030)	849 (−397 to 2039)	864 (−385 to 2125)
3500	987 (−422 to 2463)	996 (−354 to 2278)	928 (−554 to 2393)	1016 (−315 to 2452)	1006 (−376 to 2357)	995 (−442 to 2382)	1011 (−422 to 2457)
4000	1132 (−465 to 2774)	1138 (−386 to 2597)	1067 (−619 to 2731)	1162 (−325 to 2764)	1152 (−422 to 2678)	1141 (−478 to 2725)	1157 (−460 to 2789)
4500	1276 (−494 to 3095)	1280 (−413 to 2903)	1206 (−678 to 3070)	1308 (−373 to 3087)	1297 (−468 to 2999)	1287 (−529 to 3057)	1303 (−496 to 3142)
5000	1420 (−523 to 3440)	1423 (−440 to 3229)	1344 (−736 to 3384)	1453 (−395 to 3416)	1442 (−514 to 3315)	1433 (−583 to 3390)	1449 (−530 to 3501)

A&E, accident and emergency; CI, [bootstrap] confidence interval; GM, general paediatric ward.

a Imputed case analysis included placebo $n = 256$, magnesium $n = 252$.

Based on 1000 bootstrap replicates of the data set.

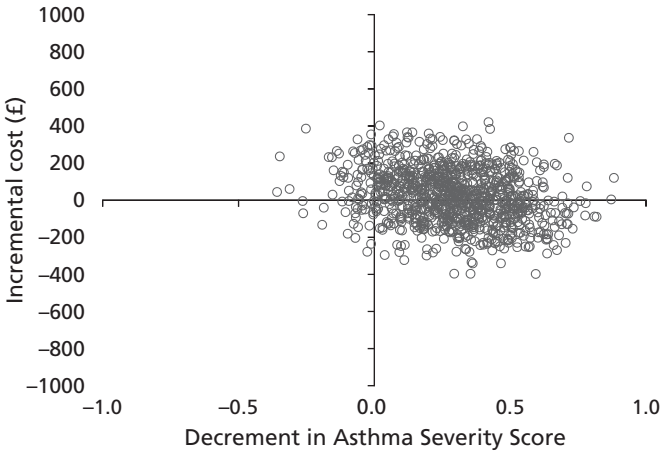


FIGURE 8 Cost-effectiveness plane for CEA base-case analysis: analyses following multiple imputation.

for costing purposes and that, consequently, the inpatient bed would not be filled until the end of that 24-hour period, and varying the average cost of an ED attendance and general medical ward admission, had less impact on the cost-effectiveness results. CEACs generated following each sensitivity analysis are shown in *Figure 9*. Estimates of net monetary benefits for notional cost-effectiveness thresholds per unit decrement in ASS are shown in *Table 23* for each sensitivity analysis.

Analysis of health-related quality of life and utility measures

Parents were asked to describe the QoL of their children at 1 month using the PedsQL™ Asthma Scales. In addition, children aged ≥ 5 years were asked to describe their own health-related QoL at 1 month with the help of a parent or guardian using the PedsQL™ Asthma Scales. The PedsQL™ was designed to provide a modular approach to measuring QoL in healthy children and adolescents, as well as those with acute and chronic health conditions, across the broadest empirically feasible age groups. Of particular relevance is that, unlike other widely used non-preference-based measures of health-related QoL designed for childhood, such as the KIDSCREEN and Child Health Questionnaire, the PedsQL™ has been validated for use in children of < 5 years.[61] The PedsQL™ Asthma Scales comprise parallel child self-report [ages 5–7 years (young child), 8–12 years (child) and 13–18 years (adolescent)] and parent proxy-report [ages 2–4 years (toddler), 5–7 years

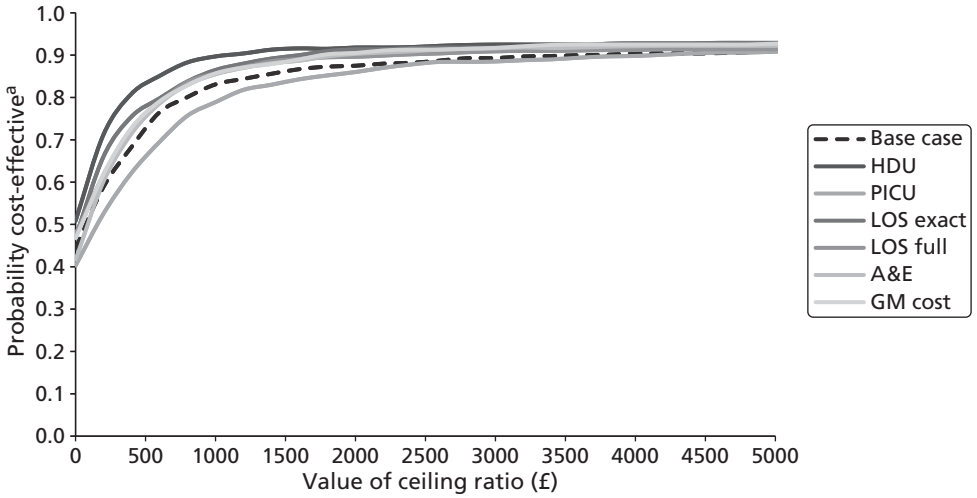


FIGURE 9 Cost-effectiveness acceptability curves for CEA base-case analyses and sensitivity analyses: analyses following multiple imputation. a, Each CEAC shows the probability that magnesium is cost-effective with changes in the amount that society is willing to pay for a unit reduction in the asthma ASS. A&E, a lower NHS reference cost applied to A&E department attendances; GM, a higher per diem cost applied to general paediatric ward care; HDU, a lower per diem cost applied to higher level care; LOS exact, part of a day spent by a child in an inpatient ward equated to a proportional period for costing purposes; LOS full, part of a day spent by a child in an inpatient ward equated to a full 24-hour period for costing purposes; PICU, a higher per diem cost applied to higher level care.

(young child), 8–12 years (child) and 13–18 years (adolescent)] formats. The items for each of the age-specific modules and self-report or proxy-report formats are essentially identical, differing only in terms of developmentally appropriate language, or first or third person tense. The PedsQL™ Asthma Scales contain 28 items covering asthma symptoms (11 items), treatment problems (11 items), worry (three items) and communication (three items). A five-point response scale is utilised across each item (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem) (for self-reports by young children a three-point response scale is utilised). Items are reverse scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0) with higher scores indicating improved QoL. For subscale and total scores, the mean is computed as the sum across all items divided by the number of items answered, thereby accounting for missing data.

Of the 508 1-month postal questionnaires sent to parents, 230 (45%) questionnaires were returned (118 from the magnesium group and 112 from the placebo group). In both groups, the majority (> 70%) of the questionnaires were returned to the research team within 60 days. The 1-month postal questionnaire was carefully designed to ensure that parents were fully aware of the time period under consideration for each question in the questionnaire.

A total of 228 parents completed the PedsQL™ Asthma Scales as part of the 1-month postal questionnaire; 116 in the magnesium arm of the trial and 112 in the placebo arm of the trial. There were no significant differences in baseline clinical and sociodemographic characteristics between the trial groups for whom parent-reported PedsQL™ Asthma Scales data were provided. The mean score on the asthma symptoms, treatment problems, worry and communication subscales was 63.90, 83.57, 73.19 and 77.33, respectively, in the magnesium arm, and 59.55, 80.35, 75.04 and 75.00, respectively, in the placebo arm (*Table 24*). The mean (SE) total parent-reported PedsQL™ asthma score was 73.92 (1.56) in the magnesium arm and 70.24 (1.63) in the placebo arm ($p = 0.104$). The distributions of parent-reported PedsQL™ asthma subscale and total scores across quartiles of the relevant scales are shown in *Table 25*. A total of 52 (45%) children in the magnesium arm had a total parent-reported PedsQL™ asthma score of ≥ 76 compared with 38 (34%) in the placebo arm.

A total of 93 children aged ≥ 5 years separately completed the PedsQL™ Asthma Scales as part of the 1-month postal questionnaire; 47 in the magnesium arm of the trial and 46 in the placebo arm of the trial. There were no significant differences in baseline clinical and sociodemographic characteristics between the trial groups for whom child-reported PedsQL™ Asthma Scales data were provided. The mean score on the asthma symptoms, treatment problems, worry and communication subscales was 53.69, 74.67, 67.57 and 67.02, respectively, in the magnesium arm, and 53.44, 75.62, 68.60 and 57.75, respectively, in the placebo arm (*Table 26*). The mean (SE) total child-reported PedsQL™ asthma score was 65.48 (2.68) in the magnesium arm and 64.02 (2.67) in the placebo arm ($p = 0.701$). The distributions of child-reported PedsQL™ asthma subscale and total scores across quartiles of the

TABLE 24 Subscale descriptives for the PedsQL™ Asthma Module (parent proxy-report[a])

		Magnesium ($n = 116$)		Placebo ($n = 112$)		
Subscale	No. of items	*n*	Mean (SE)	*n*	Mean (SE)	*p*-value[b]
Asthma symptoms	11	114	63.90 (1.98)	109	59.55 (1.96)	0.1202
Treatment problems	11	116	83.57 (1.55)	109	80.35 (1.64)	0.1566
Worry	3	115	73.19 (2.83)	109	75.04 (2.72)	0.5763
Communication	3	111	77.33 (2.59)	106	75.00 (2.72)	0.5322
Total scale score	28	109	73.92 (1.56)	103	70.24 (1.63)	0.1042

a The study population includes all children for whom there was some parent completed PedsQL™ data available.
b Comparisons between trial arms carried out using Student's *t*-tests for continuous variables.

TABLE 25 Distribution of scores for the PedsQL™ Asthma Module (parent proxy-report[a]) by subscales

PedsQL™ subscale/ total scale scores	Score (*n*, %)							
	Magnesium (*n* = 116)				Placebo (*n* = 112)			
	0 to < 26	26 to < 51	51 to < 76	76 to 100	0 to < 26	26 to < 51	51 to < 76	76 to 100
Asthma symptoms	5 (4)	27 (23)	42 (36)	40 (34)	6 (5)	32 (29)	43 (38)	28 (25)
Treatment problems	0 (0)	6 (5)	24 (21)	86 (74)	2 (2)	5 (4)	33 (29)	69 (62)
Worry	13 (11)	19 (16)	19 (16)	64 (55)	9 (8)	16 (14)	25 (22)	59 (53)
Communication	8 (7)	18 (16)	22 (19)	63 (54)	10 (9)	18 (16)	23 (21)	55 (49)
Total scale score	0 (0)	10 (9)	47 (41)	52 (45)	2 (2)	9 (8)	54 (48)	38 (34)

a The study population includes all children for whom there was some parent completed PedsQL™ data available.

TABLE 26 Subscale descriptives for the PedsQL™ Asthma Module (child self-report[a])

Subscale	No. of items	Magnesium (*n* = 47)		Placebo (*n* = 46)		*p*-value[b]
		n	Mean (SE)	*n*	Mean (SE)	
Asthma symptoms	11	47	56.39 (3.52)	45	53.44 (3.04)	0.5273
Treatment problems	11	47	74.67 (2.59)	45	75.62 (2.65)	0.7990
Worry	3	46	67.57 (4.02)	43	68.60 (3.61)	0.8493
Communication	3	47	67.02 (4.05)	43	57.75 (5.03)	0.1546
Total scale score	28	46	65.48 (2.68)	43	64.02 (2.67)	0.7013

a The study population includes all children for whom there was some PedsQL™ data available.
b Comparisons between trial arms carried out using Student's *t*-tests for continuous variables.

relevant scales are shown in *Table 27*. A total of 14 (30%) children in the magnesium arm had a total child-reported PedsQL™ asthma score of ≥ 76 compared with 11 (24%) in the placebo arm.

Ordinary least squares regressions were conducted using the total child-reported PedsQL™ asthma score (model 1) and total parent-reported PedsQL™ asthma score (model 2) as the dependent variables (*Table 28*). Potential confounders replicated the covariates incorporated into the main clinical analyses. Robust Ses were estimated to account for potential heteroscedasticity in the distribution of residuals. Following controls for clinical and sociodemographic covariates, magnesium was associated with a 1.33 increase in the total child-reported PedsQL™ asthma score ($p = 0.734$) and a 4.84 increase in the total parent-reported PedsQL™ asthma score ($p = 0.043$). In model 2, no other clinical or sociodemographic covariate was a significant predictor of the total PedsQL™ asthma score. We do not consider there to be a clinically plausible reason why there may be a relationship between PedsQL™ and late night admission.

Parents of children aged ≥ 5 years were asked to describe the QoL of their children at 1 month using the proxy version of the EuroQol EQ-5D instrument. The EQ-5D is the generic, multiattribute, preference-based measure preferred by NICE for broader cost-effectiveness comparative purposes.[46] The parents were asked to complete only the EQ-5D descriptive system, which defines QoL in terms of five dimensions: 'mobility', 'self-care', 'usual activities', 'pain/discomfort' and 'anxiety/depression', and not the separate EQ-5D visual analogue scale. Responses in each dimension of the descriptive system are divided into three ordinal levels coded (1) no problems; (2) some or moderate problems; and (3) severe or extreme problems. For the purposes of this study, the York A1 tariff was applied to each set of responses to the descriptive system to generate an EQ-5D utility score at 1 month for each child.[52]

TABLE 27 Distribution of scores for the PedsQL™ Asthma Module (child self-report[a]) by subscales

PedsQL™ subscale/ total scale scores	Score (*n*/%)							
	Magnesium (*n* = 47)				Placebo (*n* = 46)			
	0 to < 26	26 to < 51	51 to < 76	76 to 100	0 to < 26	26 to < 51	51 to < 76	76 to 100
Asthma symptoms	4 (9)	18 (38)	11 (23)	14 (30)	3 (7)	17 (37)	20 (43)	5 (11)
Treatment problems	0 (0)	7 (15)	15 (32)	25 (53)	0 (0)	3 (7)	19 (41)	23 (50)
Worry	4 (9)	12 (26)	14 (30)	16 (34)	2 (4)	11 (24)	13 (28)	17 (37)
Communication	4 (9)	16 (34)	9 (19)	18 (38)	10 (22)	13 (28)	5 (11)	15 (33)
Total scale score	0 (0)	13 (28)	19 (40)	14 (30)	1 (2)	5 (11)	26 (57)	11 (24)

a Study population includes all children for whom there were some PedsQL™ data.

TABLE 28 Ordinary least squares of marginal effects for PedsQL™ total scores

Variable (unit)	Self-reported PedsQL™ (child completed[a])			Proxy PedsQL™ (parent completed[b])		
	Fully adjusted β (robust SE)	$p > \|t\|$	(95% CI)	Fully adjusted β (robust SE)	$p > \|t\|$	(95% CI)
Trial arm (referent = placebo)						
Magnesium	1.336 (3.911)	0.734	−6.455 to 9.126	4.836 (2.372)	0.043	0.156 to 9.515
Age (years)	0.598 (0.569)	0.296	−0.534 to 1.731	−0.648 (0.414)	0.119	−1.464 to 0.169
Gender (referent = female)						
Male	9.200 (4.219)	0.032	0.796 to 17.603	3.584 (2.408)	0.138	−1.167 to 8.335
Duration of most recent asthma attack (referent = last ≤ 6 hours)						
For the last few days	−10.738 (4.616)	0.023	−19.933 to −1.543	−0.539 (3.294)	0.870	−7.038 to 5.959
For the last 24 hours	−11.611 (5.927)	0.054	−23.417 to 0.196	−1.615 (3.956)	0.684	−9.419 to 6.190
SaO_2 (value)	0.472 (0.601)	0.435	−0.726 to 1.670	0.290 (0.342)	0.398	−0.385 to 0.964
Assessment at baseline (severity score)	2.188 (1.561)	0.165	−0.922 to 5.299	1.619 (1.027)	0.117	−0.407 to 3.645
Respiratory rate	0.206 (0.194)	0.291	−0.180 to 0.591	0.006 (0.160)	0.971	−0.311 to 0.322
Oxygen therapy required (referent = no)						
Yes	−0.401 (3.910)	0.919	−8.190 to 7.389	0.952 (2.498)	0.704	−3.976 to 5.880
Time of day randomisation occurred (referent = 0000–1700)						
1701–2200	4.112 (4.078)	0.317	−4.013 to 12.236	2.659 (2.400)	0.270	−2.078 to 7.395
2201–0859	14.612 (4.815)	0.003	5.021 to 24.203	4.674 (3.646)	0.201	−2.59 to 11.868

a The study population includes all children for whom there was some PedsQL™ data available.
b The study population includes all children for whom there was some parent completed PedsQL™ data available.

A total of 89 parents of children aged ≥ 5 years completed the proxy version of the EuroQol EQ-5D as part of the 1-month postal questionnaire: 46 in the magnesium arm of the trial and 43 in the placebo arm of the trial. There were no significant differences in baseline clinical and sociodemographic characteristics between the trial groups for whom parent-reported EQ-5D data were provided. The mean (SE) EQ-5D utility score was 0.86 (0.04) in the magnesium arm and 0.88 (0.04) in the placebo arm ($p = 0.710$). *Table 29* shows the distribution of functional levels across the five EQ-5D dimensions for the two trial groups. *Table 30* shows suboptimal levels of function within EQ-5D dimensions by trial group. There were no significant differences in suboptimal level of function across EQ-5D dimensions between the trial groups. Finally, two alternative methods of multivariate analysis were used to model the association between EQ-5D utility scores (dependent variables) and trial intervention: OLS and Tobit (*Table 31*). OLS regression is the most widely used estimator in the literature. It relies on the Gauss–Markov assumptions about the data and variables used in the model, which need to be met in order to produce unbiased estimators. Tobit regression was used to

TABLE 29 EQ-5D levels of function by trial arm (children aged ≥5 years[a])

EQ-5D dimension	Magnesium (*n* = 46): *n* (%)	Placebo (*n* = 43): *n* (%)
Mobility		
Level 1	38 (82.6)	38 (88.4)
Level 2	7 (15.2)	5 (11.6)
Level 3	0 (0.0)	0 (0.0)
Missing	1 (2.2)	0 (0.0)
Self-care		
Level 1	38 (82.6)	39 (90.7)
Level 2	4 (8.7)	2 (4.7)
Level 3	2 (4.3)	1 (2.3)
Missing	2 (13.0)	1 (2.3)
Usual activities		
Level 1	32 (69.6)	37 (86.0)
Level 2	12 (26.1)	5 (11.6)
Level 3	0 (0.0)	1 (2.3)
Missing	2 (4.3)	0 (0.0)
Pain/discomfort		
Level 1	31 (67.4)	33 (76.7)
Level 2	12 (26.1)	9 (20.9)
Level 3	1 (2.2)	1 (2.3)
Missing	2 (4.3)	0 (0.0)
Anxiety/depression		
Level 1	33 (71.7)	34 (79.1)
Level 2	10 (21.7)	7 (16.3)
Level 3	0 (0.0)	2 (4.7)
Missing	3 (6.5)	0 (0.0)

a The study population includes all children aged ≥ 5 years for whom there were some EQ-5D data available.

TABLE 30 Patients with suboptimal levels of function[a] within each EQ-5D dimension (children aged ≥5 years[b])

Dimension	Magnesium (*n* = 46): *n* (%)	Placebo (*n* = 43): *n* (%)	*p*-value[c]
Mobility	7 (15.2)	5 (11.6)	0.758
Self-care	6 (13.0)	3 (7.0)	0.485
Usual activities	12 (26.1)	6 (14.0)	0.186
Pain/discomfort	13 (28.3)	10 (23.3)	0.628
Anxiety/depression	10 (21.7)	9 (20.9)	1.000

a Suboptimal levels of function defined as levels 2 or 3 for each EQ-5D dimension.
b The study population includes all children aged ≥ 5 years for whom there were some EQ-5D data available.
c Calculated using Fisher's exact test for equality of proportions comparing trial arm A and trial arm B.

TABLE 31 Ordinary least squares and Tobit estimator of marginal effects for EQ-5D utility scores (children of ≥5 years[a])

	OLS			Tobit		
Variable (unit)	Fully adjusted β (robust SE)	*p* > |t|	95% CI	Fully adjusted β (robust SE)	*p* > |t|	95% CI
Trial arm (referent = placebo)						
Magnesium	−0.023 (0.062)	0.705	−0.146 to 0.099	−0.100 (0.126)	0.430	−0.351 to 0.151
Age (years)	0.012 (0.011)	0.277	−0.010 to 0.033	0.011 (0.021)	0.603	−0.031 to 0.053
Gender (referent = female)						
Male	0.074 (0.067)	0.272	−0.059 to 0.207	0.107 (0.136)	0.433	−0.164 to 0.378
Duration of most recent asthma attack (referent = last ≤ 6 hours)						
For the last few days	−0.054 (0.048)	0.265	−0.150 to 0.042	−0.182 (0.197)	0.359	−0.574 to 0.211
For the last 24 hours	−0.132 (0.076)	0.088	−0.284 to 0.020	−0.408 (0.211)	0.057	−0.828 to 0.012
SaO_2 (value)	−0.007 (0.006)	0.236	−0.020 to 0.005	−0.015 (0.017)	0.374	−0.048 to 0.018
Assessment at baseline (severity score)	0.036 (0.025)	0.165	−0.015 to 0.086	0.077 (0.051)	0.135	−0.025 to 0.178
Respiratory rate	0.002 (0.002)	0.436	−0.003 to 0.006	0.006 (0.007)	0.383	−0.008 to 0.020
Oxygen therapy required (referent = no)						
Yes	−0.030 (0.064)	0.636	−0.158 to 0.097	−0.096 (0.132)	0.468	−0.358 to 0.166
Time of day that randomisation occurred (referent = 0900–1700)						
1701–2200	−0.068 (0.056)	0.227	−0.043 to 0.180	0.263 (0.147)	0.078	−0.031 to 0.556
2201–0859	0.060 (0.077)	0.437	−0.094 to 0.214	0.210 (0.245)	0.394	−0.278 to 0.697

a The study population includes all children aged ≥ 5 years for whom there were some EQ-5D data available.

account for the non-trivial proportion of the study population with maximum EQ-5D utility scores. Potential confounders replicated the covariates incorporated into the main clinical analyses. In both the OLS and Tobit regressions, magnesium was associated with non-significant reductions in the mean EQ-5D utility score at 1 month: 0.023 and 0.100, respectively. There were no significant associations between any of the clinical and sociodemographic covariates incorporated into both models and the EQ-5D utility score.

A number of mapping models were developed on the basis of data collected for 5- to 16-year-old children for whom both EQ-5D and PedsQL™ responses were available. The best fitting model, in terms of the

lowest RMSE and lowest AIC statistic, was model 3 (described in *Chapter 2*), namely an OLS model that incorporated the four PedsQL™ subscale scores, squared PedsQL™ subscale scores and interaction terms derived using the product of two PedsQL™ subscale scores, as well as age and gender, as independent variables. Mapping algorithms developed from this model were used to estimate EQ-5D utility scores for 2- to 4-year-old children in MAGNETIC for whom the validated toddler module of the PedsQL™ Asthma Scales had been completed; the RMSE for this preferred model – model 3 – was 0.026 compared with 0.039 for model 1 and 0.038 for model 2.

Following this estimation procedure for health utilities at 1 month, QALY estimates were available for a total of 218 children: 111 in the magnesium arm of the trial and 107 in the placebo arm of the trial. By contrast, the multiple imputation procedure filled all missing values for both costs and health utilities.

Results of the cost–utility analysis

Complete case analysis

The CUA evaluated the cost–utility of magnesium in terms of QALYs, a preference-based measure of health outcome recommended by decision-makers such as NICE for cost-effectiveness comparative purposes. The time horizon for the CUA covered the period between randomisation and 1 month post randomisation. The incremental cost–utility of magnesium is initially shown in *Table 32* for the 218 children (111 receiving magnesium and 107 receiving placebo) for whom we had complete cost and QALY data over the 1-month time horizon. Within the base-case analysis, the average cost was £1056 in the magnesium group compared with £1126 in the placebo group, generating a mean cost saving of £70. The costs presented in *Table 32* differ from those presented in *Table 34*, as the latter represents a multiple imputation analysis including all 508 trial participants.

In the base-case analysis, the incremental cost–utility of magnesium was estimated at £175,598 per QALY gained (south-west quadrant of cost-effectiveness plane). The magnitude of this ICER is being driven by the small baseline-adjusted QALY difference between the trial groups (– 0.0004; denominator of ICER). Moreover, there was substantial stochastic uncertainty around this finding. The variability around the base-case estimates of cost–utility is shown in *Figure 10*. Although the majority of the bootstrapped replications of the ICER fall in the south-west quadrant of the cost-effectiveness plane (representing lower costs but poorer outcomes), some bootstrapped replications fall in the other three quadrants of the cost-effectiveness plane. The CEAC for the QALY outcome measure is displayed in *Figure 11*. The CEAC shown in *Figure 11* indicates that the probability that use of magnesium is cost-effective varies between 60% and 70%, depending on the value of the cost-effectiveness threshold. If decision-makers are willing to pay £20,000 per additional QALY (NICE 2008),[46] the probability that use of magnesium is cost-effective is 67.6%.

Mean net benefits were estimated for alternative cost-effectiveness thresholds per QALY gain (*Table 33*). Assuming that the cost-effectiveness threshold equals £20,000 per QALY gain generates a mean net benefit to the health service attributable to magnesium of £63 (i.e. on average, there is a net gain to the health service in monetary terms). This is analogous to stating that if the actual health benefit of magnesium, in terms of QALY gain, is multiplied by an assumed willingness to pay of £20,000 per QALY gained, and the net cost is subtracted, then the benefit to the NHS of adopting magnesium is, on average, positive in monetary terms. Note, however, that, as with the CEA results, the 95% CI surrounding the mean net benefit (– 219 to 334) includes negative values, i.e. there is a possibility of a net monetary loss associated with adopting magnesium (see *Table 33*). If the cost-effectiveness threshold is increased as high as £100,000 per QALY gain, there is little effect on mean net benefit.

Sensitivity analyses were conducted to determine the impact of changing particular parameter values or assumptions on the ICER (see *Tables 32* and *33*; see *Figure 11*). Assuming linear interpolation of health utilities over the entire follow-up period, rather than assuming that the health gain was achieved immediately following hospital discharge, had the largest effect on the ICER. This assumption increased the mean

TABLE 32 Incremental cost-effectiveness ratios for the CUA base-case analysis and sensitivity analyses: complete case analyses

	Mean costs (95% CI)			Mean QALYs gained relative to baseline utility (95% CI)				Probability that magnesium is:		
Analysis[a]	Magnesium (£)	Placebo (£)	Difference (£)	Magnesium	Placebo	Difference	Incremental cost/QALY	More effective (%)	Less costly (%)	Cost-effective at a £20,000 cost-effectiveness threshold (%)
Base case[a]	1056 (855 to 1256)	1126 (904 to 1347)	−70 (−369 to 228)	0.00133 (0.00098 to 0.00169)	0.00173 (0.00131 to 0.00216)	−0.00040 (−0.00095 to 0.00015)	175,598	8.5	69.1	67.6
Linear[b] (U)	1056 (855 to 1256)	1126 (904 to 1347)	−70 (−369 to 228)	0.02530 (0.02060 to 0.02999)	0.03047 (0.02539 to 0.03555)	−0.00517 (−0.01209 to 0.00174)	13,607	7.0	67.3	40.6
Lower (U)	1056 (855 to 1256)	1126 (904 to 1347)	−70 (−369 to 228)	0.00236 (0.00198 to 0.00275)	0.00268 (0.00225 to 0.00312)	−0.00032 (−0.00090 to 0.00026)	219,930	14.4	66.4	64.4
Higher (U)	1056 (855 to 1256)	1126 (904 to 1347)	−70 (−369 to 228)	0.00073 (0.00048 to 0.00099)	0.00102 (0.00072 to 0.00133)	−0.00029 (−0.00069 to 0.00011)	240,906	7.6	69.6	68.2
Societal perspective	1145 (937 to 1352)	1211 (977 to 1443)	−66 (−378 to 246)	0.00133 (0.00098 to 0.00169)	0.00173 (0.00131 to 0.00216)	−0.00040 (−0.00095 to 0.00015)	164,303	8.1	64.1	63.2

U, utility value.

a Complete case analysis included magnesium ($n = 111$) and placebo ($n = 107$).

b Linear interpolation of health utilities over the entire follow-up period, rather than assuming that the health gain was achieved immediately following hospital discharge.

TABLE 33 Net benefits for the CUA base case and sensitivity analyses: complete case analyses

Analysis:[a] value of threshold (£)	Base case: % cost-effective	Base case analysis: mean net benefit (95% CI)	Linear (U):[b] % cost-effective	Linear (U): mean net benefit (95% CI)	Lower (U): % cost-effective	Lower (U): mean net benefit (95% CI)	Higher (U): % cost-effective	Higher (U): mean net benefit (95% CI)	Societal: % cost-effective	Societal: mean net benefit (95% CI)
0	69.10	71 (–215 to 351)	67.30	69 (–249 to 362)	66.4	66 (–229 to 377)	69.6	79 (–218 to 369)	64.1	61 (–247 to 360)
10,000	68.20	67 (–217 to 342)	53.80	17 (–292 to 324)	65.5	63 (–230 to 372)	69.0	76 (–222 to 367)	63.8	57 (–248 to 353)
20,000	67.60	63 (–219 to 334)	40.60	–36 (–354 to 293)	64.4	60 (–228 to 365)	68.2	73 (–226 to 364)	63.20	53 (–249 to 347)
30,000	66.20	59 (–219 to 327)	30.90	–89 (–441 to 266)	63.8	57 (–231 to 360)	67.5	70 (–229 to 361)	62.90	49 (–250 to 340)
40,000	65.50	55 (–220 to 321)	23.20	–141 (–548 to 250)	63.3	53 (–228 to 351)	66.7	67 (–231 to 356)	61.9	45 (–251 to 333)
50,000	64.80	52 (–221 to 315)	19.30	–194 (–661 to 248)	62.6	50 (–225 to 343)	66	64 (–234 to 351)	61.10	41 (–252 to 327)
60,000	64.10	48 (–223 to 309)	16.20	–246 (–771 to 234)	62.0	47 (–222 to 337)	64.9	61 (–235 to 345)	60.0	37 (–257 to 323)
70,000	63.60	44 (–224 to 303)	14.70	–299 (–872 to 233)	61.30	44 (–222 to 331)	64.1	58 (–234 to 342)	59.3	33 (–257 to 320)
80,000	62.20	40 (–227 to 299)	12.90	–352 (–978 to 259)	60.10	41 (–222 to 325)	63	55 (–233 to 338)	58.0	29 (–254 to 317)
90,000	60.90	36 (–232 to 296)	11.40	–404 (–1081 to 260)	59.80	37 (–222 to 317)	62.10	53 (–231 to 333)	56.80	25 (–255 to 310)
100,000	60.00	32 (–236 to 291)	10.80	–457 (–1200 to 269)	59.10	34 (–223 to 309)	61.4	50 (–232 to 329)	55.40	21 (–258 to 303)

U, utility value.

a Complete case analysis included magnesium ($n = 111$) and placebo ($n = 107$).

b Linear interpolation of health utilities over the entire follow-up period, rather than assuming that the health gain was achieved immediately following hospital discharge.

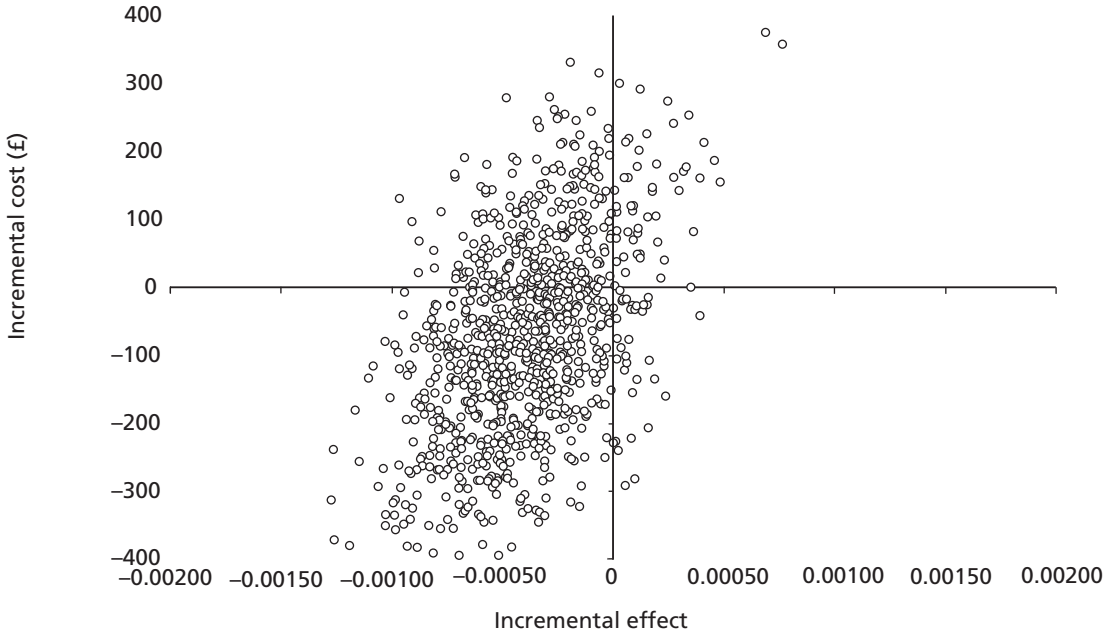


FIGURE 10 Cost-effectiveness plane for CUA base-case analysis: complete case analyses.

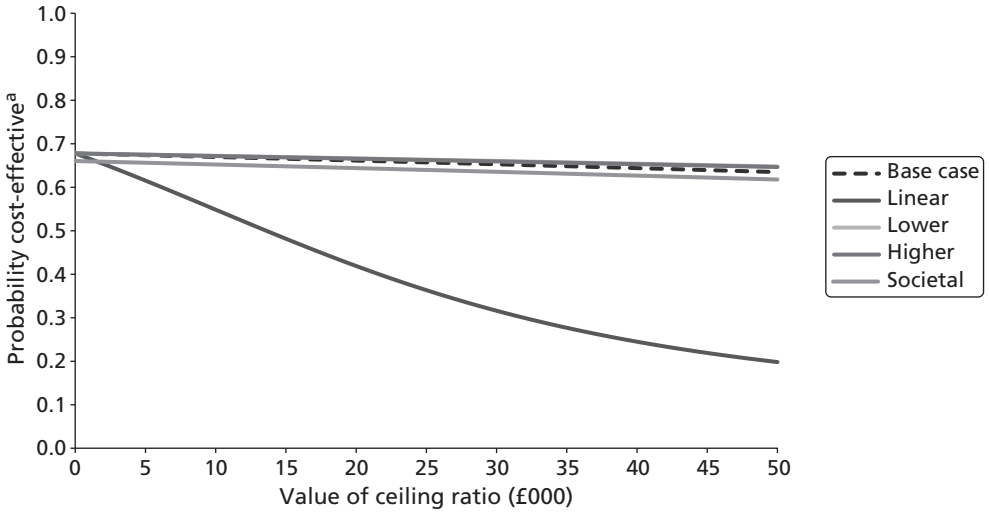


FIGURE 11 Cost-effectiveness acceptability curves for CUA base-case analyses and sensitivity analyses: complete case analyses. a, Each CEAC shows the probability that magnesium is cost-effective with changes in the amount that society is willing to pay for a QALY. A&E, a lower NHS reference cost applied to A&E department attendances; GM, a higher per diem cost applied to general paediatric ward care; HDU, a lower per diem cost applied to higher level care; LOS exact, part of a day spent by a child in an inpatient ward equated to a proportional period for costing purposes; LOS full, part of a day spent by a child in an inpatient ward equated to a full 24-hour period for costing purposes; PICU, a higher per diem cost applied to higher level care.

baseline-adjusted QALY difference between the trial groups to – 0.005, and reduced the probability that magnesium is cost-effective to 40.6% at a £20,000 cost-effectiveness threshold (mean ICER £13,607; south-west quadrant of cost-effectiveness plane). In contrast, assuming baseline ASS mapped on to EQ-5D health states with higher utility scores than in the baseline analysis increased the probability that magnesium is cost-effective to 68.2% at a £20,000 cost-effectiveness threshold (mean ICER £240,906; south-west quadrant of cost-effectiveness plane). Assuming that baseline ASS mapped on to EQ-5D health states with lower utility scores than in the baseline analysis, and adopting a societal perspective for the economic evaluation, only slightly reduced the probability that magnesium is cost-effective. CEACs generated following each sensitivity analysis are shown in *Figure 11*. Estimates of net monetary benefits for notional cost-effectiveness thresholds per QALY gain are shown in *Table 33* for each sensitivity analysis.

Analyses following multiple imputation

The CUA, expressed in terms of incremental cost per QALY gained, was repeated for all 508 trial participants (252 receiving magnesium and 256 receiving placebo) following multiple imputation of missing cost and outcomes data. As with the complete case analysis, the time horizon for this analysis covered the period between randomisation and 1 month post randomisation. The incremental cost–utility of magnesium is shown in *Table 34*. Within the base-case analysis, the average cost was £1009 in the magnesium group compared with £1014 in the placebo group, generating a mean cost saving of £5. There was no statistically significant difference in costs between the two trial groups, with 49.0% of bootstrap replicates finding magnesium to be less costly than placebo.

In the base-case analysis, the incremental cost–utility of magnesium was estimated at £11,886 per QALY gained (south-west quadrant of cost-effectiveness plane). However, as in the complete case analysis, substantial stochastic uncertainty surrounded this finding. This is displayed in the cost-effectiveness plane in *Figure 12*. The CEAC shown in *Figure 13* indicates that, at the notional cost-effectiveness threshold of £20,000 per QALY gained, the probability that use of magnesium is cost-effective is 50.9%. If the cost-effectiveness threshold is increased to £30,000 per QALY gained, there is little effect on the probability of cost-effectiveness. Mean net benefits were also estimated for alternative cost-effectiveness thresholds per QALY gained following the multiple imputation procedures (*Table 35*). Assuming that the cost-effectiveness threshold equals £20,000 per QALY gained generates a mean net loss to the health service attributable to magnesium of £2 (95% CI – £171 to £168). If the cost-effectiveness threshold is increased to £30,000 per QALY gained, the mean net loss to the health service attributable to magnesium increases to £6 (95% CI – £173 to £162).

Finally, sensitivity analyses were conducted to determine the impact of changing particular parameter values or assumptions on the ICER (see *Tables 34* and *35*, and *Figure 13*). As in the complete case analysis, assuming linear interpolation of health utilities over the entire follow-up period, rather than assuming that the health gain, was achieved immediately following hospital discharge, had the largest effect on the ICER. This assumption increased the mean QALY difference between the trial groups to – 0.006, and reduced the probability that magnesium is cost-effective to 14.6% at a £20,000 cost-effectiveness threshold (mean ICER £816; south-west quadrant of cost-effectiveness plane). Assuming that baseline ASS mapped on to EQ-5D health states with either lower or higher utility scores than in the baseline analysis, and adopting a societal perspective for the economic evaluation, each had less impact on the cost–utility results. CEACs generated following each sensitivity analysis are shown in *Figure 13*. Estimates of net monetary benefits for notional cost-effectiveness thresholds per QALY gain are shown in *Table 35* for each sensitivity analysis.

Generalised linear model on costs

For the GLMs performed on costs, a gamma distribution and identity link function was selected in preference to alternative distributional forms and link functions on the basis of its low AIC statistic. *Table 36* summarises the results of three GLM models that regressed costs on intervention mode as well the prespecified sociodemographic and clinical covariates. Robust SEs were estimated to account for potential heteroscedasticity in the distribution of residuals. In model 1, NHS costs to discharge from the ED or CAU, or the hospital where the child was admitted to an inpatient ward immediately following attendance, acted as the dependent variable. In model 2, NHS and Personal Social Services costs to 1 month acted as the dependent variable, whereas in model 3 societal costs to 1 month acted as the dependent variable. In all three models, the use of magnesium did not have a significant effect on economic costs. All three models revealed that male gender is associated with increased economic costs, whereas increased SaO_2 values at baseline are associated with reduced economic costs.

TABLE 34 Incremental cost-effectiveness ratios for the CUA base-case analysis and sensitivity analyses: analyses following multiple imputation

	Mean costs (95% CI)			Mean QALYs gained relative to baseline utility (95% CI)				Probability that magnesium is:		
Analysis[a]	Magnesium (£)	Placebo (£)	Difference (£)	Magnesium	Placebo	Difference	Incremental cost/QALY	More effective (%)	Less costly (%)	Cost-effective at a £20,000 cost-effectiveness threshold (%)
Base case	1009 (877 to 1140)	1014 (895 to 1131)	−5 (−181 to 172)	0.00138 (0.00116 to 0.00159)	0.00176 (0.00153 to 0.00200)	−0.00038 (−0.00070 to −0.00007)	11,886	1.0	51.0	50.9
Linear (U)	1009 (877 to 1140)	1014 (895 to 1131)	−5 (−181 to 172)	0.02458 (0.02161 to 0.02755)	0.03018 (0.02709 to 0.03326)	−0.00560 (−0.00988 to −0.00132)	816	0.8	50.4	14.6
Lower (U)	1009 (877 to 1140)	1014 (895 to 1131)	−5 (−181 to 172)	0.00257 (0.00235 to 0.00278)	0.00275 (0.00253 to 0.00298)	−0.00019 (−0.00050 to 0.00013)	24,562	14.2	53.0	50.6
Higher (U)	1009 (877 to 1140)	1014 (895 to 1131)	−5 (−181 to 172)	0.00063 (0.00048 to 0.00077)	0.00088 (0.00071 to 0.00105)	−0.00025 (−0.00047 to −0.00003)	18,088	1.6	51.4	49.6
Societal perspective	1111 (975 to 1246)	1112 (987 to 1236)	−1 (−185 to 183)	0.00138 (0.00116 to 0.00159)	0.00176 (0.00153 to 0.00200)	−0.00038 (−0.00070 to −0.00007)	2390	0.7	50.5	48.4

U, utility value.

a Imputed case analysis included placebo ($n = 256$) and magnesium ($n = 252$).

b Linear interpolation of health utilities over the entire follow-up period, rather than assuming that the health gain was achieved immediately following hospital discharge.

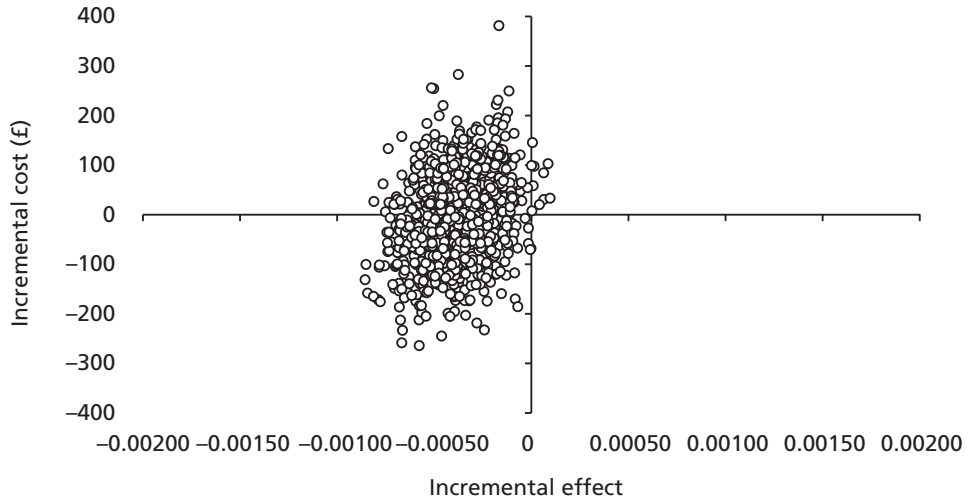


FIGURE 12 Cost-effectiveness plane for CUA base-case analysis: analyses following multiple imputation.

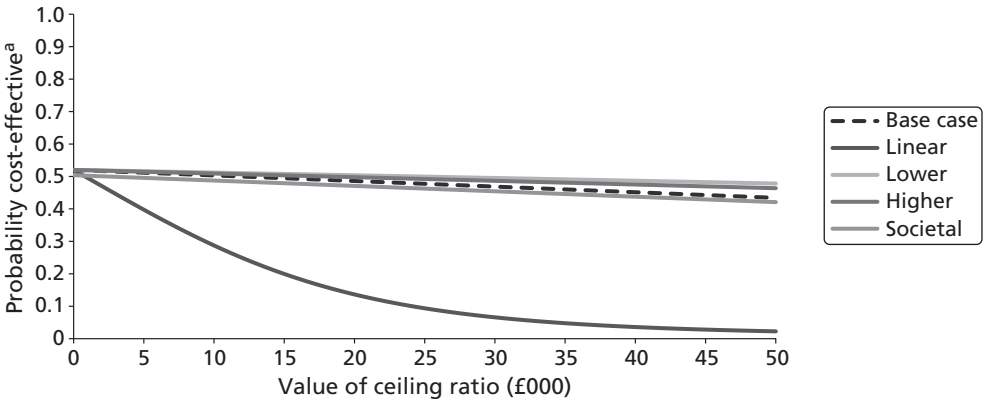


FIGURE 13 Cost-effectiveness acceptability curves for CUA base-cases analyses and sensitivity analyses: analyses following multiple imputation. a, Each CEAC shows the probability that magnesium is cost-effective with changes in the amount that society is willing to pay for a QALY. A&E, a lower NHS reference cost applied to A&E department attendances; GM, a higher per diem cost applied to general paediatric ward care; HDU, a lower per diem cost applied to higher level care; LOS exact, part of a day spent by a child in an inpatient ward equated to a proportional period for costing purposes; LOS full, part of a day spent by a child in an inpatient ward equated to a full 24-hour period for costing purposes; PICU, a higher per diem cost applied to higher level care.

TABLE 35 Net benefits for the CUA base case and sensitivity analyses: analyses following multiple imputation

Analysis: a value of threshold (£)	Base case: % cost-effective	Base case analysis: mean net benefit (95% CI)	Linear (U):[b] % cost-effective	Linear (U): mean net benefit (95% CI)	Lower (U): % cost-effective	Lower (U): mean net benefit (95% CI)	Higher (U): % cost-effective	Higher (U): mean net benefit (95% CI)	Societal: % cost-effective	Societal: mean net benefit (95% CI)
0	53.7	6 (–165 to 177)	54.5	11 (–163 to 197)	52.5	2 (–173 to 164)	51.2	4 (–169 to 172)	51.3	1 (–185 to 187)
10,000	52.5	2 (–168 to 173)	31.0	–45 (–223 to 138)	51.3	0 (–174 to 161)	50.3	1 (–171 to 169)	49.9	–3 (–186 to 182)
20,000	50.9	–2 (–171 to 168)	14.6	–101 (–291 to 89)	50.6	–1 (–175 to 159)	49.6	–1 (–173 to 166)	48.4	–6 (–188 to 178)
30,000	49.4	–6 (–173 to 162)	8.3	–158 (–367 to 56)	49.8	–3 (–175 to 156)	48.7	–4 (–175 to 162)	46.7	–10 (–192 to 172)
40,000	48.2	–9 (–175 to 157)	4.6	–214 (–453 to 26)	48.6	–5 (–175 to 154)	47.8	–6 (–178 to 158)	44.5	–14 (–199 to 166)
50,000	46.8	–13 (–177 to 153)	2.6	–271 (–534 to 4)	47.8	–7 (–175 to 151)	46.8	–9 (–182 to 155)	43.1	–18 (–204 to 160)
60,000	45.1	–17 (–179 to 151)	1.7	–327 (–621 to –27)	47.4	–9 (–175 to 148)	45.4	–11 (–184 to 153)	40.8	–22 (–205 to 154)
70,000	43.3	–21 (–182 to 148)	1.2	–384 (–716 to –51)	46.3	–11 (–175 to 145)	44.2	–14 (–185 to 151)	39.1	–25 (–207 to 149)
80,000	41.1	–24 (–185 to 144)	1.0	–440 (–798 to –68)	45.2	–12 (–176 to 144)	43.1	–16 (–188 to 148)	37.4	–29 (–211 to 146)
90,000	38.7	–28 (–188 to 140)	0.8	–496 (–903 to –90)	44.7	–14 (–177 to 143)	41.5	–19 (–190 to 146)	36.0	–33 (–213 to 141)
100,000	36.7	–32 (–192 to 136)	0.7	–553 (–1006 to –110)	43.5	–16 (–178 to 142)	41.0	–21 (–194 to 143)	35.0	–37 (–218 to 138)

U, utility value.

a Imputed case analysis included placebo $n = 256$ and magnesium $n = 252$.

b Linear interpolation of health utilities over the entire follow-up period, rather than assuming that the health gain was achieved immediately following hospital discharge.

TABLE 36 Generalised linear model estimator of marginal effects for costs

Variable (unit)	NHS costs up to discharge			NHS and PSS costs to 1 month			Societal costs to 1 month		
	Fully adjusted β (robust SE)	$p > \|t\|$	95% CI	Fully adjusted β (robust SE)	$p > \|t\|$	95% CI	Fully adjusted β (robust SE)	$p > \|t\|$	95% CI
Trial arm (referent = placebo)									
Magnesium	−0.40 (64.33)	0.995	−126.48 to 125.69	−13.60 (64.83)	0.834	−140.66 to 113.47	−25.17 (65.90)	0.702	−154.34 to 103.99
Age (years)	54.35 (13.83)	0.000	27.25 to 81.45	62.11 (14.24)	0.000	34.20 to 90.02	72.47 (14.64)	0.000	43.77 to 101.17
Gender (referent = female)									
Male	−26.55 (59.99)	0.658	−144.13 to 91.02	−97.69 (66.65)	0.143	−228.33 to 32.95	−158.03 (70.49)	0.025	−296.18 to −19.88
Duration of most recent asthma attack (referent = last ≤ 6 hours)									
For the last few days	2.48 (89.84)	0.978	−173.59 to 178.56	8.68 (94.81)	0.927	−177.14 to 194.50	2.87 (93.50)	0.976	−180.39 to 186.13
For the last 24 hours	42.47 (104.63)	0.685	−162.62 to 247.55	19.18 (111.55)	0.863	−199.46 to 237.82	38.40 (111.08)	0.730	−179.31 to 256.11
SaO_2 (value)	−36.84 (9.99)	0.000	−56.42 to −17.26	−40.66 (10.13)	0.000	−60.51 to −20.81	−45.37 (10.63)	0.000	−66.21 to −24.54
Assessment at baseline (severity score)	50.23 (22.25)	0.024	6.63 to 93.83	51.84 (24.53)	0.035	3.77 to 99.91	52.43 (24.40)	0.032	4.60 to 100.26
Respiratory rate	235.90 (80.91)	0.004	−1.48 to 12.47	6.41 (3.74)	0.087	−0.93 to 13.74	6.76 (3.90)	0.083	−0.88 to 14.40
Oxygen therapy required (referent = no)									
Yes	−0.030 (0.064)	0.636	77.32 to 394.47	235.47 (81.69)	0.004	75.35 to 395.58	267.18 (90.62)	0.003	89.57 to 444.79
Time of day randomisation occurred (referent = 0900–1700)									
1701–2200	−72.40 (53.98)	0.180	−178.20 to 33.40	−104.17 (57.83)	0.072	−217.51 to 9.17	−87.17 (60.20)	0.148	205.15 to 30.82
2201–0859	375.15 (276.52)	0.175	−166.82 to 917.11	246.30 (236.33)	0.297	−216.90 to 709.51	308.35 (246.70)	0.211	−175.17 to 791.88

Chapter 5 Discussion

Main findings

MAGNETIC is the largest, randomised, double-blind, placebo-controlled study examining standard inhaled bronchodilator therapy in acute severe asthma to date in children aged between 2 and 16 years. The study compares the addition of three doses of nebulised isotonic $MgSO_4$ or placebo (isotonic saline) to standard treatment in children aged between 2 and 16 years. The study has shown a statistically significant difference in ASS at 60 minutes post treatment in favour of the magnesium treatment, after three doses of nebulised isotonic magnesium, given as an adjuvant to the standard therapy of nebulised salbutamol and ipratropium bromide administered three times in the first hour of treatment at presentation to secondary care as per the BTS/SIGN guidelines.[3] This effect on ASS continues to be statistically significant up to 240 minutes post initial treatment.

Overall, the size of the effect at T60 adjusted for ASS at presentation (see *Table 8*), although statistically significant is only 0.25 (95% CI 0.02 to 0.48) of a difference in the ASS scale. This is unlikely to be a clinically meaningful difference. This statistically significant difference continues over the 240 minutes (see *Appendix 5*, *Table 46*) but again, of minimum clinical significance at 0.20 (95 CI% 0.01 to 0.40).

However, this effect is more marked in children who have had a more severe exacerbation (as defined by oxygen saturation in air on presentation) and in those children who have had a shorter duration of symptoms of their exacerbation (as defined by parental report) of < 6 hours. Thus there is a more marked effect on improvement of ASS that is more likely to be clinically significant.

The magnesium regimen in this study, three doses in the first hour, did not show any statistically significant difference in need for intravenous bronchodilator therapy, admission to intensive care, length of stay in hospital, admission rate or number of doses of salbutamol given after the initial treatment of the first hour compared with standard treatment. The main side effects reported during the study associated were flushing, vomiting, headache and asymptomatic self-correcting and transient hypotension. There was no important difference between the groups. There were no severe unexpected AEs associated with the use of $MgSO_4$.

We would conclude that in children with acute severe asthma, nebulised isotonic $MgSO_4$ might be added without harm to the initial regimen combined with ipratropium bromide and salbutamol, especially in those children with a more severe episode and a short history of deterioration of symptoms.

Strengths of the study

Study design

The study was a pragmatic study, using the standard BTS/SIGN guidelines for treating acute asthma,[3] recruiting patients from 30 centres across the UK. Although there are data to show that guidelines are not always followed completely,[62] we felt that a randomised placebo-controlled study designed around a current treatment regimen and current practice was more likely to be completed successfully. We defined acute severe asthma using the BTS definitions for severe asthma: a usable, nationally accepted, published definition. On presentation each patient was treated for their acute symptoms with nebulised bronchodilator (salbutamol with and without ipratropium), while informed consent was obtained with randomisation and the first study treatment given within 30 minutes. This was a similar study design to the study of Hughes *et al.*[16] and was noted to be a safe approach to recruiting. Patient status was monitored for safety for 4 hours post randomisation. Oxygen saturation, respiratory rate and blood pressure were recorded twice

during screening, approximately 20, 40 and 60 minutes post randomisation, and follow-up checks at 120, 180 and 240 minutes. The research team was prompted to check for AEs at each assessment point. AEs were followed up until discharge from hospital.

The randomisation process occurred where the study drug was manufactured before distribution to each study centre. There was random sequence generation in variable-sized blocks and adequate allocation concealment and so low risk of selection bias. The study was blinded to patients, researchers, clinicians, parents and study personnel, and so there was a low risk of performance bias. Outcome assessment was also blinded to all so there was a low risk of detection bias. These data were followed up as much as possible but there were incomplete outcome data, especially the 1-month health economic data, for which the return rate was only 50%, so there is the potential for attrition bias. The data remained blinded to all those analysing the data and only when the SAP was completed successfully, were the data unblinded.

There were no differences in baseline characteristics of our two groups following the randomisation process. This reinforces the internal validity of the study results. Using the LRNs of the MCRN allowed the study to recruit patients from a combination of smaller general hospitals, larger general hospitals as well as tertiary paediatric centres. We recruited patients from both EDs and CAUs – this makes our data more generalisable to the typical clinical situations in which acute asthma presents in the UK.

The involvement of the LRNs was crucial to the success of the trial, offering organisation and support to recruitment. The use of a central CTU, with a dedicated trials manager, data manager and statistical support improved the quality of data. Finally, regular meetings of the TMG, TSC and IDSMC ensured regular research governance and guidance for successful completion of the study over the 2 years of recruitment.

Outcomes

The power of the study was calculated on the basis of the ASS reported by Bishop and Yung[29,30] as the primary outcome of interest. It comprises three clinical signs: wheezing, accessory muscle use and heart rate with the total score a sum of each component, giving a minimum score of 0 and a maximum score of 9. Although there are over 20 ASSs,[39,41,42] the Bishop and Yung score is well validated and easy to use, and allows comparability with other studies.[63] The score has been validated as a measure of asthma severity in children, demonstrated to be reproducible and reliable[29] with good interobserver agreement, and correlates well with severity as defined by oxygen saturations at presentation and FEV_1 at presentation.[30] This score is clinically easy to use and involves standard assessments, used routinely by medical and nursing staff while managing acute asthma.

In order to detect a difference between the two groups at 60 minutes post treatment of 0.5 points on the ASS at the 5% significance level with 80% power, 500 children were required. A difference of 0.5 in ASS was deemed to be the minimum worthwhile clinically important difference to be detected by the research team. There are no studies demonstrating what is a clinically relevant change in an ASS to the patient. As a group of experienced clinicians and researchers we felt a change of 0.5 would be an important difference. There is no evidence base to underpin this pragmatic decision and one of the future studies generated from this work would be to examine what is a clinically relevant change to the patient. Thus the main issue is the clinical relevance of a statistically significant difference in an ASS – this question remains a challenge to those working in acute asthma research.

Severity of asthma exacerbation in the children recruited

We used the BTS definition of 'severe' acute asthma and our initial concern was that we were recruiting children into the study who may only have been included because of their tachycardia, especially the younger children. This is an aspect of this definition identified previously as a concern needing further exploration.[64] We did not have comprehensive screening data of the population presenting at the recruitment centres and so external validity of our population could be a concern.

However, data from a national audit of UK asthma admissions of 9428 children, by Davies *et al.*,[64] between 1998 and 2005, and a recent update of this national audit from November 2011 (J Paton, Royal Hospital for Sick Children, Glasgow, March 2012, personal communication), suggest that we have identified a more severe group of patients. Although the presenting arterial oxygen saturation in air was 94% (IQR 91–96%) in the national audit[64] and in this population was slightly lower at 93.6% (range 81–100%), the use of intravenous bronchodilators as a marker of severity, was 4–5% in the national audit[64] and in the same level in November 2011 and in this population was 11% (see *Table 10*). So we feel that we have identified a group of children with acute severe asthma, which does represent the more severe end of the asthma exacerbation population presenting to unscheduled care facilities in the UK and thus our study has external validity.

We now have a data set of over 500 acute episodes of asthma, which will allow us to explore the BTS definitions of severity further, as has been suggested by Davies *et al.*[64] The magnesium effect is most marked in those children with a more severe exacerbation, as defined here by oxygen saturation in air at presentation. With further analysis of our data using a receiver operating characteristic (ROC) curve we may be able to define where the cut-off point in oxygen saturation at presentation may be to gain maximal effect from the addition of magnesium.

Treatment–covariate interactions

In the initial SAP (see *Appendix 3*), the plan was to formally test a treatment–covariate interaction for the effect of age by including the interaction term in a regression model. Exploratory analysis was planned to examine the impact on any treatment effect of other factors, such as gender or presenting clinical signs. However, blinded to the results, the treatment–covariate interaction hypotheses were discussed further by the statistical and clinical leads (PW, RD, CP, ID) and several changes to the SAP were made as we felt that this approach would be more robust (see *Appendix 3*, *Changes to statistical analysis plan*). Treatment–covariate interactions were investigated for two clinically important baseline covariates, SaO_2 level at presentation and duration of symptoms of the asthma attack. Other factors, such as age or gender, may affect the response but a number of possible patterns of interaction could be argued. Prognostic factors affecting response will be examined in further analysis outside the scope of this report.

Oxygen saturation at presentation

There is evidence that the more severe the exacerbation of asthma, the more likely a child will have a better response to magnesium.[4,6,31] Our hypothesis would be that the effect of the addition of magnesium to the standard regimen would be greater in those with more severe disease. We thus took SaO_2 level at presentation to be the best marker of severity to examine as a potential treatment effect modifier.[3] Further exploration of this relationship will be undertaken outside this report, where we investigate heart rate and respiratory rate in relation to age and response to magnesium.

Duration of attack

The second hypothesis was that the shorter the duration of symptoms then the more marked response to magnesium. This hypothesis is based on the concepts of phenotypes of acute asthma and an understanding of the proposed mechanism for the effect of magnesium on the acutely constricted airway.

(a) There has been a suggestion in the adult literature that there are at least two phenotypes of acute asthma – so-called rapid-onset acute asthma (ROAA) and slow-onset acute asthma (SOAA).[65] Definitions used by this prospective study of 403 adults with severe acute asthma (defined as PEFR < 50% predicted at presentation) are that ROAA is < 6 hours' duration of symptoms and SOAA is > 6 hours' symptoms. Their hypothesis is that prolonged symptoms may give an indication of more airway inflammation and the shorter duration may suggest prominent airway smooth muscle contraction,[65] the latter responding more rapidly to treatment.[66] The incidence of ROAA in this severe group of acute asthma was 11.3%.[67] Barr *et al.*[67] demonstrated in 800 adult patients with acute severe asthma (defined as PEFR of < 50% predicted) 14% (95% CI 11% to 16%) had ROAA.[67] Martin *et al.*[68] demonstrated a prevalence of 17% of ROAA in a study of 30 children with near fatal asthma attacks.

Our study recruited 15% of children with an exacerbation with < 6 hours' symptom duration. Three categories (< 6 hours, < 24 hours and > 24 hours) were established by the research team to define duration of attack. These data were collected and recorded based on parental report, which may be subject to recall bias and previous experience of acute asthma attacks; however, we considered that these data and definitions were sufficiently robust to be able to explore the duration of attack effect.

(b) Nebulised magnesium acts as a smooth muscle bronchodilator as described previously. In a guinea pig model of acute asthma (triggered by histamine challenge) the main effect of nebulised magnesium is in the early phase of bronchoconstriction, where a greater bronchodilator response is evident compared with the later more inflammatory phase in which the effect is less marked.[59]

Thus we felt that the hypothesis that the effect of magnesium may be more marked in those with a shorter duration of attack and shorter duration of symptoms was justified. The concept of phenotypes of acute asthma in children needs to be explored further and will be investigated using these data outside this report.

Longitudinal assessment

We also assessed the effects of the addition of magnesium to changes in the ASS over 240 minutes. So, rather than a cross-sectional measurement at T60 we were able to see the effect, longitudinally up to 4 hours after treatment. This is a novel approach to assessing ASS and has not been presented in the acute asthma literature before.[39] Longitudinal ASS data were summarised by the AUC. The AUC is a summary measure that integrates repeated assessments over the duration of the treatment.

Figure 3 illustrates the mean longitudinal profiles over the first hour. There was no significant difference in AUC over the first hour during the treatment regimen ($p = 0.21$; see *Table 9*). However when we examined the effect over 240 minutes, even accounting for missing values and dropouts we can demonstrate that the statistically significant effect seen at the cross sectional T60 measurement (see *Table 8*) is sustained up to 240 minutes (see *Appendix 5*, *Figures 15* and *16*, and *Table 46*). Again, the clinical significance of this difference is unlikely to be important [treatment effect on ASS 0.20 (95% CI 0.01 to 0.40)], but it does emphasise that there is a pharmacological effect and that this is sustained over 240 minutes in the overall group. This effect would need to be explored further to examine the magnitude and length of the effect in those with a more severe attack and shorter duration of symptoms. The data from MAGNETIC will allow further exploration of the AUC as a potential core outcome for future acute asthma studies.

Secondary outcomes

We examined secondary outcomes frequently measured in acute asthma studies[32,39] (see *Appendix 1*): need for intravenous bronchodilator therapy, need for PICU admission and intubation, stepping down of treatment after 1 hour, length of stay and additional bronchodilators given. We found no evidence of a difference between those who received magnesium and those who received standard therapy. No paediatric studies of nebulised magnesium have found any evidence of differences in these outcomes but none, including the current study, are powered individually to do so.

The only 'new' outcome reported in this study is the 'stepping down' of treatment from nebuliser to spacer. We were unable to detect a difference between the two groups: 33% in the magnesium group and 30% in the placebo group ($p = 0.53$). In the study by Kelly *et al.*,[43] among 720 patients (adults and children) presenting to 36 EDs in Australia, asthma severity improved from severe to moderate after an hour of treatment in 50%, resulting in a change from nebuliser to spacers – thus 'step-down'. Stepping down is thus considered to be a proxy for the clinician considering the child to be clinically better and is based, rather than on a score, on a clinician's subjective impression. However, the fact that only one-third stepped down at 1 hour in this study would suggest that we have a group of children with more severe acute asthma attacks than the mixed population of all levels of severity in those presenting to EDs in the Kelly *et al.* study;[43] the mixed age groups and wider spectrum of severity may explain the difference. This concept of stepping down of treatment needs to be further developed for further studies in acute asthma.

An outcome that we did not analyse is the concept of mean duration in supplemental oxygen. Khashabi 2008[37] (presented in abstract form only) examined 40 children with acute asthma (mean age 3.55 years) but found no difference in an ASS 1 hour after two doses of either nebulised magnesium and salbutamol or salbutamol and placebo, but they did find a difference in mean duration of supplemental oxygen therapy (not defined in the abstract): 15.2 hours (95% CI 9.3 to 21.5 hours) compared with 19.0 hours (95% CI 12.4 to 25.8 hours).[37] This outcome should be defined and explored further in future studies of acute asthma.

Centre effect

A sensitivity analysis was performed to investigate the robustness of ignoring a centre effect in the primary analysis. Two models were fitted when the centre was treated as either a fixed effect or as a random effect. Both models were adjusted for baseline ASS. Reassuringly, there was no evidence that the treatment effect varies by centre (see *Appendix 6*, *Table 47*).

Timing of treatment administration

There could be concern that there was significant variation in the timing of the administration of the study medication in the two groups. Reassuringly, there was no clinically significant deviation in the mean prescribed times between the treatment groups on any of the three occasions (see *Table 5*) and the mean time to administration in both groups was 5.8 (SD 8.3) minutes after randomisation, 23.4 (SD 5.5) minutes after the first dose and 23.3 (SD 6.2) minutes after the second dose, which was as per the protocol. We had previously stated that 15 minutes leeway was clinically acceptable, and *Table 6* has shown that only 53/508 instances were considered to be protocol deviations, with 10% in the magnesium group and 12% in the placebo group.

Potential limitations

Dose of magnesium given

We used the same dose of isotonic $MgSO_4$ for all ages on each of the three administrations in the first hour (2.5 ml of 250 mmol/l, tonicity 289 mOsm, 151 mg per dose). This was the dose used by Hughes *et al.*[16] in their adult study of 52 patients where they demonstrated a significant effect in lung function improvement at 90 minutes post treatment.[16]

The ideal dose for children has not yet been clarified and whether the dose needs to be changed with age/weight or whether one standard dose is sufficient, modulated by the child's tidal volume, is yet to be ascertained. There is clearly a dose–response effect in the guinea pig model of magnesium effect and bronchoconstriction[59] with guinea pigs with stable tidal volumes but the examination of this issue has not had any exploration in this acute asthma literature.

In the nebulised magnesium studies including children, so far one dose has been used for all ages but these have differed in frequency, formulation and combination with other bronchodilators (see *Appendix 1*, *Table 39*). This illustrates how difficult it is to make any comparison and firm conclusion when comparing the literature.[32] This is also a similar research consideration in the adult data.

- Aggarwal *et al.*[22] (ages 13–60 years, $n = 110$) 1 ml $MgSO_4$ (500 mg) three doses 20 minutes apart with β_2-agonist; total magnesium used: 1500 mg (3 × 500 mg).
- Ashtekar *et al.*[27] and this study, MAGNETIC (ages 2–16 years, $n = 508$) 2.5 ml of 250 mmol/l, tonicity 289 mOsm, 151 mg per dose; total magnesium used: 453 mg (3 × 151 mg).
- Drobina *et al.*[23] (ages 12–60 years, $n = 110$) 125 mg $MgSO_4$ 0.25 ml of 50% solution (three doses 20 minutes apart with β_2-agonist; total magnesium used: 375 mg (3 × 125 mg).
- Khashabi *et al.*[37] (ages mean age 3.55 years) two doses of isotonic $MgSO_4$ not stated.
- Mangat 1998[14] (ages 12–60 years, $n = 33$) 3 ml (95 mg) $MgSO_4$ (four doses, 20 minutes apart) compared with β_2-agonist; total magnesium used: 380 mg (4 × 95 mg).

- Mahajan *et al.*[18] (ages 5–17 years, $n = 62$) 2.5 ml isotonic $MgSO_4$ solution (6.3%) with single dose of β_2-agonist (dose).
- Meral 1996[19] (ages < 16 years, $n = 40$) 2 ml of $MgSO_4$ 280 mmol/l).

No studies have examined the use of frequent doses of nebulised magnesium outside the first hour of treatment. Dose used and frequency given need further research in the clinical setting of acute asthma in children.

Different nebulisers and outputs

This was a pragmatic study and thus did not define a standard nebuliser for each centre but they were all oxygen driven from wall oxygen supplies. We felt that in order to produce a generalisable result we should use what is currently being used in the EDs and CAUs in the UK. Each centre used the same type of nebuliser for all patients within that centre, but different types of nebuliser were used in different centres. There are some American data to suggest that there is variable output from different nebulisers.[69] The PARI LC Star® (PARI Respiratory Equipment, Midlothian, VA, USA) had an appropriate particle size distribution but a very slow aerosol output rate. The Omron MicroAir® [Clement Clarke International (CCI), Harlow, UK] had an even slower output rate and a larger particle size distribution, which would be inappropriate for smaller children. In vitro lung deposition with the Aeroneb Go with Idehaler (Aerogen, Galway, Ireland) was 16.0 ± 0.4 mg/minute in older children and approximately one-fifth of that in toddlers. This presumably relates to lung deposition and not necessarily therapeutic effect; some effect may be due to absorption across mucous membranes and independent of lung deposition. Their conclusion was that the Aeroneb Go with Idehaler was the ideal one for a nebulised magnesium study currently under way in the USA.

Unblinding of randomised treatments during the study and protocol deviations and missing values

Unblinding of randomised treatments during the study

The treatment allocation was unblinded during the course of the trial for only two children, one in each group (see *Table 14*), and the children were withdrawn from the study owing to SAEs that both resolved. Both events were considered to be unlikely to be related to the study medication and will not have affected the outcome of the study.

Protocol deviations

Table 6 illustrates the protocol deviations that occurred and these were related to the timing of administration (53), age of patient (2), recruitment more than once (1), and pretreatment with spacers rather than with nebulisers (14). These were thus few and not likely to represent any danger to the children. It was reassuring that there was no imbalance across treatment groups.

Missing values

Although we achieved the expected recruitment rates, there were concerns about the missing values in the data collated in the CRFs early on in the course of recruitment. The concern was that these missing values could influence the conclusions of the study.

Primary outcome data

There were 36 (7%) children recruited into the study who had insufficient data to complete an ASS at T60 (see *Appendix 5*, *Table 41*). The reasons for the missing components of the ASS in these 36 cases are illustrated in *Appendix 5*, *Table 42*. The main issues were missing components of the ASS in 22 (4.3%) of cases. This illustrates how well the training of the ASS by the PI and research nurses in the study was completed. The lack of difference in the key baseline characteristics between observed patients and those missing at T60 indicates the plausibility of the MCAR assumption.

Three sensitivity analyses were performed (see *Appendix 5*, *Tables 43–45*) to explore this assumption:

1. reason for missingness (see *Appendix 5*, *Table 43*); adjusted difference in mean [– 0.32 (95% CI – 0.56 to – 0.08), $p < 0.01$]
2. multiple imputations (see *Appendix 5*, *Table 44*); adjusted difference in mean [– 0.28 (95% CI – 0.51 to – 0.05)]
3. joint modelling of the longitudinal first 60 minutes' data (see *Appendix 5*, *Table 45*).

Thus the sensitivity analysis did not suggest a substantially different conclusion from the assumption that the missing values were missing at random and they did not influence the final conclusion of the analysis.

Longitudinal data

The relationship between the ASS and dropout from the study over the entire length of the study was examined by joint modelling. In *Appendix 5*, *Figures 15* and *16*, and *Table 46* illustrate that the dropout in the magnesium group was due to those subjects getting better (see *Figure 16*) and not getting worse. This does not affect the final conclusion that the effect of magnesium on a ASS of 0.2 (95% CI 0.01 to 0.40) over the 240 minutes is sustained statistically. Thus the effect of any missing value in either treatment arm does not significantly affect the conclusions from the study.

Safety

There were no major safety issues of clinical concern reported and this study suggests that the doses and frequency given in this regimen can be considered safe. We did not measure the serum levels of magnesium, but there are adult data to suggest[70] that it is safe not to do so. However, if further studies were to be undertaken using higher or more frequent doses in children, concerns over safety might mandate the measurement of serum magnesium levels and pharmacokinetic studies with dose–response measurements may be necessary.

The AEs reported in the study 99/507 (19.5%) were mainly mild and of similar magnitude in both groups; magnesium 19% and placebo 20%. Vomiting was the most commonly reported feature in both groups; magnesium 8.3% and placebo 9.4%. Headache was reported more commonly in the magnesium group (2% compared with the 0.4% in the placebo group). Further analysis of these AE may be useful; if the vomiting and headaches were related to the use of intravenous bronchodilators (e.g. aminophylline), especially the vomiting, then the incidence related to the magnesium may even be reduced further.

There were 15 SAEs (three on magnesium and 12 on placebo), only one of which was considered to be possibly related to the study drug, but this was a child in the placebo group (see *Table 14*). There were no SUSARs. One can thus conclude that, although the study was not powered to identify every difference in AE and SAE or rates of SUSAR, the administration of nebulised magnesium at these doses and frequency is safe. This is supported by the data from all published 16 studies using nebulised $MgSO_4$ (see *Appendix 1*, *Table 39*[32]).

Comparison with other studies

MAGNETIC is the first clinical trial of such size to address standard treatment as per BTS guidelines with the addition of nebulised magnesium in the UK. The conclusion from the systematic review by Mohammed and Goodacre[4] was that 'insufficient data exist to draw reliable conclusions regarding the role of nebulised $MgSO_4$ in children'.

Only two paediatric studies[18,19] were included in this review and the conclusion was based on the lack of significant effect on respiratory function (SMD 20.26; 95% CI – 1.49 to 0.98; $p = 0.69$) or hospital admission (RR 2.0; 95% CI 0.19 to 20.93; $p = 0.56$) in children. But these two studies[18,19] were of insufficient power

and methodological rigour to draw any other conclusion. Our data are of adequate power and reliability, and are sufficiently generalisable, to suggest that there is a significant clinical effect on acute asthma using nebulised $MgSO_4$, especially in severe exacerbations of short duration. There are sufficient data in this study to suggest that the addition of nebulised magnesium to the standard regimen for acute severe asthma in children is justified.

Almost universally in the published studies showing a beneficial effect of the addition of magnesium to standard treatment, it is the more severe patients – both adults and children – who gain the most benefit.[4,6,32] The conclusion from the MAGNETIC study is therefore supported by the literature and firms up the recommendation that can be given about the use of nebulised magnesium in severe acute asthma in children.

We have shown a more marked effect of nebulised magnesium on children with a shorter duration of symptoms. There is little published evidence on different phenotypes of acute asthma, and the MAGNETIC data set will enable us to explore this topic outside the scope of this report. As described above (see *Duration of attack*), we generated the hypothesis that response may be more marked in those children with a shorter duration of symptoms, based on data suggesting different phenotypes of acute asthma and an understanding of how magnesium may work. The main criticism about the definition used here could be that the duration of symptoms is defined by parental report and these could be subject to bias from a number of areas: experience of symptoms previously and length of diagnosis of asthma, responsiveness of parents to getting medical help and recognising symptoms, some children may have had only their first attack of wheezing and so parental understanding may be variable, and what constitutes the onset of symptoms may be different in different families; all may have an effect on the reporting of onset of symptoms.

Data from asthma mortality studies also suggest at least two mechanisms for death in acute asthma. These two mechanisms may highlight the two different phases of an acute asthma response – an immediate asthma response followed by a later response – which are well-described phases in airway compromise seen in exercise-induced and methacholine and histamine challenge test-induced airway constriction.[71] Slow-onset cases fatality have shown to be more eosinophilic inflammatory-mediated response and the more sudden onset a more neutrophil-mediated response with acute bronchospasm.[72] More recent data[73] suggest that there are different inflammatory profiles during acute asthma in children and adults. Although a small study, it suggested that adult acute asthma was more likely to be neutrophil driven, whereas in children it was more likely to be eosinophilic. Indeed, this group has suggested that there are a number of phenotypes: eosinophilic, neutrophilic, mixed granulocytic and paucigranulocytic asthma.[74] The frequency in acute childhood asthma has not yet been determined but there is sufficient evidence to suggest there may well be different mechanisms during an acute episode to warrant exploration of our data.

Finally, as described in *Chapter 1*, magnesium appears to work at a number of levels in acute asthma. It may affect the inflammatory process in asthma, especially attenuating neutrophil burst associated with an asthma response and thus acting as an anti-inflammatory agent.[8] Indeed, in a guinea pig model of asthma developed by part of this current research group, a reduction in neutrophil numbers has been demonstrated.[58] Again, this would support the concept of examining those children with a shorter duration of symptoms, perhaps neutrophil mediated, responding differently to those with a longer duration of symptoms.

Thus, we have demonstrated a greater effect in those children who have had a shorter duration of exacerbation, supporting the animal model's implication that nebulised magnesium has more of an effect on the early asthma bronchoconstriction response. When one examines the conflicting literature in the adult nebulised magnesium studies, this becomes evident. Aggarwal *et al.*,[22] in a RCT of reasonable power, found no effect in 100 adults with acute asthma. However, in both study groups asthma history preceding their recruitment to the study averaged 72 hours; thus, the later inflammatory response may have predominated in those subjects, explaining the lack of clinical response.[22] A recent study by Gallegos-Solórzano *et al.*[36] found a significant difference in response adding nebulised magnesium in a RCT involving 60 patients, and their duration of attack was shorter – between 15 and 23 hours – again demonstrating a shorter duration of

exacerbation associated with improved lung function, post-treatment oxygen saturation and a reduced admission rate.

In a low-powered RCT by Kokturk *et al.*[21] involving 26 patients, no difference in PEFR or clinical scores was seen when nebulised magnesium was added to a standardised regimen. The duration of attack was not reported and thus the relationship between duration of attack and response cannot be commented on. There were also no data on the duration of attack in the Hughes study.[16]

Mahajan *et al.*[18] studied 62 children in whom lung function had shown a minimal short-term response to nebulised magnesium. The average duration of attack of 42 hours was in both groups, shorter than in the subjects in the study by Aggarwal *et al.*,[22] but still longer than in the children in our study, who showed a more marked clinical response.

The topic of phenotypes of acute asthma and this apparently more marked response to magnesium needs further exploration outside the scope of this report.

Health economics data

The economic evaluation undertaken alongside the MAGNETIC trial compared the addition of $MgSO_4$ to standard treatment with standard treatment only in children with acute severe asthma who presented at a hospital ED or CAU. It represents, to our knowledge, the first economic evaluation of $MgSO_4$ in children with asthma. The economic evaluation was conducted according to nationally-agreed design and reporting standards.[46,47] The economic evaluation has three key strengths. First, it is based on prospective collection of cost and QoL data from the MAGNETIC trial, which recruited over 500 children from the UK; this means that the source of the data is likely to be reliable and appropriate to inform health-care decision-making in the NHS. Second, some of the approaches used to measure children's QoL outcomes in the CUA are novel and perhaps will pave the way for future empirical research into the measurement of QoL of children with asthma. Third, there has been a substantial collection of non-NHS data from patients in the trial. Describing the results of the economic evaluation from the perspective of the NHS and Personal Social Services and from the wider societal perspective means that decision-makers can make a more informed choice when deciding whether or not to invest scarce health-care resources in treatments for children with acute severe asthma.

The cost and outcomes data collected in the MAGNETIC trial were analysed within two alternative frameworks: (1) a CEA that used the child's ASS score as the health outcome of interest and (2) a CUA that used the child's QALY profile as the health outcome of interest. A series of sensitivity analyses were carried out for each analysis to account for uncertainty surrounding key components of the economic evaluation; in addition, the implications of missing data were explored via multiple imputation analyses and the results were incorporated into both the CEA and the CUA.

In the CEA, the economic evaluation was restricted to the time period from randomisation to hospital discharge and the perspective was that of the NHS and Personal Social Services. As resource-use data were collected via the trial CRFs, complete health economics data were available for analyses and we are therefore confident that we have been able to identify, measure and value resource use reliably for both groups of children. There were no statistically significant differences demonstrated between the magnesium and the placebo groups for any of the cost categories except for the cost of the study intervention. However, there was a statistically significant difference in ASS at T60 between the groups (the primary outcome of the MAGNETIC trial) in favour of the MAGNETIC group. Consequently, the results of the CEA demonstrate that adding magnesium to standard treatment yields a relatively high probability (75%) that magnesium is cost-effective at a threshold of £1000. Increasing the cost-effectiveness threshold illustrates that adding magnesium to standard treatment becomes increasingly cost-effective; at a threshold of £5000, the probability that magnesium is cost-effective increases to 85.5%. Clearly, how much society or the NHS may or should be willing to pay to reduce a child's ASS is unknown and this is the challenge faced by health-care

decision-makers. Future preference elicitation studies in this area should aid their decision-making. The results of the sensitivity analysis confirm that the probability of magnesium being cost-effective compared with no magnesium in the base-case analysis is robust; probabilities of cost-effectiveness range from 68.3% (applying a higher PICU cost to higher-level inpatient care) to 81.5% (applying a lower HDU cost to higher-level inpatient care). The results of the multiple imputation analyses support the findings of the base-case CEA and show that the likelihood that magnesium is cost-effective ranges between 78.9% and 89.7% at threshold of £1000.

In the CUA, the economic evaluation was covered a longer time horizon than the CEA; costs and benefits were analysed from randomisation to 1 month after the child's initial visit to ED/CUA. The base-case CUA was undertaken from the perspective of the NHS and Personal Social Services. None of the NHS costs was found to be statistically significantly different between the two groups. Initially, the CUA was restricted to the trial population for whom questionnaires were returned and so the CUA was based on data from fewer children than the CEA (230 vs. 508, respectively); the full population was included in the CUA using multiple imputation methods. In the base-case analysis for the CUA, the ICER is high at £175,598 per QALY gained. The size of the ICER is largely driven by the very small mean difference in QALY scores between the two trial groups; there is a 0.0004 difference in QALYs in favour of the placebo group. However, the results of the base-line CUA demonstrate that adding magnesium to standard treatment is likely to yield probabilities of 60–70% of cost-effectiveness across thresholds ranging from £0 to £100,000. At a cost-effectiveness threshold of £20,000 per QALY gained, the results of the sensitivity analysis show that the conclusion of the base-line CUA is relatively robust and that the only parameter change that leads to a relatively low (40%) probability of cost-effectiveness is related to the assumption that the EQ-5D health state has not been immediately achieved following hospital discharge; clinical opinion is that the EQ-5D health state is likely to be achieved following discharge. The results of the sensitivity analysis which uses societal (NHS, Personal Social Services, families and carer) rather than NHS costs only support the conclusion of the base-line CUA that adding magnesium to standard treatment is likely to be cost-effective at the £20,000 per QALY threshold. The results following multiple imputation analyses are less favourable showing lower probabilities of cost-effectiveness as thresholds increase.

As always, a number of caveats should be noted when interpreting the results of any economic evaluation.

First, in both the CEA and the CUA there is considerable stochastic uncertainty around the size of the base-case ICERs; this means that it is important to focus on the interpretation of the results of the CEA and the CUA, as illustrated by the CEACs. When results show that the size of the ICER is uncertain, it is more meaningful to state how likely the intervention is to be cost-effective compared with the control, rather than affirming that the intervention is or is not cost-effective. The CEAC offers a means of communicating the inherent uncertainty around the size of the ICER and simultaneously offers health-care decision-makers a foundation to support any decision made.

Second, another limitation of the economic evaluation is that the QoL and cost data describing health status and resource use from hospital discharge to 1 month post randomisation are available only from the returned and completed parental questionnaires. This means that the data cannot be verified and reliability is determined by the parent or carer's recollection of events during the 1-month period after discharge from hospital; however, asking parents to recall events related to their children that took place in the previous 4 weeks is considered to be reasonable. As the aim of treatment with magnesium is to quickly reduce the ASS, there is further confidence in the reliability of the post-discharge data, as there were no statistically significant differences in the majority of QoL and economic outcomes that were explored.

The third limitation relates to the nature and quantity of the QoL data collected from children in the MAGNETIC trial and there are three distinct but related issues to consider. Owing to the design of the MAGNETIC trial, the only clinical outcome that it was possible to measure at screening and randomisation as well as post treatment was the ASS; the EQ-5D was measured uniquely 1 month after treatment. In order to generate before treatment QALY scores for children, the baseline ASS for each patient was translated into a

baseline EQ-5D score by the health economics research team taking advice from asthma experts (doctor and nurses) who routinely treat children with asthma. Clearly, it would have been preferable to have baseline EQ-5D scores for all children but as this was not possible owing to ethical considerations, converting the ASS score in this way was considered to be a valid approach. Next, post-treatment EQ-5D scores were not available for all patients and it was necessary for the research team to map data from completed PedsQL™ Asthma Modules to the EQ-5D scoring system in order to generate QALYs that could be incorporated into the economic evaluation (for those patients with PedsQL™ data but without EQ-5D data). It was also necessary to map data from completed PedsQL™ Asthma Modules to the EQ-5D scoring system for those children of < 5 years whose parents/carers completed the EQ-5D questionnaire while unaware that they were not required to do so.

Finally, the choice of EQ-5D scores used in the sensitivity analysis requires further discussion. The research team considered that it was appropriate to vary the before treatment QALY values used in the base-case analyses in order to check that the translation from ASS to QALY was reasonable and that the CUA results held firm when QALY values were increased or decreased slightly. The range of variation for the baseline EQ-5D scores was dictated by experts (and not directly informed by the experience of children in the trial or elsewhere) but it is anticipated that it reflects the experience of children with slightly higher or lower ASS and therefore offers an analytical check on the appropriateness of the original before treatment utility values used. There is a final general concern there are some aspects of health status relevant to young children that are not captured by either the EQ-5D or the PedsQL™ Asthma Module. However, until both generic and specific QoL instruments are designed to successfully reflect experiences across all stages of childhood, health economists have to rely on the available, but often constrained, measures for the purposes of economic evaluation.

In conclusion, the results of our base-case analyses suggest that from an NHS and Personal Social Services perspective, the addition of magnesium to standard treatment is likely to be cost-effective compared with standard treatment only. The results of both sets of analyses (CEA and CUA) show that the probability of magnesium being cost-effective is over 60% at cost-effectiveness thresholds of £1000 per unit decrement in ASS and £20,000 per QALY gained, respectively, and is highest in the CEA. It is anticipated those data collected on the costs and QoL of children with acute severe asthma as part of the MAGNETIC trial will be used to inform future economic evaluations and other empirical research studies in this area.

Conclusions

This study has had extremely and rigorous management of all aspects of research governance, the recruitment process, data collection, data analysis and examination of the results before unblinding. Despite the possible limitations of the study discussed above, the defence of the limitations and the strength of the study would suggest that the study has good external and internal validity.

Interpretation

There are sufficient data in this study to support the use of nebulised isotonic $MgSO_4$ at the dose of 151 mg given three times in the first hour of treatment as an adjuvant to standard treatment, when a child presents with an acute episode of severe asthma. The response is likely to be more marked in those children with more severe attacks and with a shorter duration of exacerbation. Although the study was not powered to demonstrate this, the data certainly support the hypotheses that nebulised magnesium has a greater clinical effect in children who have more severe exacerbation with shorter duration of symptoms.

Implications for health care

The results of the base-case economic analyses suggest that, from an NHS and Personal Social Services perspective, the addition of magnesium to standard treatment may be cost-effective compared with standard treatment only, though there remains substantial uncertainty around this finding. The results of both sets of analyses (CEA and CUA) show that the probability of magnesium being cost-effective is over

60% at cost-effectiveness thresholds of £1000 per unit decrement in ASS and £20,000 per QALY gained respectively; it is noted that for some parameter variations this probability is much lower, reflecting the impact of variation on the small differences in QALY and costs seen in this trial.

Recommendations for research

Further studies on dose–response at different ages and frequency of administration during an attack are required. The effect on secondary outcomes such as need for intravenous bronchodilators and PICU admissions and length of stay with different nebulised magnesium treatment regimen (dose and frequency) needs further exploration. The concept of different phenotypes and severity where the use of nebulised magnesium can be tailored to the features of the exacerbation needs further exploration.

Currently, three further analyses are planned using these data:

1. exploration of the relationship between ASS and the BTS definition of acute severe asthma
2. assessment of the value of the AUC analysis of ASS
3. examination of the concept of acute phenotypes of asthma in children and the response to treatment.

It may be that these data are sufficient to recommend that nebulised magnesium is added to standard treatment, particularly in those who have a severe attack and those with a short history. Further studies of dose–response pharmacokinetics and frequency of doses, nebuliser use, compatibility studies and animal models to clarify the mechanisms of magnesium use are also to be considered.

Setting trial in context of existing research

The results of this large study are timely. One large study in adults, the 3MG study, is coming to a conclusion[4] and another paediatric study in the USA is currently under way.[69] There are limited trial data in children, with only four published studies[14,18,19,27] (including the pilot study MAGNET[27]). This is the largest study of nebulised $MgSO_4$ in children to date. These data will add further evidence, which may help to improve and strengthen the recommendations of national and international guidelines on the management of acute asthma in childhood.

Chapter 6 Other information

Registration

Identifying numbers:

- HTA 05/503/10
- ISRCTN81456894
- EudraCT no. 2007–006227–12
- MREC 07/H1010/101.

Protocol

The MAGNETIC trial protocol is available from www.hta.ac.uk/project/1615.asp (accessed October 2011).

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Dr Ruwanthi Kolamunnage-Dona (trial statistician) was a member of the TMG, performed the statistical analyses and reviewed a draft of the report.

Dr Angela Boland was a member of the TMG, performed the health economic analyses and reviewed a draft of the report.

Professor Stavros Petrou (Professor of Health Economics, Warwick University) led the health economics team, contributed to the design of the study and reviewed a draft of the report.

Mr John Lowe was the trial co-ordinator, a member of the TMG and he prepared the report for publication.

Dr Iolo Doull (Consultant Respiratory Paediatrician) was a member of the TMG, contributed to the design and conduct of the study, and reviewed a draft of the report.

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References

1. Sennhauser F. The burden of asthma in children. *Paediatr Resp Rev* 2005;**6**:2–7. http://dx.doi.org/10.1016/j.prrv.2004.11.001
2. Department of Health (DoH). URL: www.dh.gov.uk (accessed 12 April 2013).
3. British Thoracic Society (BTS), Scottish Intercollegiate Guidelines Network (SIGN). *British Guideline on the Management of Asthma. A national clinical guideline*. London: BTS; revised May 2011.
4. Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis. *EMJ* 2007;**24**:823–30. http://dx.doi.org/10.1136/emj.2007.052050
5. Goodacre S. The 3Mg Study: a randomised trial of intravenous or nebulised magnesium sulphate versus placebo for acute severe asthma. URL: www.sheffield.ac.uk/scharr/sections/hsr/emergency/3mg (accessed March 2012).
6. Blitz M. Inhaled magnesium sulphate in the treatment of acute asthma (a review). *Cochrane Database Syst Rev* 2005;**3**:CD003898.
7. Blitz M, Blitz S, Hughes R, Diner B, Beasley R, Knopp J, *et al.* Aerosolised magnesium sulphate for acute asthma: a systematic review. *Chest* 2005;**128**:337–44.
8. Cairns CB, Kraft M. Magnesium attenuates the neutrophil respiratory burst in adult asthmatic patients. *Acad Emerg Med* 1996;**3**:1093–7. http://dx.doi.org/10.1111/j.1553-2712.1996.tb03366.x
9. Gourgoulianis KI, Chatziparasidis G, Chatziefthimiou A, Molyvdas PA. Magnesium as a relaxing factor of airway smooth muscles. *J Aerosol Med* 2001;**14**:301–7. http://dx.doi.org/10.1089/089426801316970259
10. Silverman R. Intravenous magnesium sulphate in the treatment of acute severe asthma. A multi-centre randomised controlled trial. *Chest* 2002;**122**:489–97.
11. Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo CA Jr. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. *Cochrane Database Syst Rev* 2000;**2**:CD001490. http://dx.doi.org/10.1002/14651858.CD001490
12. Hill J, Britton J. Dose-response relationship and time-course of the effect of inhaled magnesium sulphate on airflow in normal and asthmatic subjects. *Br J Clin Pharmacol* 1995;**40**:539–44. http://dx.doi.org/10.1111/j.1365-2125.1995.tb05798.x
13. Zanddsteeg AMG, Hirman P, Pamsa HR, Yska JP, ten Brinke A. Effect of $MgSO_4$ on FEV1 in stable severe asthma patients with chronic airflow limitation. *Magnesium Res* 2009;**22**:256–61.
14. Mangat H. Nebulised magnesium sulphate versus nebulised salbutamol in acute bronchial asthma: a clinical trial. *Eur Resp J* 1998;**38**:341–4.
15. Nannini L, Pendino J, Corna R, Mannarino S, Quispe R. Magnesium sulphate as a vehicle for nebulised salbutamol in acute asthma. *Am J Med* 2000;**108**:193–7.
16. Hughes R. The use of isotonic nebulised magnesium as an adjuvant to salbutamol. *Lancet* 2003;**361**:2114–17. http://dx.doi.org/10.1016/S0140-6736(03)13721-X
17. Bessmertny O, DiGregorio R, Cohen H, Becker E, Looney D, Golden J, *et al.* A randomized clinical trial of nebulised magnesium sulphate in addition to albuterol in the treatment of acute mild-to-moderate asthma exacerbations in adults. *Ann Emerg Med* 2002;**39**:585–91.

18. Mahajan P, Haritos D, Rosenberg N, Thomas R. Comparison of nebulised magnesium sulphate plus albuterol plus saline in children with exacerbations of mild to moderate asthma. *J Emerg Med* 2004;**27**:21–5.

19. Meral A. Inhalation therapy with $MgSO_4$. *Turk J Pediatr* 1996;**38**:169–75.

20. Costello J, Howes M. Nebulised magnesium in asthma. *Emerg Med J* 2004;**21**:586–7. http://dx.doi.org/10.1136/emj.2004.017939

21. Kokturk N, Turktas H, Kara P, Mullaoglu S, Yilmaz F, Karamercan A. A randomized clinical trial of magnesium sulphate as a vehicle for nebulized salbutamol in the treatment of moderate to severe asthma attacks. *Pulm Pharmacol Ther* 2005;**18**:416–21. http://dx.doi.org/10.1016/j.pupt.2005.03.003

22. Aggarwal P, Sharad S, Handa R, Dwiwedi SN, Irshad M. Comparison of nebulised magnesium sulphate and salbutamol combined with salbutamol alone in the treatment of acute bronchial asthma: a randomised study. *Emerg Med J* 2006;**23**:358–62. http://dx.doi.org/10.1136/emj.2005.026203

23. Drobina BJ, Kostic MA, Roos JA. Nebulized magnesium has no benefit in the treatment of acute asthma in the emergency department. *Acad Emerg Med* 2006;**13**:S26. http://dx.doi.org/10.1197/j.aem.2006.03.047

24. Dwan K, Gamble C, Kolamunnage-Dona R, Mohammed S, Powell C, Williamson P. Assessing the potential for reporting bias in a review: a tutorial. *Trials* 2010;**11**:52–62. http://dx.doi.org/10.1186/1745-6215-11-52

25. Rolla G, Bucca C, Arossa W, Bugiani M. Magnesium attenuates methacholine-induced bronchoconstriction in asthmatics. *Magnesium* 1987;**6**:201–4.

26. Rolla G, Bucca C, Caria E. Dose-related effect of inhaled magnesium-sulfate on histamine bronchial challenge in asthmatics. *Drugs Exp Clin Res* 1988;**14**:609–12.

27. Ashtekar CS, Powell C, Hood K, Doull I. Magnesium nebuliser trial (MAGNET): a randomised double-blind placebo controlled pilot study in severe acute asthma. *Arch Dis Child* 2008;**93**:A100–6.

28. Conway S. Admission to hospital with asthma. *Arch Dis Child* 1985;**60**:636–9. http://dx.doi.org/10.1136/adc.60.7.636

29. Bishop J, Carlin J, Nolan T. Evaluation of the properties and reliability of the clinical severity scale for acute asthma in children. *J Clin Epidemiol* 1992;**45**:71–6. http://dx.doi.org/10.1016/0895-4356(92)90190-X

30. Yung M, South M, Byrt T. Evaluation of an asthma severity score. *JPCH* 1996;**32**:261–4. http://dx.doi.org/10.1111/j.1440-1754.1996.tb01567.x

31. Fischl, MA, Pitchenik A, Gardner LB. An index predicting relapse and need for hospitalization in patients with acute bronchial asthma. *N Engl J Med* 1981;**305**:783–9. http://dx.doi.org/10.1056/NEJM198110013051402

32. Powell C, Dwan K, Milan SJ, Beasley R, Hughes R, Knopp-Sihota JA, *et al.* Inhaled magnesium sulfate in the treatment of acute asthma. *Cochrane Database Syst Rev* 2012;**12**:CD003898. http://dx.doi.org/10.1002/14651858.CD003898.pub5

33. Abreu-Gonzalez J, Rodríguez-Díaz CY. Magnesium and bronchodilator effect of beta-adrenergic. *Am J Resp Crit Care Med* 2002;**165**:A185.

34. Gaur SN, Singh A, Kumar R. Evaluating role of inhaled magnesium sulphate as an adjunct to salbutamol and ipratropium in severe acute asthma. *Chest* 2008;**134**:91003s.

35. Gallegos-Solórzano MC, Pérez-Padilla R, Hernández-Zenteno RJ. Usefulness of inhaled magnesium sulfate in the co-adjuvant management of severe asthma crisis in an emergency department. *Pulm Pharmacol Ther* 2010;**23**:432–7.

36. Neki NS. A comparative clinical efficacy and safety profile of inhaled magnesium sulphate and salbutamol nebulisations in severe asthma. *Indian J Allergy Asthma Immunol* 2006;**20**:131.

37. Khashabi J, Asadolahi S, Karamiyar M, Salari Lak S. Comparison of magnesium sulfate to normal saline as a vehicle for nebulized salbutamol in children with acute asthma: a clinical trial. *European Respiratory Society Annual Congress*, 2008, Berlin, abstract no. 4597.

38. Dadhich P, Tailor M, Gupta ML, Gupta R. Magnesium sulphate nebulisation in acute severe asthma. *Indian J Allergy Asthma Immunol* 2005;**19**:117.

39. Rafai Z. *Systematic review of outcomes in acute asthma in childhood*. MSc Thesis. Cardiff: Cardiff University; 2012.

40. Gorelick MH, Stevens MW, Schultz T, Scribano PV. Difficulty in obtaining peak expiratory flow measurements in children with acute asthma. *Pediatr Emerg Care* 2004;**20**:22–6. http://dx.doi.org/10.1097/01.pec.0000106239.72265.16

41. Van der Mindt DA, Nagelkerke AF, Bouter LM, Dankert-Roelse JE, Veerman JP. Clinical scores for acute asthma in preschool children: a review of the literature. *Epidemiology* 1994;**47**:635–46.

42. Birken CS, Parkin PC, Macarthur C. Asthma severity scores for preschoolers displayed weaknesses in reliability, validity and responsiveness. *J Clin Epidemiol* 2004;**57**:1177–81. http://dx.doi.org/10.1016/j.jclinepi.2004.02.016

43. Kelly AM, Kerr D, Powell C. Is severity assessment after one hour of treatment better for predicting the need for admission in acute asthma? *Respir Med* 2004;**98**:777–81. http://dx.doi.org/10.1016/j.rmed.2004.01.008

44. Elashoff JD. *nQuery Advisor Version 4.0 User's Guide*. Los Angeles, CA: Statistical Solutions; 2000. URL: http://statistical-solutions-software.com/wp-content/uploads/nQ70_version2_manual.pdf (accessed 12 April 2013).

45. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part I: Introduction and design. *Br J Cancer* 1976;**34**:585–612. http://dx.doi.org/10.1038/bjc.1976.220

46. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal. *Sections 5.4.1 to 5.4.4*. 2008. URL: www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf (accessed 12 April 2013).

47. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes*. 3rd edn. Oxford: Oxford University Press; 2005.

48. Curtis L. *Unit costs of health and social care 2009*. Canterbury: PSSRU, University of Kent; 2009. URL: www.pssru.ac.uk/uc/uc2009contents.htm (accessed 12 April 2013).

49. Department of Health (DoH). *NHS reference costs 2009-2010*. London: DoH; 2011. URL: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591 (accessed 12 April 2013).

50. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary*. No. 60, September 2010. London: BMA and RPS; 2010. URL: www.bnf.org/bnf/ (accessed 12 April 2013).

51. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. *The University of York, Centre for Health Economics discussion paper 172. 1999*. Centre for Health Economics, University of York; 1999. URL: www.euroqol.org/eq-5d/what-is-eq-5d.html (accessed 12 April 2013).

52. Dolan P, Gudex C, Kind P, Williams A. 1995. *A social tariff for EuroQol: Results from a UK general population survey*. York: Centre for Health Economics, University of York; pp. 1–19.

53. Petrou S. Methodological issues raised by preference-based approaches to measuring the health status of children. *Health Econ* 2003;**12**:697–702. http://dx.doi.org/10.1002/hec.775

54. Brazier JE, Yang Y, Tsuchiya A, Rowen DL. A review of studies mapping (or cross walking) non-preference based measures of health to generic preference-based measures. *Eur J Health Econ* 2010;**11**:215–25. http://dx.doi.org/10.1007/s10198-009-0168-z

55. Longworth L, Rowen D. The use of mapping methods to estimate health state utility values. *NICE DSU technical support document 10*. Sheffield: Decision Support Unit, ScHARR, University of Sheffield; 2011.

56. Briggs A, Clark T, Wolstenholme J, Clarke P. Missing … presumed at random: cost-analysis of incomplete data. *Health Econ* 2003;**12**:377–92. http://dx.doi.org/10.1002/hec.766

57. Briggs AH, Gray AM. Handling uncertainty when performing economic evaluation of healthcare interventions. *Health Technol Assess* 1999;**3**(2).

58. Stinnett AA, Mullahy J. Net health benefits: A new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998;**18**:S65–80. http://dx.doi.org/10.1177/0272989X9801800209

59. Turner D, Broadley K, Ford, Kidd E, Powell C. *Nebulised magnesium sulphate bronchodilator and bronchoprotective?* London: British Pharmacological Society Proceedings; 2011. p. 26.

60. Szefler SJ, Zeiger RS, Haselkorn T, Mink DR, Kamath TV, Fish JE, *et al.* Economic burden of impairment in children with severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol* 2011;**107**:110–19. http://dx.doi.org/10.1016/j.anai.2011.04.008

61. Eiser C, Morse R. Quality-of-life measures in chronic diseases of childhood. *Health Technol Assess* 2001;**5**(4).

62. Babl FE, Sherrif N, Borland M, Acworth J, Neutze J, Krieser D, *et al.* Paediatric acute asthma management in Australia and New Zealand: practice patterns in the context of clinical practice guidelines. *Arch Disease Child* 2008;**93**:307–12. http://dx.doi.org/10.1136/adc.2007.125062

63. Yung M, South M. Randomised controlled trial of aminophylline for severe acute asthma. *Arch Dis Child* 1998;**79**:405–10. http://dx.doi.org/10.1136/adc.79.5.405

64. Davies G, Paton J, Beaton S, Young D, Lenney W. Children admitted with acute wheeze/asthma during. November 1998–2005: a national UK audit. *Arch Dis Child* 2008;**93**:952–8. http://dx.doi.org/10.1136/adc.2007.133868

65. Rodrigo G, Rodrigo C. Rapid onset asthma attack: a prospective cohort study about characteristics and response to emergency department treatment. *Chest* 2000;**118**:1547–52. http://dx.doi.org/10.1378/chest.118.6.1547

66. Woodruff P, Edmond S, Singh A, Carmargo C. Sudden onset severe acute asthma: clinical features and response to therapy. *Acad Emerg Med* 1998;**5**:695–701. http://dx.doi.org/10.1111/j.1553-2712.1998.tb02488.x

67. Barr R, Woodruff P, Clark S, Camargo C. Sudden onset asthma exacerbations: clinical features, response to therapy and 2-week follow up. *Eur Resp J* 2000;**15**:266–73. http://dx.doi.org/10.1034/j.1399-3003.2000.15b08.x

68. Martin A, Campbell D, Gluyas P, Coates J, Ruffin R, Roder D, *et al.* Characteristics of near fatal asthma in childhood. *Pediatr Pulmonol* 1995;**20**:1–8. http://dx.doi.org/10.1002/ppul.1950200102

69. Coates AL, Leung K, Vecellio L, Schuh S. Testing of nebulizers for delivering magnesium sulfate to pediatric asthma patients in the emergency department. *Respir Care* 2011;**56**:314–18. http://dx.doi.org/10.4187/respcare.00826

70. DiGregorio RV, Bessmertny O, Pringle G, Cohen H. Effect of nebulized magnesium sulfate on serum magnesium levels in asthmatic patients. *ASHP Midyear Clinical Meeting 1999*, vol. **34**:[P–383E].

71. Coates JE. *Lung function: assessment and application to medicine*. 5th edn Oxford: Blackwell Scientific Publication; 1993.

72. Sur S, Cotty T, Kephart G, Hyma B, Colby T, Reed C, *et al.* Sudden onset asthma. A distinct entity with few eosinophils and more neutrophils in the airway mucosa. *Am Rev Resp Dis* 1993;**148**: 713–19.

73. Wang F, He X, Baines K, Gunawardhana L, Simpson J, Li F, *et al.* Different inflammatory phenotypes in adults and children with acute asthma. *Eur Resp J* 2011;**38**:567–74. http://dx.doi.org/10.1183/09031936.00170110

74. Simpson J, McElduff P, Gobson P. Assessment and reproducibility of non-eosinophilic asthma using induced sputum. *Respiration* 2010;**79**:147–51. http://dx.doi.org/10.1159/000245899

75. Davis WJ, Pang LM, Chernack WJ, Mellins RB. Terbutaline in the treatment of acute asthma in childhood. *Chest* 1977;**72**:614–17. http://dx.doi.org/10.1378/chest.72.5.614

76. Friede T, Keisser M. Sample size recalculation for binary data in internal pilot study designs: a review. *Biometrical J* 2006;**48**:537–55.

77. European Medicines Agency (EMA) (The European Agency for the Evaluation of Medical Products). *Points to consider on adjustments for baseline covariates*. 2003. URL: www.emea.europa.eu/pdfs/human/ewp/286399en.pdf (accessed 12 April 2013).

78. Pham B, Cranney A, Boers M, Verhoeven AC, Wells G, Tugwell P. Validity of area-under-the-curve analysis to summarize effect in rheumatoid arthritis clinical trials. *J Rheumatol* 1999;**27**:712–16.

79. Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *BMJ* 1990;**300**:230–5. http://dx.doi.org/10.1136/bmj.300.6719.230

80. Efron B, Tibshirani R. *An introduction to the bootstrap*. New York, NY: Chapman and Hall; 1993.

81. Wood AM, White IR, Thompson SG. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. *Clin Trials J* 2004;**1**:368–76. http://dx.doi.org/10.1191/1740774504cn032oa

82. van Buuren S, Oudshoorn K. Flexible multiple imputation by MICE. *Technical report PG/VGZ/99.054*. Leiden: TNO Prevention and Health; 1999. URL: www.multiple-imputation.com/ (accessed 12 April 2013).

83. Unnebrink K, Windeler J. Sensitivity analysis by worst and best case assessment: is it really sensitive? *Drug Inf J* 1999;**33**:835–9. http://dx.doi.org/10.1177/009286159903300324

84. Wood AM, White IR, Hillsdon M, Carpenter J. Comparison of imputation and modelling methods in the analysis of a physical activity trial with missing outcomes. *Int J Epidemiol* 2005;**34**:89–99. http://dx.doi.org/10.1093/ije/dyh297

85. Henderson R, Diggle P, Dobson A. Joint modelling of longitudinal measurements and event time data. *Biostatistics* 2000;**1**:465–80. http://dx.doi.org/10.1093/biostatistics/1.4.465

86. Clarke M, Hopewell S, Chalmers I. Reports of clinical trials should begin and end with up-to-date systematic reviews of other relevant evidence: a status report. *J R Soc Med* 2007;**100**:187–90. http://dx.doi.org/10.1258/jrsm.100.4.187

Appendix 1 Summary of the features of the 16 published randomised controlled trials on nebulised magnesium up to 2012

TABLE 37 Summary of severity, definitions used and age of population examined

Study	Severity	Based on	Adult/mixed/paediatric (years)
Abreu-Gonzalez 2002[33]	Moderate	FEV_1 and PEFR at baseline	Adults (?)
Aggarwal 2006[22]	Severe and life-threatening	BTS definition clinical features and PEFR	Mixed (13–60)
Ashtekar 2008[27]	Severe	BTS definition clinical features	Paediatric (2–16)
Bessmertny 2002[17]	Moderate to severe	PEFR between 40% and 80%	Adults (18–65)
Dadhich 2005[38]	Severe	PEFR < 50%	Adults (?)
Drobina 2006[23]	Unclear	Used PEFR and clinical signs	Adults (?)
Gallegos-Solórzano 2010[35]	Moderate to severe	FEV_1 < 60%	Adults > 18
Gaur 2008[34]	Severe	FEV_1 < 30%	Adults (18–60)
Hughes 2003[16]	Severe	FEV_1 < 50%	Adults (16–65)
Khashabi 2008[37]	Unclear	Clinically defined as respiratory distress	Paediatric (mean age 3.55 years)
Kokturk 2005[21]	Moderate to severe	Clinical scores and PEFR	Adults (18–60)
Mahajan 2004[18]	Moderate to severe	FEV_1 between 45% and 75%	Paediatric (5–17)
Mangat 1998[14]	Moderate to severe	PEFR < 300 l/minute	Mixed (12–60)
Meral 1996[19]	Moderate to severe	PEFR < 75%	Paediatric (? age)
Nannini 2000[15]	Severe	PEFR < 50%	Adult (> 18)
Neki 2006[36]	Severe	FEV_1 < 40% or PEFR < 300 l/minute	Adult (15–60)

?, age limits not recorded.

TABLE 38 Summary of characteristics of the studies, where patients were recruited from, additional treatment, exclusion criteria and side effects

Study	Presentation to which department?	Origin	Primary outcome(s)	Side effects (patients in study)	Pharmaceutical exclusions	Other interventions
Abreu-Gonzalez 2002[33]	Not clear	Tenerife, Spain	FEV_1 and PEFR	None documented (24)	None documented	None documented
Aggarwal 2006[22]	ED	New Delhi, India	PEFR	Palpitations (salbutamol/Mg 13, and salbutamol/placebo 11) and tremors (7 and 7). Nothing else noted (100)	None documented	Clinicians free to administer steroids, more salbutamol if needed – intravenous hydrocortisone
Ashtekar 2008[27]	CAU after GP referral	Cardiff, Wales	ASS (Yung 1996)	One given magnesium had tingling in fingers and another one TSLH with facial flushing (17)	None documented	2 mg/kg prednisolone
Bessmertny 2002[17]	ED	Brooklyn, USA	FEV_1 (% predicted)	No SAEs noted (74)	No theophylline or anticholinergic drugs 2 hours prior to presentation	2 mg/kg hydrocortisone 6 hourly
Dadhich 2005[38]	ED	Ajmer, India	PEFR	*'Side effects were self limiting'* (71)	Not stated	Not stated
Drobina 2006[23]	ED	USA	PEFR and admissions	No comment (110)	Not stated	50 mg oral prednisolone
Gallegos-Solórzano 2010[35]	ED	Mexico City, Mexico	Percentage change FEV_1, O_2 post treatment and admission rates	dry and bitter mouth in magnesium group (1) and dizziness (one in each) (60)	Use of steroids prior to presentation	1 mg/kg/day for 10 days' prednisolone
Gaur 2008[34]	ED	Delhi, India	FEV_1	None documented (60)	None stated	Intravenous hydrocortisone
Hughes 2003[16]	ED	Wellington, New Zealand	FEV_1	None reported (52)	None	100 mg hydrocortisone
Khashabi 2008[37]	Unclear	Urmia, Iran	Mean duration of O_2 therapy and respiratory distress score (? which one)	There were no side effects (40)	Not stated	Not stated

Study	Presentation to which department?	Origin	Primary outcome(s)	Side effects (patients in study)	Pharmaceutical exclusions	Other interventions
Kokturk 2005[21]	ED	Gazi University, Ankara, Turkey	PEFR difference	TSLH in magnesium group (2) and palpitation (1) in salbutamol only group. No other side effect reported (26)	None mentioned	1 mg/kg prednisolone to all but additional theophylline, anticholinergic drugs and salbutamol given at clinician's discretion
Mahajan 2004[18]	ED	Detroit, USA	Percentage change in FEV_1	No side effects occurred (62)	Having received steroids, ipratropium or theophylline in the last 3 days	2 mg/kg prednisolone
Mangat 1998[14]	ED	St John's College, Agra, India	PEFR, Fischl index score and admissions	TSLH (1), palpitation (1), tremors (2), all in control group and only one TSLH *n* in magnesium group (33)	Oral parenteral bronchodilators (6 hours) steroids (last 12 hours)	100 mg intravenous hydrocortisone
Meral 1996[19]	Not clear	Izmir, Turkey	Percentage change in PEFR ASS (Davis–Leffert–Dabbous score)[75]	No side effects noted (blood pressure and heart rate monitored) (40)	No medication taken in the previous 12 hours (β_2-agonists and theophylline)	No other medication given
Nannini Jr 2000[15]	ED	Four hospitals in Argentina	PEFR and admissions	None observed (35)	Oral or parenteral steroids in the last 7 days	None stated
Neki 2006[36]	Not clear	Amritsar, Punjab, India	PEFR, RR and Fischl index	Not commented on (40)	Oral, inhaled or parenteral bronchodilators in past 6 hours and steroids in last 12 hours	All given 100 mg intravenous hydrocortisone

TSLH, transient self-limiting hypotension.

TABLE 39 Summary of interventions and controls

Study	Magnesium dose	Mixed with	Control comparison	Mixed with
Abreu-Gonzalez 2002,[33] 24 patients	2 ml $MgSO_4$ (isotonic), 13 patients	400 µg salbutamol (? once)	2 ml of a physiological serum of an inhaled form, 11 patients	400 µg salbutamol
Aggarwal 2006,[22] 100 patients	1 ml of 500 mg/ml $MgSO_4$, AS – 29, ALT – 21	1 ml salbutamol (? dose) 8 ml distilled water (295 mOsm/kg) × 3 in 1 hour (ultrasonic nebuliser)	7.5 ml normal saline, AS – 30, ALT – 20	1 ml salbutamol (? dose) 1.5 ml distilled water (287 mOsm/kg) × 3 in 1 hour
Ashtekar 2008,[27] 17 patients	2.5 ml isotonic $MgSO_4$ sulphate (151 mg/dose), seven patients	500 µg ipratropium bromide 2.5 mg salbutamol or 5 mg salbutamol (2–5 and > 5 years) Three times in 1 hour	2.5 ml of isotonic saline, 10 patients	500 µg ipratropium bromide 2.5 mg salbutamol or 5 mg salbutamol (2–5 and > 5 years) Three times in 1 hour
Bessmertny 2002,[17] 74 patients	$MgSO_4$ (384 mg), 34 patients (three withdrawn)	Followed by (i.e. not mixed) salbutamol 2.5 mg/ml Three times in 1 hour	Normal saline (no volume documented), 34 patients (three withdrawn)	Followed by (i.e. not mixed) salbutamol 2.5 mg/ml Three times in 1 hour
Dadhich 2005,[38] 71 patients	Gp A $n = 24$ salbutamol Gp B $n = 26$ salbutamol and magnesium Gp C $n = 21$ magnesium alone	No doses in any group		
Drobina 2006,[23] 110 patients	150 mg $MgSO_4$ (0.3 ml of 50% $MgSO_4$ heptahydrate), 60 patients (from Mohammed and Goodacre[4])	Salbutamol sulphate (0.5%) 5 mg/ml and 0.5 mg ipratropium bromide (0.02% inhalation solution) Unclear how frequent	No placebo so volume will be less, i.e. blinding may be an issue, 50 patients (from Goodacre)	Salbutamol sulphate (0.5%) 5 mg/ml) and 0.5 mg ipratropium bromide (0.02% inhalation solution)
Gallegos-Solórzano 2010,[35] 112 patients (60 completed)	3 ml (333 mg) of 10% isotonic $MgSO_4$ (1g/10 ml), 60 randomised, 30 completed	2.5 mg salbutamol and 500 µg ipratropium Three doses in 1 hour	3 ml of isotonic saline, 52 randomised, 30 completed	2.5 mg salbutamol and 500 µg ipratropium Three doses in 1 hour

Study	Magnesium dose	Mixed with	Control comparison	Mixed with
Gaur 2008,[34] 60 patients	3 ml (3.2 g%), 30 patients isotonic $MgSO_4$, 30 patients	Salbutamol and ipratropium (no doses cited) No comment about frequency	Saline as placebo, 30 patients	Salbutamol and ipratropium (no doses cited) No comment about frequency
Hughes 2003,[16] 52 patients	2.5 ml isotonic $MgSO_4$ (250 mmol/l 151 mg), 28 patients	2.5 mg salbutamol, patients unable to distinguish solutions Three times every 30 minutes	2.5 ml normal saline, 24 patients	2.5 mg salbutamol Three times every 30 minutes
Khashabi 2008,[37] 40 patients	Isotonic $MgSO_4$, (? dose), unclear how many	Salbutamol (? dose) Possible two doses	2.5 ml normal saline, unclear how many	Salbutamol (? dose) Possibly two doses
Kokturk 2005,[21] 26 patients	Isotonic $MgSO_4$ (2.5 ml), 14 patients	Salbutamol (? dose) Three doses in 1 hour then hourly for the rest of the 4 hours)	2.5 ml normal saline, 12 patients	Salbutamol (? dose) Three doses in 1 hour then hourly for the rest of the 4 hours
Mahajan 2004,[18] 62 patients	2.5 ml isotonic (6.3%) $MgSO_4$ solution, 31 patients	Salbutamol 2.5mg, one dose only	2.5 ml normal saline, 31 patients	Salbutamol 2.5 mg, one dose only
Mangat 1998,[14] 33 patients	3.2% solution $MgSO_4$ = 95 mg, 16 patients	Four doses every 20 minutes	3 ml (2.5 mg) salbutamol, 17 patients	Four doses every 20 minutes
Meral 1996,[19] 40 patients	2 ml $MgSO_4$ (280 mmol/l 258 mOsm, pH 6.7), 20 patients	? one dose given over 10–15 minutes	Salbutamol 2.5 mg in 2.5 ml, 20 patients	? one dose given over 10–15 minutes
Nannini Jr 2000,[15] 35 patients	3 ml isotonic $MgSO_4$ (286 mOsm, 7.5%, 225 mg), 19 patients	0.5 ml 2.5 mg salbutamol, ? one dose given only	3 ml normal saline, 16 patients	0.5 ml 2.5 mg salbutamol, ? one dose given only
Neki 2006,[36] 40 patients	20 patients, 3.2 g% $MgSO_4$, 20 patients	Four doses, 20 minutes apart	3 ml of ?25 mg salbutamol, 20 patients	Four doses 20 minutes apart
Total: 896 randomised but 33 interventions and 25 control subjects withdrawn after randomisation, so *total completed studies* = 838	452 + the Drobina study[23] presumed 20 = 472, minus the 33 withdrawals = 439 completed intervention studies		404 + the Drobina study[23] presumed 20 = 424 minus the 25 control subjects withdrawn = 399 completed the control studies	

ALT, acute life-threatening; AS, acute severe; ?, unclear how frequent doses were given.

Appendix 2 Summary of methods of resource-use valuation

From randomisation to discharge	
Intervention	Only the unit costs of magnesium, salbutamol and ipratropium were estimated. No consumable costs were included in total cost estimates. Cost source: BNF 60[50] Not all patients received the full dose of the intervention/placebo. Full data were available from the CRF to ensure that all doses were costed appropriately. Dosages were estimated in accordance with age of the child
A&E department visit	All children incurred the cost of an A&E department visit. The cost estimate used in the analysis depended on whether or not the child was admitted to hospital as a result of attendance Cost source: PSSRU 2010[48] • Visit leading to admitted (£131) • Visit *not* leading to admitted (£97) In the sensitivity analysis, NHS reference costs 2009–10[49] were used: • Visit leading to admitted (£97) (VB09Z; category 1 investigation with category 1–2 treatment) • Visit *not* leading to admitted (£90) (VB09Z; category 1 investigation with category 1–2 treatment)
Hospital stay	Hospital stays were divided into two categories: per diem general medical ward and per diem HDU/PICU The per diem general medical ward cost (£368) was taken from the NHS reference costs 2009–10[49] (DZF15F-Asthma without complications without intubation). This closely matched a general ward per diem estimate of £348, provided by the Finance/Accounts Department of Alder Hey Hospital, Liverpool As the difference between HDU and PICU costs was large, a weighted average of the two costs was estimated Cost source: NHS reference costs 2009–10[49] (Critical Care Paediatric Bed-days) HDU cost: XB07Z (£868) PICU cost: XB05Z (£2225) Weighted average: (£1471.96) In the base case, total general medical ward stay and total HDU/PICU stay were estimated in terms of hours and minutes. If a child had spent more than 12 hours in a ward, a full per diem cost was applied. If a child had spent < 12 hours in a ward, a half day cost was applied. Full days incurred the full per diem cost The duration, and therefore cost, of inpatient stay is a key driver in the economic evaluation and required careful consideration in the sensitivity analysis where various approaches were used to test the robustness of the economic evaluation results to changes in the cost of hospital inpatient admission In the sensitivity analysis, a cost of £392 was used (NHS reference costs 2009–10,[49] DZ15E-Asthma with complications without intubation) to estimate the cost of a per diem general medical ward stay; the weighted average cost was replaced by the HDU cost (low estimate) and the PICU cost (high estimate); hours and minutes of inpatient stays on either/both wards were costed exactly, i.e. taking account of fractions of time and, finally, all inpatient stays of < 12 hours were not costed in the analysis
AEs	The cost of concomitant medications used to treat AEs were estimated using Prescription Costs Analysis data (2010).[49] The costs of additional days in hospital as a result of an AE were included in the hospital stay costs up until discharge

From randomisation to discharge	
From discharge to 4 weeks post randomisation	
Medication costs	All medication costs were estimated using the net ingredient cost per prescription stated in the Prescription Cost Analysis (2010) data.[49] For all medications, the total for chemical entity value was used
Inhaler costs	All inhaler-related costs were estimated using the net ingredient cost per prescription stated in the Prescription Cost Analysis (2010) data.[49] For all items, the total for chemical entity value was used
Overnight hospital stay	All overnight stay costs were estimated using per diem general medical ward cost (£368) from the NHS reference costs 2009–10[49] (DZF15F-Asthma without complications without intubation). This closely matched a general ward per diem estimate of £348 provided by the Finance/Accounts Department of Alder Hey Hospital, Liverpool
Outpatient attendance	All costs were taken from PSSRU Unit Costs of Health Care 2010[48] Outpatient attendance costs were divided into three separate cost categories: • A&E department attendance (not leading to admission) (£97) • Consultant-led outpatient attendance (£163.71) • Non-consultant-led outpatient attendance (£134)
Non-hospital costs	A variety of sources were used to estimate non-hospital costs The following costs were taken from the Unit Costs of Health Care (PSSRU 2010):[48] • GP surgery visit (£36) • GP telephone call (£22) • GP out of hours visit/GP home visit (£120) • Practice nurse surgery visit (£12) • Community nurse/practice nurse telephone call* (£7.32) • Community nurse home visit (£27) • Health visitor home visit (£42) • Health visitor telephone call** (£7.56) *Cost of telephone call was estimated using the GP surgery to telephone call cost ratio (0.61) using practice nurse surgery visit cost ** Cost of telephone call was estimated using the GP home visit to telephone call cost ratio (0.18) using health visitor home visit cost The following costs were taken from NHS Reference Costs 2009–2010:[49] • Out of hours walk-in appointment (£38) (VB11Z, no investigation with no significant treatment) In the sensitivity analysis, the NHS reference cost (2009–10)[49] out of hours walk-in appointment cost of £45 was used (VB09Z, category 1 investigation with one to two significant treatments)
Non-NHS costs	
Travel	As recorded by the respondent. Travel costs included car parking fees, petrol/fuel costs, public transport fares, taxi fares and 'other' costs Travel costs were only estimated in relation to the time period from the child's initial hospital visit up until discharge Estimates were presented for parent/carer of the child, partner of parent/carer of the child and relatives/friend of the child
Expenses	As recorded by the respondent. Expenses costs were only estimated in relation to the time period from initial hospital visit to discharge Expenses were those costs resulting from lost earnings, child care costs, hospital expenses (e.g. snacks/gifts) and 'other' costs Estimates were presented for parent/carer of the child, partner of parent/carer of the child and relatives/friends of the child

From randomisation to discharge	
Extras	As recorded by the respondent. Extras were only estimated in relation to the time period from discharge to 4 weeks post randomisation Extras were those costs resulting from visits to the family doctor or hospital, and included travel costs, lost earnings due to taking time off work, child care costs and 'other' expenses. Expenses also included a specific 'other' cost category, for example, help with housework, telephone bills, special equipment for child or 'other' expenses Estimates were presented for parent/carer of the child, partner of parent/carer of the child and relatives/friends of the child
Over-the-counter medicines	As recorded by the respondent. In a few cases only the names of the medicines were stated. If this medicine had already been mentioned by other respondents then an average cost was used. If the medicine had not already been mentioned by other respondents, then costs were taken from Boots (www.boots.com) or Chemist Direct (www.chemistdirect.co.uk). All internet costs were accessed in 2012

A&E, accident and emergency.

Appendix 3 Statistical analysis plan

Introduction

The SAP provides a detailed and comprehensive description of the main, preplanned analyses for the study 'MAGnesium NEbuliser Trial In Children (MAGNETIC) – A randomised, placebo-controlled study of nebulised magnesium in acute severe asthma in children'. This study is 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.

These planned analyses will be performed by the trial statistician. The analysis results will be described in a statistical analysis report, to be used as the basis of the primary research publications according to the study publication plan.

All analyses are performed with standard statistical software (R or SAS). More specialised software in R will be used in the joint analysis of longitudinal and time to event data. The final analysis data sets, programs and outputs are archived following good clinical practice guidelines (ICHE9). The testing and validation of the statistical analysis programs will be performed following the relevant standard operation procedure.

Design

Study design

This is a multicentre, randomised, placebo-controlled study involving 20–25 sites throughout the UK that plans to recruit 500 children, 250 into each of the study arms. All patients recruited into the study will have standard treatment as per BTS guidelines plus either nebulised $MgSO_4$ (2.5 ml of isotonic nebulised $MgSO_4$) or placebo (2.5 ml of isotonic nebulised saline). Each site randomises patients to one of two treatment arms in a 1 : 1 ratio.

Study objectives

The main objective is to compare the ASS at 1 hour of children with acute severe asthma given nebulised $MgSO_4$ when used as an adjunct to nebulised salbutamol and ipratropium bromide to those given nebulised salbutamol, ipratropium bromide and placebo. The proportion of patients who required a 'stepping up' of medication at 1 hour, progression to intravenous treatment, intubation and/or admittance to HDU/PICU will be compared between the two groups.

Secondary objectives are:

Does nebulised $MgSO_4$ used as an adjunct to nebulised salbutamol and ipratropium bromide for 1 hour in children with acute severe asthma, when compared with nebulised salbutamol, ipratropium bromide and placebo, have an effect on:

(a) clinical outcomes in terms of additional treatment/management while in hospital
(b) length of stay in hospital
(c) patient outcomes in terms of quality of life, time off school and health-care resource usage over the following month
(d) parent outcomes in terms of time off work over the following month
(e) overall cost to the NHS and society.

Primary and secondary outcomes

Primary outcome

Asthma Severity Score after 60 minutes of treatment.

Secondary outcomes

Clinical (during hospitalisation):

- 'stepping down' of treatment at 1 hour, i.e. changed to having hourly treatment after the initial three 20-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 PICU.

Patient outcomes at follow-up (1 month):

- paediatric quality of life (PedsQL™) asthma module parental report for all children and self-completion if aged > 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).

Inclusion/exclusion criteria

Inclusion criteria

Severe acute asthma as defined by the BTS/SIGN guidelines.[3]

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

(a) oxygen saturations of < 92% while breathing room air
(b) too breathless to talk
(c) heart rate greater than 120 b.p.m.
(d) respiratory rate of > 30 breaths per minute
(e) use of accessory neck muscles.

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

(a) oxygen saturations of < 92% while breathing room air
(b) too breathless to talk
(c) heart rate greater than 130 b.p.m.
(d) respiratory rate > 50 breaths per minute
(e) use of accessory neck muscles.

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 3 months preceding screening.

Sample size

In order to detect a difference between the two groups at 60 minutes post treatment of 0.5 points on the ASS at a 5% significance level with 80% power, 500 children are required. This assumes an SD of 1.95, based on a similar population in Australia.[30] The SD was estimated from the Cardiff pilot study[27] (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.

Recruitment

The date the first patient recruited was 3 January 2009. Expected date of end of recruitment and expected date of end of follow-up will be 31 October 2010 and 31 December 2010, respectively. There are 30 sites recruiting patients into the trial and the proposed recruitment targets are given in *Table 1*.

Description of study population

Representativeness of study sample and patient throughput

Details of patients assessed for eligibility, those who meet the study inclusion criteria, those who are eligible and randomised, those who are eligible but not randomised (with reasons as far as possible), those who withdraw from the study after randomisation (with reasons as far as possible) and those who are lost to follow-up (with reasons as far as possible) will be summarised in a CONSORT flow diagram. Eligible patients who are randomised will be described with respect to demographic details and history (gender, age at randomisation, age at asthma onset, current asthma medication, allergy history, previous admission for asthma, duration of the most recent asthma attack, treatment/nebulisers received pre-admission and ASS, SaO_2, blood pressure, respiratory rate, oxygen therapy at baseline). The number of ineligible patients randomised will be reported.

Baseline comparability of randomised groups

Patients in each treatment group (magnesium and placebo) will be described separately with respect to gender, age at randomisation, age at asthma onset, current asthma medication, allergy history, previous admission for asthma, duration of the most recent asthma attack, treatment/nebulisers/steroids received pre-admission and ASS, SaO_2, blood pressure, respiratory rate, oxygen therapy at baseline. Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted.

Follow-up assessments and losses to follow-up

The number (and percentage) of patients with scheduled follow-up assessments at 20, 40, 60, 120, 180 and 240 minutes post randomisation will be reported by treatment group. The number lost to follow-up within each treatment group will be reported and reasons where known will be documented in the CONSORT flow diagram. Any deaths and their causes will be reported. Any unblinded events will be reported. The rate of patient and parent outcome questionnaires return at one month will be reported by treatment group.

Description of compliance with therapy

In this study, treatment should be directly observed. Deviations from intended treatment (e.g. withdrawals from randomised treatment) will be summarised for each treatment group. The distribution of timing of treatment administration will be summarised by treatment groups.

TABLE 1 Planned recruitment targets at each centre

Recruiting centre	Minimum target accrual per centre
Royal Devon and Exeter Hospital	20
Leicester Royal Infirmary	20
Royal Albert Edward Infirmary, Wigan	20
St Thomas' Hospital	20
Whiston Hospital	10
Blackpool Victoria Hospital	20
Countess of Chester Hospital	10
Birmingham Heartlands Hospital	20
Bristol Royal Hospital for Children	20
Birmingham Children's Hospital	20
Royal London Hospital	20
Royal Preston Hospital	20
Derbyshire Children's Hospital	20
Wythenshawe Hospital	20
Queens Hospital, Burton on Trent	20
Ormskirk District General Hospital	10
Queens Medical Centre, Nottingham	20
Leighton Hospital	10
Sheffield Children's Hospital	20
Macclesfield District General Hospital	10
Singleton Hospital, Swansea	10
Royal Aberdeen Children's Hospital	20
Royal Hospital for Sick Children, Glasgow	20
Fairfield General Hospital	20
Tameside General Hospital	10
Craigavon Area Hospital	10
North Staffordshire	20
University Hospital of Wales	20
Altnagelvin Area Hospital	10
Antrim Area Hospital	10

Trial monitoring

Internal pilot

The SD that was used for the original sample size calculation will be checked after approximately 30 patients have been randomised.

The only outcome data that will be analysed within the interim analyses will be the primary outcome of the study which is defined in the protocol as the ASS after 60 minutes of treatment.

This blinded internal pilot will not have any significant impact on the final analysis.[76]

Interim analysis plan

In order to estimate the effect of nebulised $MgSO_4$ 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% CIs calculated for the effect estimate. 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.

If the trial is stopped early then the analysis will contain all the patients that have been randomised up until that point. The procedures that are described in the statistical quality assurance standard operating procedure will all be implemented before and after the interim analyses.

Unblinding of randomisation treatments

The number of patients who were unblinded will be reported for each treatment group and the reasons as to why they were unblinded will be recorded. Unblinding envelopes for the remaining patients will be checked to ensure they were not opened or tampered with.

Patients groups for analysis

Intention-to-treat analysis of efficacy outcomes

To provide a pragmatic comparison of the policies of the different drug treatments, the principle of invention to treat, as far as is practically possible, will be the main strategy of analysis adopted for the primary end point. These analyses will be conducted on all patients who have primary outcome data, assigned to the two treatment groups – magnesium or placebo as randomised – regardless of the study treatment or non-study treatment received. A sensitivity analysis will be applied for any missing primary outcome data (see *Data analysis*, *Analysis of missing primary outcome data*, below).

Analysis of safety outcomes

For the analysis of safety outcomes, all patients who have received at least one dose of the study drug and were available for follow-up will be included. Patients will be included in the treatment group they actually received.

Data analysis

Analysis of primary efficacy outcome

The primary endpoint is the ASS at T60.

The primary analysis will follow the ITT approach. The hypothesis of no difference between the two treatment arms will be tested using ANCOVA. A *p*-value of 0.05 (5% level) will be used to declare statistical significance and 95% CIs of the estimated effects will be reported. The primary analysis using ANCOVA will not adjust for any missing data. However, reasons for missing outcome data will be reported and a sensitivity analysis will be undertaken (see *Data analysis*, *Analysis of missing primary outcome data*, below).

The assumptions that are made when using ANCOVA (i.e. normality of ASS at treatment levels, homogeneity of variance, homogeneity of regression slopes, linear regression) will be assessed. Histogram of ASS will be

plotted for checking normality and a suitable transformation (e.g. square root, log) will be considered to correct non-normally distributed data. Levene's test will be used to test the assumption of homogeneity of variance. Assumptions of linear regression (magnitude of the scatter of the points is the same throughout the length of regression line) and homogeneity of regression slopes (direction and strength of this relationship must be similar in each treatment group) will be detected by examining simple scatterplots between ASS and covariates. If unequal variances, non-linearity and/or non-parallel slopes are present, a suitable transformation of ASS will be used to improve the linearity and to promote equality of the variances.

Randomisation is stratified by centre; however, owing to the large number of small centres, centre will not be included in the model as a covariate, and this is due to the fact that including a large number of small centres may lead to unreliable estimates of the treatment effect and *p*-values that may be too large or too small.[77] To test the robustness of ignoring the centre effect in the primary analysis, sensitivity analyses will be performed. A GLM type II analysis will be carried out with treatment, centre and treatment-by-centre interaction and baseline measurement included as covariates. Centre will be treated as both fixed and random in separate analyses to assess if there is any effect of this assumption. If the sensitivity analysis suggests the results are not robust to how centre is handled in analysis, centre characteristics (e.g. university hospital, DHS, specialist centre) will be explored further.

All longitudinal ASS data collected will be used in a secondary analysis, with a resulting increase in power. Longitudinal ASS data will be summarised by the AUC. The AUC is a summary measure that integrates repeated assessments of a patient's end point over the duration of the treatment. AUC measures preserved discriminant validity in treatment comparisons and reported more precise treatment effect estimates.[78,79] As the study drug is aimed to lower the ASS over three time intervals, AUC is the most appropriate measure for the treatment comparison.

Analysis of secondary efficacy clinical outcomes

The five clinical secondary outcomes of interest are:

- 'stepping down' of treatment at 1 hour
- number and frequency of additional salbutamol administrations
- length of stay in hospital
- requirement for intravenous bronchodilator treatment
- intubation and/or admission to a PICU.

The proportion of patients who required a 'stepping up' of medication at 1 hour, progression to intravenous treatment, intubation and/or admittance to HDU/PICU will be compared between the two arms using a chi-squared test. As these are centre-specific outcomes, a sensitivity analysis will be undertaken to account for centre characteristics.

The mean (SD) or median (IQR) of number (frequency) of additional salbutamol administrations will be computed depending on whether it is skewed or not, and compared across treatment groups using a *t*-test or Mann–Whitney *U*-test.

Summaries of length of stay in hospital will be presented as means (SDs) or medians (IQRs) depending on whether it is normally distributed or not, and compared across treatment groups.

A formal test of a treatment–covariate interaction will be conducted for the effect of age (2–5 years and $\geq$ 6 years) by including the interaction term in a regression model. Exploratory analysis will be conducted as to the impact on any treatment effect of other factors such as gender or presenting clinical signs.

A *p*-value of 0.05 (5% level) will be used to declare statistical significance and 95% CIs of the estimated effects will be reported.

Analysis of secondary outcomes of quality-of-life and health economic measures at 1 month

There are four patient/parent secondary outcomes at 1-month follow-up of interest:

- paediatric quality of life (PedsQL™) asthma module parental report for all children and self-completion if aged > 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).

Independent-sample *t*-tests will be used to test for differences in resource use, costs, utility scores (generated by the EQ-5D multiattribute utility measure), and QALYs between treatment groups. All statistical tests will be two-tailed and considered statistically significant at *p*-value of < 0.05.

Handling missing health economic data

The ICE command within Stata (version 10.0) will be used to impute missing data for economic outcomes. Following the methods of Briggs *et al.*[56] for handling missing data, five imputed data sets will be generated through multiple imputation using non-parametric bootstrapping[80] in Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA, USA) and the results will be combined using equations described by Briggs *et al.*[56] to calculate SEs around mean costs and effects that incorporate uncertainty around imputed values as well as sampling variation. SEs will be used to calculate 95% CIs around total and incremental costs and QALYs based on Student's *t*-distribution.

Cost-effectiveness acceptability curves (CEACs)[57] showing the probability that nebulised $MgSO_4$ is cost-effective relative to placebo at a range of ceiling ratios will be generated based on the proportion of bootstrap replicates (across all five imputed data sets) with positive incremental net benefits.[58] Incremental net benefit can be defined as the incremental QALY gain multiplied by the ceiling ratio minus the incremental cost[58] where the ceiling ratio (or threshold) represents the maximum society is willing or able to pay for each additional QALY. All statements about cost-effectiveness will be based on a £20,000 per QALY gained threshold. The probability of nebulised $MgSO_4$ being less costly or more effective will be based on the proportion of bootstrap replicates that have negative incremental costs or positive incremental benefits, respectively. No discounting will be applied to costs and health effects as the time horizon for the economic evaluation will be < 1 year.

A series of multiway and probabilistic sensitivity analyses will be performed to explore the implications of uncertainty surrounding variables with a degree of uncertainty.

Analysis of missing primary outcome data

Three nebulised study treatments will be given at T0, T20 and T40. The primary analysis will be of the ASS at T60. To investigate how sensitive the results of the primary analysis are to missing data a number of strategies will be used. These sensitivity analyses will involve joint modelling as well as imputing values for missing ASS at T60.

These sensitivity analyses will be carried out as secondary analyses of the study data. The results of these analyses will be compared with the relative effect of missing data on the conclusions of the primary analysis.

Description of missing data

The proportion of patients with missing outcome data will be reported by treatment arm together with reasons for missingness.

Further descriptions of the missing outcome data will be reported in terms of:

- Differences in key baseline characteristics between treatment arms in those with observed ASS T60.

This description will be used to assess whether the patients with missing outcomes affect the randomisation balance.[81]

- Differences in key baseline characteristics between patients with observed and missing ASS T60.

This description will be used to assess the plausibility of the MCAR assumption.[81]

Imputation

If missingness is due to an administrative reason (e.g. staff involved were called to an emergency), missing ASS at T60 will not be imputed. Such values are missing for reasons unrelated to any inference we wish to draw about the intervention and hence MCAR. Otherwise, missing values will be imputed depending on the reason for the data being missing.

1. *Impute with worst-case value*: If the reason for missingness is related to the patient's poor condition (e.g. death, study withdrawal owing to severity by clinician), the missing ASS at T60 will be replaced by the worst possible score for the ASS. ASS is measured on a scale between 0 and 9 (where severity increases with score); hence a missing value would be replaced with a '9'.
2. *Impute with best-case value*: If missingness is due to study withdrawal by parent/self discharge (e.g. parent felt child was well enough to go home), the missing value is replaced by the lowest score that the patient experiences at T0, T20 and T40.
3. *Model-based imputation*: If the reason for missingness is not available, missing values will be (multiply) imputed by MICE[82] algorithm conditional on all available values at T0, T20 and T40. MICE iterates through values at each time point, modelling each conditional on the others. The imputations themselves are predicted values from a regression model, with the appropriate random error included. MICE is available as an stand-alone package (WinMICE), and also in R (mice library) and SAS. As ASS is a numerical score, imputations can be generated using predictive mean matching (PMM) method.

Both (1) and (2) are ad hoc approaches, so rarely lead to unbiased estimates of the treatment effects.[81,83,84] Approach (3) is based on the MAR (missing at random) assumption.[81]

Joint modelling

The problem of non-ignorable missing ASS data will be addressed through a more advanced analysis of joint modelling of the longitudinal data and the time to dropout from the study.[85] In this analysis, patients who did not dropout from the study will be censored at the time of discharge from hospital. Dropout owing to reasons related to treatment will be treated as potentially informative, and dropout due to other reasons as a censored follow-up time.

Mean profile plots will be drawn which provide a visual representation of the variation patients may experience in terms of their ASS over time. By reversing the time axis, variation in ASS of an individual prior to informative dropout from the study will be examined.

Description of safety outcomes

Safety analysis

All AEs and SAEs reported by the clinical investigator will be presented, identified by treatment group. AEs will be grouped according to a pre-specified AE coding system and tabulated. The number (and percentage) of patients experiencing each AE/SAE will be presented for each treatment arm categorised

by severity. For each patient, only the maximum severity experienced of each type of AE will be displayed. The number (and percentage) of occurrences of each AE/SAE will also be presented for each treatment arm. No formal statistical testing will be undertaken.

Dummy AE table:

			Arm		
No.	AE (expected/unexpected)	Severity	Treatment A: *n* (%)	Treatment B: *n* (%)	Total no. of patients
1	Facial flushing (E)	Mild			
		Moderate			
		Severe			
2	Tachycardia (U)	Mild			
		Moderate			
		Severe			

Dummy SAE/SUSAR table:

	Treatment									
No.	A	B	Description	Severity	Relationship to study drug	Expectedness	Cause	Outcome	Patient status	Unblinded
1										
2										

Reporting protocol deviations

Protocol deviations will be classified according to the following table and summarised for each treatment group. They will be compared across treatment groups and any imbalance will be investigated.

Protocol specification	Potential deviation(s)	Impact	Justification (in terms of whether bias is likely in the assessment of response)
Inclusion criteria			
For children aged ≥ 6 years, severe asthma is based on at least one of the following criteria being met: 1. Oxygen saturations of < 92% while breathing room air 2. Too breathless to talk 3. Heart rate greater than 120 b.p.m. 4. Respiratory rate of > 30 breaths per minute 5. Use of accessory neck muscles	None of the specified severe asthma criteria	Major	The severity of asthma is likely to influence response
For children aged 2–5 years of age, severe asthma is based on at least one of the following criteria being met: 1. Oxygen saturations of < 92% while breathing room air 2. Too breathless to talk 3. Heart rate greater than 130 b.p.m. 4. Respiratory rate of > 50 breaths per minute 5. Use of accessory neck muscles	None of the specified severe asthma criteria	Major	The severity of asthma is likely to influence response

Protocol specification	Potential deviation(s)	Impact	Justification (in terms of whether bias is likely in the assessment of response)
Exclusion criteria			
Patient suffering from life-threatening symptoms	Patient suffering from life-threatening symptoms	Major	Patient may not be able to metabolise drug effectively thus affecting response
Patient has co-existing severe renal or liver disease	Patient has co-existing severe renal or liver disease	Major	May affect efficacy of study drug and potentially increase incidence of AEs
Patient known to have had a previous reaction to magnesium	Patient known to have had a previous reaction to magnesium	Major	True effect of magnesium on fetus is not known
Patient known to be pregnant	Patient known to be pregnant	Major	Co-existing disease may adversely affect efficacy of study drug
Patient have co-existing respiratory disease (except asthma)	Patient have co-existing respiratory disease (except asthma)	Major	Cannot be sure of effect of potential drug interactions on efficacy and/or safety of study drug
Patient been involved in a trial of a medicinal product within last 30 months	Patient been involved in a trial of a medicinal product within last 3 months	Major	May affect the way of patient response in patient-reported outcomes, which may introduce bias and affect generalisability of results
Patient previously been randomised into the MAGNETIC trial	Patient previously been randomised into the MAGNETIC trial	Minor	Arbitrary cut-off level, no physiological reason
Patient aged ≥ 16 years	Patient aged ≥ 16 years	Minor	Patient may not be able to metabolise drug effectively thus affecting response
Treatment regime			
Allocation	Patient did not receive full trial treatment as per protocol	Major	May affect ASS and outcome data
Timing	Deviations outside acceptable timing window (T = 60 + 15 minutes) without explanation	Minor	May shorten or lengthen treatment period TMG to review cases blind to allocation to determine whether minor/major deviation
Primary outcome data Assessment of ASS at T60	Deviation in the method of assessment	Major	Introduce bias in the assessment of response

Protocol specification	Potential deviation(s)	Impact	Justification (in terms of whether bias is likely in the assessment of response)
Secondary outcome data			
'Stepping down' of treatment at 1 hour No. and frequency of additional salbutamol administration Requirement for intravenous bronchodilator treatment Intubation and/or admission to a PICU Length of stay in hospital	Deviation in the method of assessment	Major	Introduce bias in the assessment of response
Patient and parental outcomes at 1-month follow-up	If the questionnaire is returned too long after 1 month and we are not confident that the data relate to 1 month	Major	Introduce bias in the assessment of response

Setting results in context of previous research

We will integrate the results of this trial within the context of an up-to-date systematic review of relevant evidence from other trials.[86] We will refer the results of this trial to the latest existing systematic review of nebulised magnesium in children with asthma.[4] This review concluded that further trials of nebulised $MgSO_4$ in children were needed. More recent trials not included in this review will be identified and reviewed.

A1 Changes to Statistical Analysis Plan

Section 7.2: One change

(1) Treatment–covariate interactions

Treatment–covariate interactions were investigated for two clinically important baseline covariates, duration of the most recent asthma attack and SaO_2, owing to reasons explained above (see *Chapter 3*, *Assessing the evidence for treatment–covariate interactions*, in the report). It was originally planned to conduct a formal test of a treatment–covariate interaction for the effect of age. Although age may affect the response, a number of possible interactions could be argued.

Section 9: One change

(1) Timing of treatment regimes

Protocol deviation was originally defined as deviations outside acceptable timing window (T = 60 + 15 minutes) without explanation. However, because the prescription time of each treatment was reported rather than the time of the end of the third treatment, it was only possible to determine the difference in prescription times between the first and third treatment which should be ≤ 55 (40 + 15) minutes. Therefore, if this timing was > 55 minutes, this was defined as a deviation outside the acceptable window.

Appendix 4 Details of protocol amendments

Final protocol, version 6.1, 18 January 2010

Amendments from version 6.0 (23 July 2009) to version 6.1 (18 January 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 September 2008) to version 6.0 (23 July 2009)

p. 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
p. 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
p. 22	7.4 Accountability procedures for study treatment(s) this section has been amended to update the procedure for storage of the trial medication
p. 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
p. 36	10.9 Responsibilities- MCRN CTU: this section has been updated to confirm that all SAEs will also be reported to the trial IDSMC
p. 43	13.4 Data Monitoring at MCRN CTU: the process for data querying as been clarified
p. 57	Appendix C: change of investigator – Fairfield General Hospital
p. 60	Appendix C: addition of participating site – City General Hospital, UHNS
p. 61	Appendix C: change of investigator – Royal London Hospital
p. 63	Appendix C: addition of participating site – University Hospital Lewisham

Amendments from version 4.0 (18 April 2008) to version 5.0 (19 September 2008)

p. 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
p. 20	6.2 Randomisation: this section has been amended to remove details of stratification of the randomisation in to two age groups
p. 29	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 (3 March 2008) to version 4.0 (18 April 2008)

p. 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
p. 24–25	8.1 Schedule for follow-up: this section has been amended to clarify that these data will be collected in the event patients are admitted to hospital. Table 2 has been updated to clarify that AEs and concomitant medication monitoring will continue in the event of admission
p. 58	Change in principal investigator at Leighton Hospital: the principal Investigator at Leighton Hospital has been changed to Dr Julie Ellison, Consultant Paediatrician
p. 62	Addition of study site: Singleton Hospital, Swansea

Amendments from version 2.0 (18 January 2008) to version 3.0 (03 March 2008)

p. 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
p. 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
p. 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
p. 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 November 2007) to version 2.0 (18 January 2008)

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

IMP, Investigational Medicinal Product.

Appendix 5 Description of missing primary outcome data and sensitivity analyses

TABLE 40 Key baseline characteristics for those with observed baseline and T60 ASS

Baseline characteristic	Magnesium (*n* = 228)	Placebo (*n* = 244)
Age (years): median (IQR), range	4.0 (3.0–7.0), 2–15	4.0 (3.0–7.0), 1–15
Male, *n* (%)	128 (56)	144 (59)
Time of day that randomisation occurred, *n* (%)		
0900–1700	164 (72)	161 (66)
1700–2200	44 (19)	57 (23)
2200–0900	20 (9)	26 (11)
ASS at baseline	(*n* = 227)	(*n* = 243)
Mean (SD), range	5.8 (1.3), 3–9	5.8 (1.4), 2–9
Duration of the most recent asthma attack, *n* (%)	(*n* = 227)	(*n* = 242)
For the last few days	48 (21)	54 (22)
For the last 24 hours	149 (66)	150 (62)
For the last 6 hours or less	30 (13)	38 (16)
SaO_2 (%)	(*n* = 227)	(*n* = 241)
Mean (SD), range	93.7 (3.5), 84–100	93.4 (3.4), 81–100
Respiratory rate (breaths per minute)	(*n* = 225)	(*n* = 238)
Mean (SD), range	43.5 (10.5), 20–72	42.4 (10.8), 20–70
Oxygen therapy, *n* (%)	(*n* = 222)	(*n* = 235)
Yes	88 (40)	94 (40)
No	134 (60)	141 (60)

TABLE 41 Key baseline characteristics for patients with observed and missing ASS at T60

Baseline characteristic	Observed ASS at T60 (*n* = 472)	Missing ASS at T60 (*n* = 36)
Age (years): median (IQR), range	4.0 (3.0–7.0), 1–15	5.5 (3.0–8.0), 2–13
Male, *n* (%)	272 (59)	21 (57)
Time of day that randomisation occurred, *n* (%)		
0900–1700	325 (69)	24 (67)
1700–2200	101 (21)	7 (19)
2200–0900	46 (10)	5 (14)
ASS at baseline	(*n* = 470)	(*n* = 32)
Mean (SD), range	5.8 (1.3), 2–9	5.0 (1.3), 2–7
Duration of the most recent asthma attack (*N* = 469): *n* (%)		
For the last few days	102 (22)	6 (17)
For the last 24 hours	299 (64)	25 (69)
For the last 6 hours or less	68 (14)	5 (14)
SaO_2 (%)	(*n* = 468)	(*n* = 35)
Mean (SD), range	93.5 (3.4), 81–100	94.4 (3.5), 84–100
Respiratory rate (breaths per minute)	(*n* = 463)	(*n* = 34)
Mean (SD), range	43.0 (10.6), 20–72	41.6 (11.5), 25–70
Oxygen therapy, *n* (%)	(*n* = 457)	(*n* = 31)
Yes	182 (40)	10 (32)
No	275 (60)	21 (68)

Reasons for exclusion of children from primary outcome analysis

There were 25 children in the magnesium group who did not contribute data for the adjusted analysis of the primary outcome of ASS at T60. There were 13 children in the placebo group who did not contribute data for

TABLE 42 Reasons for missing primary outcome data

	Magnesium		Placebo	
	T0	T60	T0	T60
Reason for missing data	No. of children	No. of children	No. of children	No. of children
Heart rate was not recorded	1	7	0	2
Muscle use was not recorded	1	6	0	4
Wheeze was not recorded	0	2	0	1
Withdrawn from study	1	4	0	3[a]
Non-compliance with trial protocol	1	0	0	0
Reason not known	0	3	0	2
Data not available	0	2	2	0
Total	4[b]	24	2[c]	12

a One of these is related to poor status.
b Three of these also had missing T60 data.
c One of these also had missing T60 data.

the adjusted analysis of the primary outcome. Four children (three from the magnesium group and one from the placebo group) could not contribute ASS data at either baseline or T60.

Sensitivity analyses of missing primary outcome

Sensitivity analyses were carried out to investigate the robustness of the conclusions concerning the analysis of the primary outcome to assumptions about the missing data. In the analysis in *Table 8*, it is assumed that the data are missing at random. Sensitivity of results to those cases with missing data for the primary outcome was assessed by three methods.

Sensitivity analysis (1)

First, if the reason for missingness of ASS at T60 was related to good status, the missing value was replaced by '0' (for three children) in the sensitivity analysis; if the reason was related to poor status, it was replaced by '9' (for one child); if the reason was unlikely to be related to status or unknown, it stays as missing (for 32 children). The results of this sensitivity analysis are presented in *Table 43*.

The statistical significance of the adjusted analysis remained unchanged; however, the minimum clinically importance difference of 0.5 points is now contained within the 95% CI.

Sensitivity analysis (2)

Secondly, a model-based imputation of MICE (see statistical analysis plan in *Appendix 3*, *Data analysis*, *Imputation*) was used to impute missing ASS values at T60 conditional on all available values at T0, T20 and T40. The R-language library 'mice' is used in this analysis. Five imputations were performed in sequence and during each imputation the missing values are imputed, and at the end of the imputations (all five in this case), the values are averaged together to take into account the variance of the missing values. The averaged final data set is used to compute the mean difference in ASS at T60 between the two treatment groups, magnesium minus placebo, adjusting for baseline ASS. The results are presented in *Table 44*.

The statistical significance of the adjusted analysis remained unchanged. The minimum clinically importance difference of 0.5 points is just contained within the 95% CI.

Sensitivity analysis (3)

Third, the problem of non-ignorable missing ASS data was addressed through joint modelling of the longitudinal data and the time to dropout from the study. In this analysis, children who withdrew from the

TABLE 43 Sensitivity analyses: single imputation based on reason for missingness

	T60 mean (SD), range		Estimate (95% CI), *p*-value	
Outcome	Magnesium: $n_m = 231$	Placebo: $n_p = 245$	Difference in mean: $n_m = 231$, $n_p = 245$	Adjusted difference in mean: $n_m = 230$, $n_p = 244$
ASS	4.66 (1.46), 0–9	4.97 (1.42), 2–9	−0.31 (−0.57 to −0.05), $p = 0.0183$	−0.32 (−0.56 to −0.08), $p = 0.0091$

TABLE 44 Sensitivity analysis (2): multiple imputation

	T60 mean (SD), range:		Estimate (95% CI), *p*-value	
Outcome	Magnesium ($n_m = 252$)	Placebo ($n_p = 256$)	Difference in mean ($n_m = 252$, $n_p = 256$)	Adjusted difference in mean ($n_m = 252$, $n_p = 256$)
ASS	4.66 (1.37), 2–9	4.95 (1.40), 2–9	−0.29 (−0.53 to −0.04), $p = 0.0214$	−0.28 (−0.51 to −0.05), $p = 0.0164$

study were considered as 'dropouts' and the time (at T0, T20, T40 or T60) they withdrew is taken as the time of event (dropout). Those who did not drop out from the study before T60 were censored at T60. In the joint analysis, dropout was modelled as potentially informative given ASS data. Therefore, the joint model combines the information from the dropout pattern (time-to-event analysis) and ASS over time (longitudinal data analysis).

Figure 3 (see *Chapter 3*, *Area under the curve for asthma severity score over three time intervals*) shows the mean longitudinal profiles over T0 to T60. As shown in *Figure 3*, the mean profiles are almost identical for both magnesium and placebo groups. However, this pattern could be an artefact of selective dropout, and it would be a biased comparison between the groups unless it is adjusted with joint modelling.

Asthma severity score data at T0 were not available for six children and their records were excluded from this analysis. Note that these six observations were not dropouts but rather the first observation over the longitudinal process was missing. There were 40 dropouts (19 at T40, 12 at T20 and 9 at T0) and 462 were censored at T60. The mean profiles prior to dropout are presented in *Figure 14*, which tends to show that dropout in the magnesium group occurred because patients get better (most children were clinically well and ready to discharge, as shown in *Table 15*), whereas dropout in placebo occurred is because patients get worse. The results from the joint model are presented in *Table 45*.

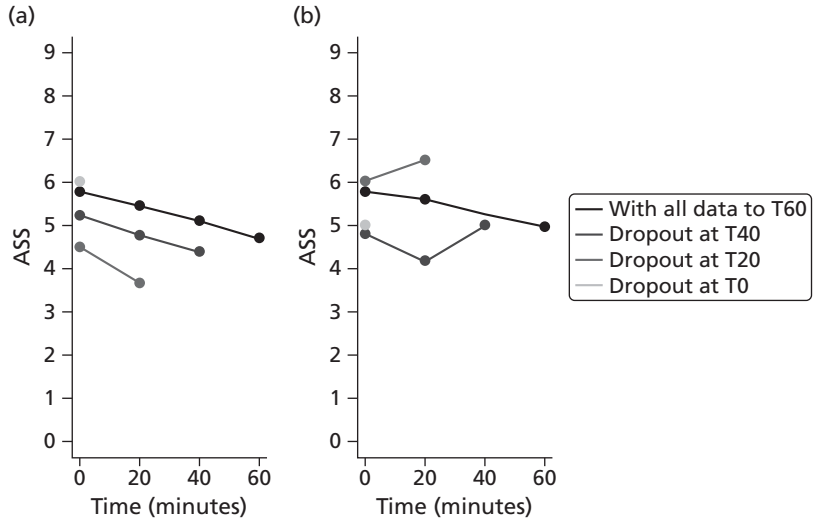


FIGURE 14 Mean profiles prior to dropout. (a) Magnesium. (b) Placebo.

TABLE 45 Sensitivity analysis (3.1): joint modelling for T60 data

Variable	Estimate (95% CI)
Longitudinal ASS	
Intercept	5.84 (5.69 to 5.99)
Time	−0.02 (−0.02 to −0.01)
Magnesium	−0.16 (−0.34 to 0.05)
Dropout	
Magnesium	0.55 (−0.10 to 1.30), HR = 1.73 (95% CI 0.90 to 3.66)
γ	−0.38 (−0.75 to −0.05)

HR, hazard ratio.

The joint analysis of longitudinal ASS and dropout show a statistically significant association between ASS and dropout (95% CI for the parameter γ does not include zero).

The relationship between ASS and dropout over entire follow-up is also examined through joint modelling. In this case, the dropout pattern is as follows: 31 at T120, 30 at T180, 27 at T60, 19 at T40, 12 at T20 and 9 at T0, and 374 were censored at T240. The longitudinal mean profiles over T0 to T240 are shown in *Figure 15* and the longitudinal mean profiles prior to dropout are shown in *Figure 16*. Pattern in *Figure 15* remains the same as that in *Figure 3* over entire follow-up, however comparison of between groups in this setting may be biased as explained above. *Figure 16* shows similar pattern to *Figure 14* that dropout in the magnesium group is due to children get better and ready to discharge. The results from the joint model are presented in *Table 46*. The analysis still shows a statistically significant association between ASS and dropout (95% CI for the parameter γ does not include zero).

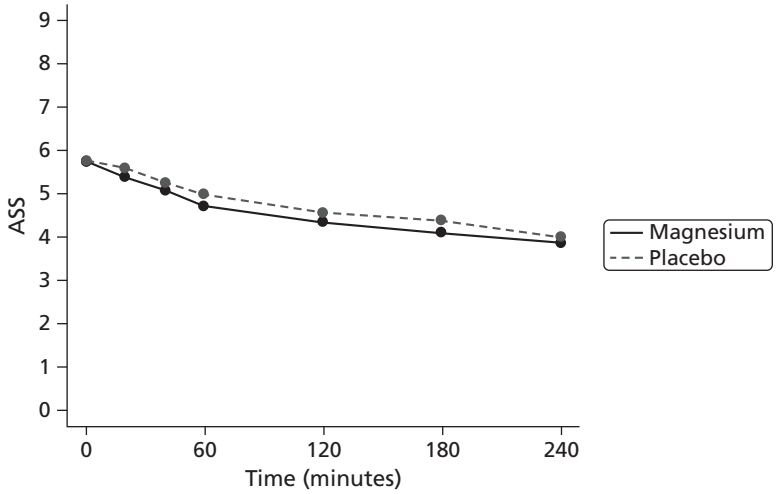


FIGURE 15 Mean profiles over entire follow-up.

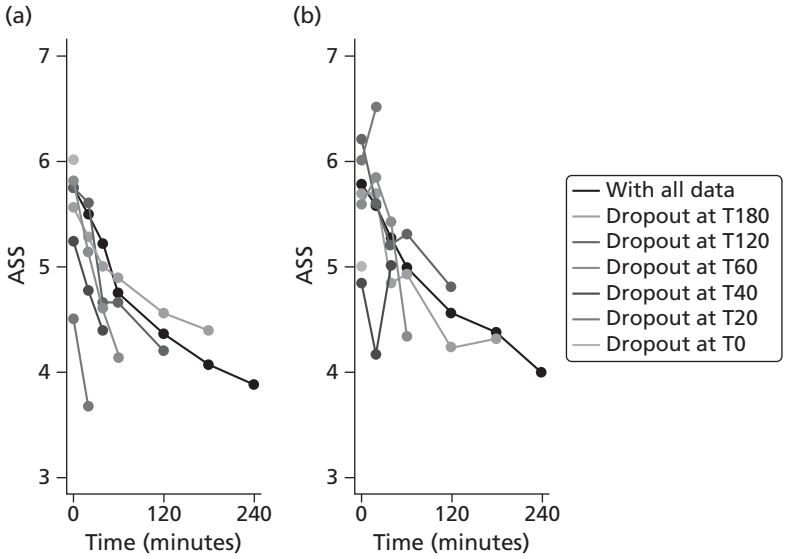


FIGURE 16 Mean profiles prior to dropout over entire follow-up. (a) Magnesium. (b) Placebo.

TABLE 46 Sensitivity analysis (3.2): joint modelling for follow-up up to T240

Variable	Estimate (95% CI)
Longitudinal ASS	
Intercept	5.62 (5.47 to 5.75)
Time	−0.01 (−0.008 to −0.007)
Magnesium	−0.20 (−0.40 to −0.01)
Dropout	
Magnesium	0.53 (0.18 to 0.92), HR = 1.70 (95% CI 1.20 to 2.51)
γ	−0.18 (−0.39 to −0.002)

HR, hazard ratio.

Appendix 6 Sensitivity analyses for centre effect

A sensitivity analysis was performed to investigate the robustness of ignoring any centre effect in the primary analysis. Two models were fitted: in the first model centre was treated as a fixed effect, and in a second model it was treated as a random effect. The second model determines the appropriate *F*-tests based on centre and treatment–centre interaction being treated as random effects. Type II SS computes the estimates for the main effects. Type III SS computes the estimates for fixed or random centre–treatment interaction effect if entered last into the model. Both models were also adjusted for baseline ASS. The results are presented in *Table 47*.

Both random-effects analysis of variance and the fixed-effects model indicated significant main effect of centre, but there is no evidence that the treatment effect varies by centre.

TABLE 47 Treatment centre interaction

Variable	Model 1: fixed effects		Model 2: random effects
	F-value, Type II SS, *p*-value	*F*-value, Type III SS, *p*-value	*F*-value, Type III SS, *p*-value
Treatment	5.53, 8.47, $p = 0.0191$	1.83, 2.81, $p = 0.1766$	2.38, 2.81, $p = 0.1265$
Centre	2.56, 113.87, $p < 0.0001$	2.31, 102.81, $p = 0.0002$	3.61, 102.81, $p = 0.0005$
ASS at T0	66.72, 102.18, $p < 0.0001$	66.72, 102.18, $p < 0.0001$	66.72, 102.18, $p < 0.0001$
Treatment–centre interaction		0.64, 28.51, $p = 0.9262$	0.64, 28.51, $p = 0.9262$

Appendix 7 Diagnostic plots for primary outcome data analysis and histograms of continuous secondary outcomes

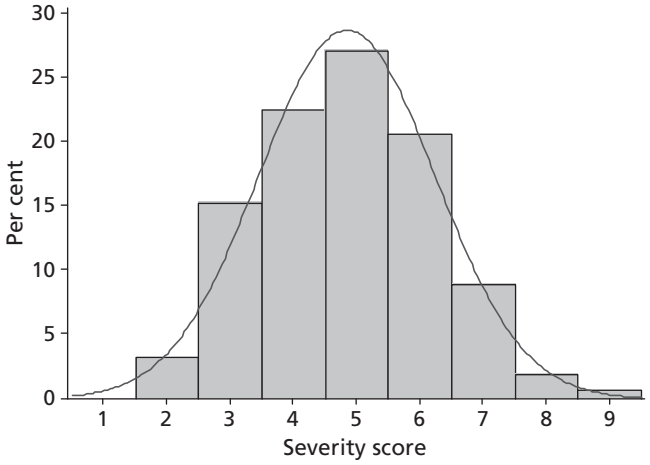


FIGURE 17 Histogram of ASS at T60 to check normality assumption.

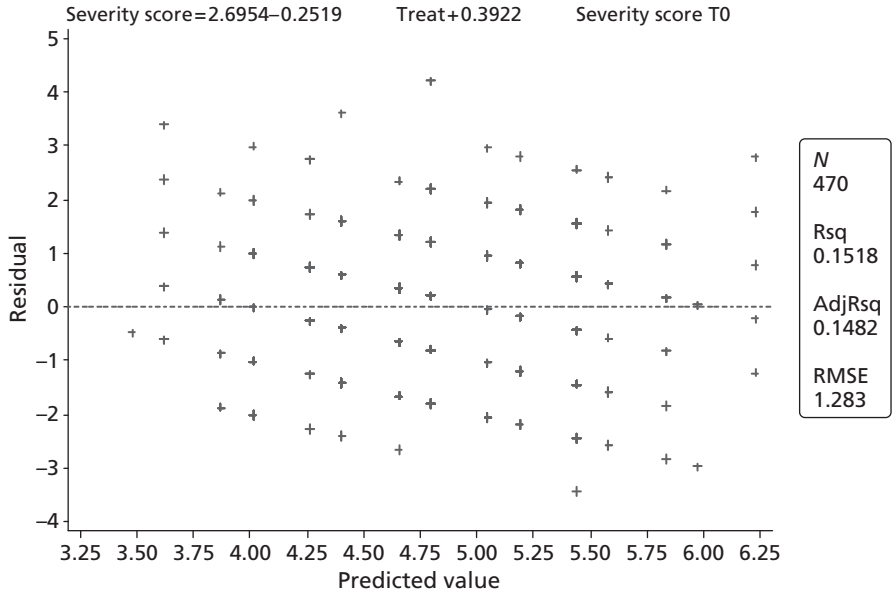


FIGURE 18 Plot of residuals vs. fitted values to check for heteroscedasticity.

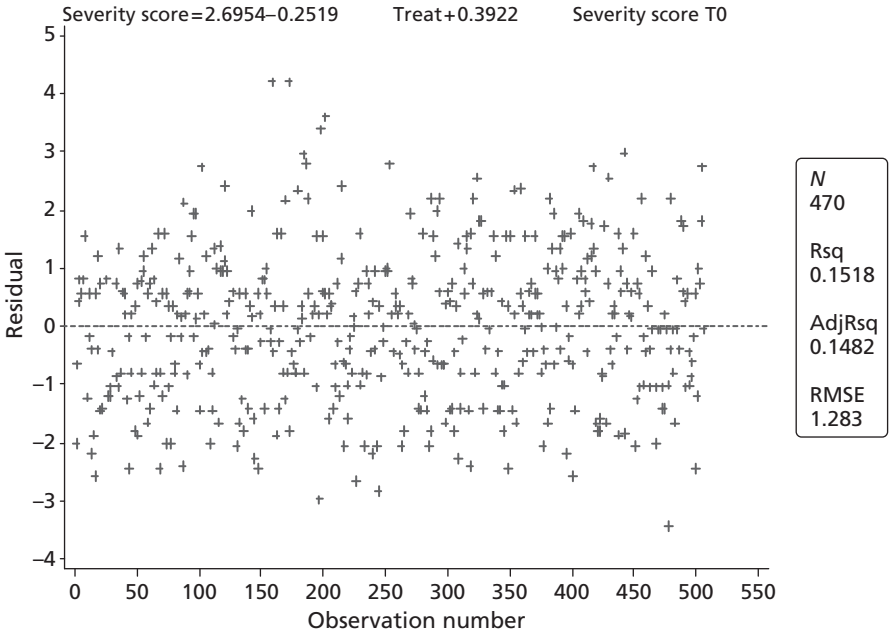


FIGURE 19 Index plot to check for correlation between observations.

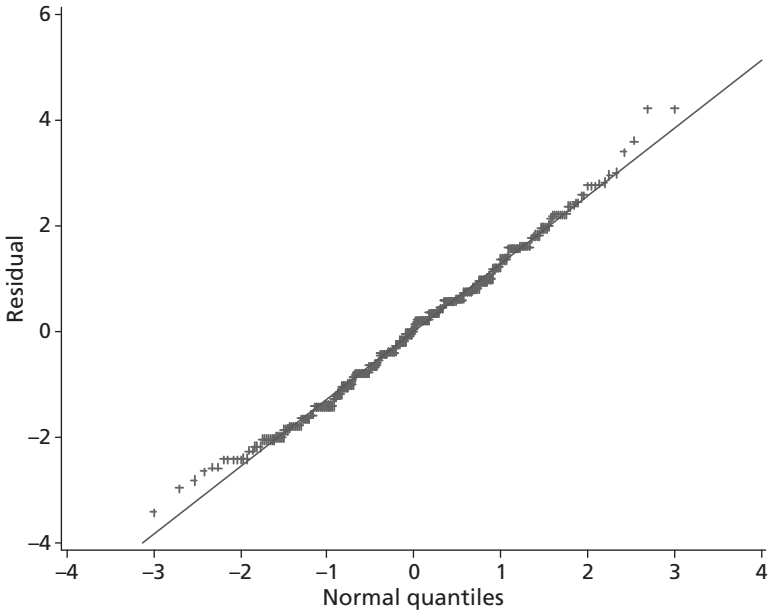


FIGURE 20 Q–Q plot to check normality of residuals.

Histograms of continuous secondary outcomes

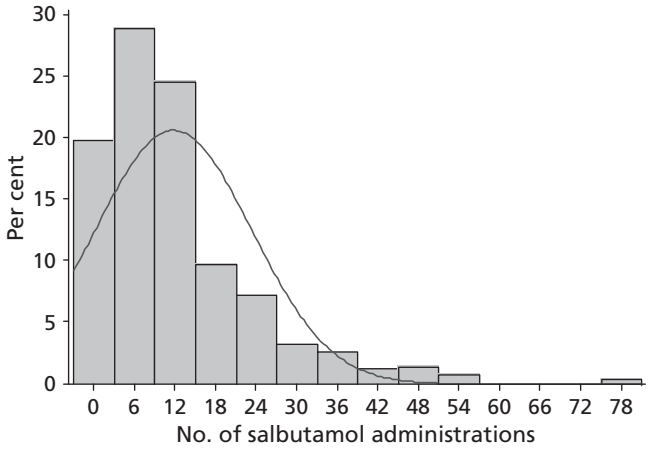


FIGURE 21 Number of salbutamol administrations.

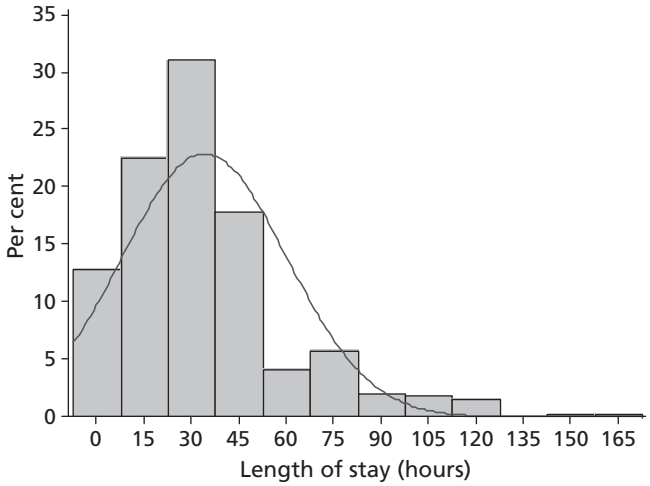


FIGURE 22 Length of stay in hours.

Appendix 8 Patient information sheets

Parent Information and Consent Form: 18/01/2008, V2.0

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

ISRCTN81456894

A study to determine the usefulness of nebulised magnesium sulphate in the management of acute severe asthma in children

You are being asked for your permission for your child to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Ask us if there is anything that is not clear or you would like more information on. Thank you for reading this.

What is the purpose of this study?

Children with bad asthma usually receive salbutamol (ventolin) mixed with ipratropium bromide (atrovent), commonly used drugs for treating asthma attacks, through a nebuliser when they come into hospital suffering from a severe asthma attack. We wish to investigate whether adding magnesium sulphate to nebulised salbutamol (ventolin) and ipratropium (atrovent) is helpful in children. We know that using magnesium can be beneficial in adults by helping to relax muscle in the airways, which tightens during an asthma attack. This treatment is sometimes given to adults directly into the bloodstream (intravenously), but we would like to see if magnesium is useful when delivered through a nebuliser mixed with salbutamol and ipratropium. This is because using a nebuliser is less invasive than using a needle and because the medication is inhaled direct to the airways where it is useful. Studies have been done in adults and it has been shown that mixing magnesium sulphate and salbutamol and using them in a nebuliser is safe.

Why has your child been chosen?

Your child has been asked to take part because they are having a severe asthma attack. We will be recruiting approximately 500 children from approximately 20-25 hospitals in the UK.

Does your child have to take part?

No, taking part is completely voluntary. It is up to you and your child (if they can) to decide whether to take part. If you decide to take part you and your child are still free to withdraw at any time without giving a reason. This will not affect the standard of care your child receives.

What will happen if my child takes part?

Your child will receive nebulised salbutamol and ipratropium as usual. However instead of mixing the salbutamol and ipratropium with normal saline, in this study it **may** be mixed with magnesium sulphate. This study is randomised, which means that whether your child receives nebulised magnesium or not is decided by chance, just like tossing a coin. It is also double blind, which means that neither you nor the doctors and nurses looking after your child will know whether your child has received the nebulised magnesium or not. However, the doctors will be able to find out which treatment they are receiving if they need to.

Your child will have three nebuliser treatments, each around twenty minutes apart. Between each treatment, a doctor or nurse will perform a quick exam to see if their symptoms have improved. We plan to give all three nebulisers even if their symptoms get better or worse (as long as the doctor thinks it is safe). This is so we can compare them with other children in the study. After the final nebuliser and assessment, we will continue to monitor your child for a further 3 hours to see what further treatment, if any, they go on to receive (as long as they remain in the hospital). In the event your child is admitted, we would also like to know how long they spend in hospital and what treatment they have

We will contact you 4 weeks after your child leaves hospital to check how they are doing, and so assess if attending hospital has affected you or your child's daily life. To do this, we would like to send you some questionnaires to fill in through the post. We would like your consent for us to pass on your contact details (address and telephone number) to the Medicines for Children Research Network Clinical Trials Unit (Institute of Child Health, University of Liverpool, Royal Liverpool Children's Hospital, Eaton Road, Liverpool, L12 2AP, http://www.liv.ac.uk/mcrn/clinical.htm). They are co-ordinating the study and will organise to send you the questionnaires.

What are the side effects of taking part?

A pilot study has been performed using inhaled magnesium in children and it was found to be safe. We know that when given intravenously (directly into the blood), magnesium occasionally causes facial flushing (a reddening of the skin which can make you feel warm), and small drops in blood pressure. This is because it widens some of the small blood vessels near the surface of the skin, which also allows heat to escape. We do not expect this to be a problem in this study because the magnesium will be delivered directly to the airways by the nebuliser, and not all around the body.

What are the possible disadvantages and risks of taking part?

We do not think there are any disadvantages or risks in taking part. Your child will receive the same standard of care regardless of their participation, and doctors and nurses will follow the same guidelines as they do for all children with severe asthma attacks.

What are the possible benefits of taking part?

If we are able to prove that adding magnesium sulphate will lead to quicker and better relief of asthma symptoms, this may lead to new ways of treating children with bad asthma attacks in the future.

What if something goes wrong?

If you have a concern about any aspect of this study, you should speak to <<PI name>>, who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints procedure. Details can be obtained from the hospital.

In the event that something goes wrong and your child is harmed during the research study there are no special compensation arrangements. If your child is harmed and this is due to someone's negligence then you may have grounds for legal action against <<NHS Trust>>, but you may have to pay your legal costs. The normal NHS complaints mechanism will still be available to you.

Will my child's participation in this study be kept confidential?

All information which is collected about your child during the course of the study is considered confidential and giving the information to anyone else (called third parties) is not allowed. However, as we mentioned earlier, we would like to have your permission to forward your contact details (address and telephone number) to the Medicines for Children Research Network Clinical Trials Unit (MCRN CTU). The MCRN CTU is co-ordinating the study and will be responsible for sending out the follow-up questionnaires approximately 1 month after your visit to hospital; they will also receive a copy of your signed consent/assent forms. The MCRN CTU, based in the University of Liverpool, is a registered data controller with the Information Commissioners Office and will ensure that you and your child's confidentiality is preserved.

We would also like your permission to use some information collected about your child on admission. This will include details of their current asthma medication, and assessments about the severity of their attack that will be kept in their medical notes. We have to collect this information to check that your child is suitable for the study, and because we do not want to delay treatment by doing repeat examinations.

What happens with the results of the research study?

Once the research is completed we would aim to present the findings to national and international asthma meetings, and to publish it in medical journals.

Who is organising and funding the research?

The research is being organised through and co-ordinated by the Medicines for Children Research Network Clinical Trials Unit. It is sponsored by Cardiff University and funded by the NHS Health Technology Assessment (HTA) programme.

Who has reviewed the study?

The study has been reviewed by and received a favourable opinion from the North West Multi-Centre Research Ethics Committee.

Contact for information

If you have any queries about the above, please contact <<contact details>>. For further information or independent advice on taking part in research projects, you can contact <<contact details>>

THANK YOU FOR READING THIS INFORMATION SHEET.

WE HOPE YOU FOUND IT USEFUL.

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

ISRCTN81456894

		Please initial
1.	I confirm that I have read and understand the information sheet dated 18/01/2008 (version 2.0) for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason, and without my care/my child's care or legal rights being affected.	
3.	I understand and accept that information collected on admission will be used to assess my child's eligibility and that this information will form part of the data collection for the study.	
4.	I understand that relevant sections of any of my child's medical notes and data collected during the study may be looked at by the clinical trial staff from the Medicines for Children Research Network Clinical Trials Unit, responsible individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my child's records.	
5.	I agree to my child's GP being informed of my child's participation in this study.	
6.	I agree for a copy of this form to be sent to the MCRN CTU	
7.	I agree to release my contact information (address and telephone number) so that the MCRN CTU can organise the 4 week follow-up.	
8.	I agree to take part in the above study.	

Name of Patient		
Name of Parent	Signature	Date
Researcher	Signature	Date

When completed, 1 MCRN CTU; 1 for researcher site file; 1 for patient, 1(original) to be kept in medical notes

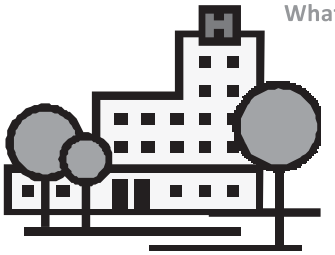
Child (5-8) Information and Assent Form: 18/01/2008, V2.0

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

ISRCTN81456894

Information Sheet for a Young Person with a Bad Asthma Attack

This information sheet is intended to be shown/read to the child by their parent/guardian.



What is happening to me?

You have been brought to the hospital because you have been having trouble breathing. While you are here we are asking if you would like to take part in a test called a 'study'.

We would like to tell you about this.

Your mummy and daddy talked to the doctors and nurses and said it was OK for you to take part in the study.

The doctor will be giving you medicine to help you get better, but as part of the study, we would like to give you an extra medicine, if that is OK with you. By taking part, you will help us find out how good the extra medicine is

How will the doctors and nurses give the medicine to me?

The medicine will be given as a mist through a mouthpiece or mask. All you have to do is try and breathe as normally as you can. We will add the extra medicine at the same time.

What will the medicine do to me?

We hope that the medicine might help you to get better more quickly. Other people have had the medicine and were OK.

Who is looking after me?

The doctors and nurses will look after you while you are being given the medicine.

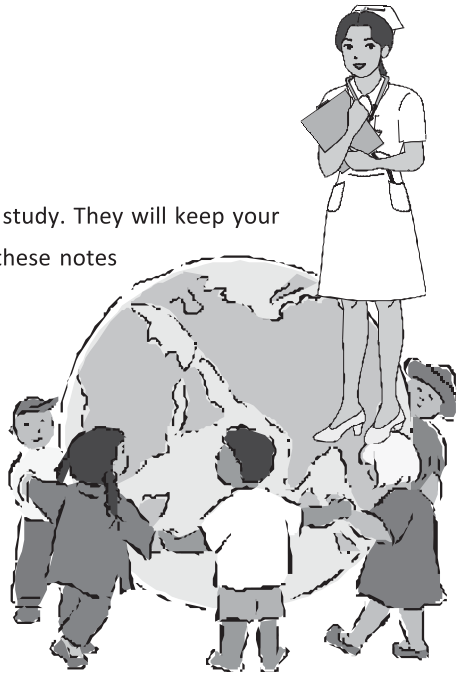
What will the doctor and nurses do?

The doctors and nurses will be checking that you are OK by listening to your chest and heart to see how hard it is for you to breathe.

How long will the study go on for?

We would like to give you the medicine 3 times. This will take an hour. You will need to stay in hospital until the doctors think you are well enough to go home.

What else will happen in the study?

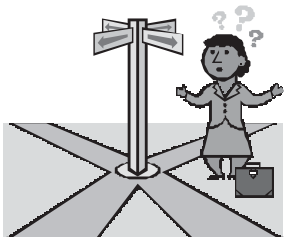


The doctors and nurses will write down notes about you for the study. They will keep your name secret so that only people at the hospital will know that these notes are about you.

Why is the study being done?

We hope that the study will help children who have the same problems as you.

Do I have to do the study?



No – not all. It's up to you. Just say if you don't want to carry on. Nobody will mind, and you will still be looked after.

If you do, you will need to write your name (if you can) on the form that comes with these sheets.

Thank you for taking the time to read this information sheet to your child. Please ask questions if you need to, or ask your child if they would like to ask any questions.

Assent Form for Children (aged 5-8): 18/01/2008, V2.0
(to be completed by the child and their parent/guardian)

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

ISRCTN81456894

Child (or if unable, parent on their behalf)/young person to circle all they agree with:

Have you read information (or had it read to you) about this project?	***Yes / No***
Has somebody else explained this project to you?	***Yes / No***
Do you understand what the project is about?	***Yes / No***
Have you asked all the questions you want?	***Yes / No***
Have you had your questions answered in a way you understand?	***Yes / No***
Do you understand it's OK to stop taking part at any time?	***Yes / No***
Are you happy to take part?	***Yes / No***

If any answers are 'no' or you **don't** want to take part, do not write your name

If you **do** want to take part, please write your name and today's date below. Your parent or guardian must also write their name here to if they are happy for you to do the project. The doctor or nurse who explained this project needs to sign as well. Thank you.

Your Name	Date	
Parent's Name	Signature	Date
Researcher	Signature	Date

When completed, 1 copy for MCRN CTU; 1 for researcher site file; 1 for patient, 1 (original) to be kept in medical notes.

Child Information and Assent Form (age 5-10) 18/01/2008, V2.0

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

ISRCTN81456894

Information Sheet for a Young Person with a Bad Asthma Attack

We thank your Mum or Dad for helping you to read this information

What is a study? Why is this study being done?

A research study is what you do when you want to learn about something or find out something new. It can help doctors and nurses and other people in the hospital find out which medicines can help children get better.

This study is to see if a medicine called magnesium sulphate helps you get better more quickly than if you had a placebo medicine. A placebo medicine is a dummy liquid and will look the same as the magnesium, but contains no medicine.

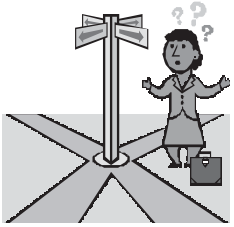
Why have I been asked to take part?

You have been asked because you are having a bad asthma attack.

Did anyone else check the study is OK to do?

Before any study is allowed to happen, it has to be checked by a group of people called an Ethics Committee. The Ethics committee is a group of experts and ordinary people who look at studies very carefully to decide whether they are OK to do. The North West Multi-Centre Research Ethics Committee have looked at this study and decided it is OK.

Do I have to take part?

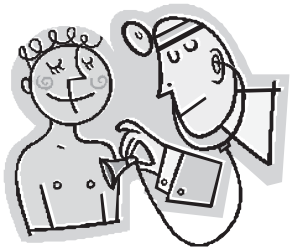


No- not at all, it's up to you. Just say if you don't want to take part; nobody will mind. If you do take part, you will need to write your name on an 'assent form'. This form is to say that you understand the study and what will happen if you take part. You will be given your own copy of the form to keep, as well as this information sheet.

What will I need to do and how long will it take?

Half of the children in the study will be given magnesium sulphate and the other half will be given the placebo medicine. You will not be able to choose which one you get, or be told which one you are taking. Your doctor and nurse will not be told which one you are taking, but they can find out if they need to.

We would like to add the magnesium sulphate or placebo to medicines we use you to help you get better. To do this we mix them together in a machine called a nebuliser, which turns medicines into a mist that you can breathe in through a face mask or mouthpiece. We plan to give you the medicine three times, and each time the nebuliser will last for 10-15 minutes. A doctor or a nurse will check soon after each nebuliser to see if you have gotten any better, any worse, or stayed the same.



After we have finished giving the medicine, we will want to keep an eye on you for another few hours and a doctor or nurse will keep checking to see if you are OK.

We would like to ask your parents some more questions about a month after you have left the hospital. To do this we will send them some forms to fill in; we have one for you to fill in as well, and your parents can help you do this.

Will the medicine upset me?

Sometimes medicines upset our body and if this happens we call them side-effects. Magnesium sulphate has been given to lots of adults and children before for different reasons and has been found to be very safe. In some people having more magnesium in their body make them feel a bit warmer than normal and might make their face go a little red. We don't think this will be a problem in the project and the doctors and nurses know it might happen.

Will joining the study help me?

We cannot promise that, but if the medicine helps you get better more quickly we will be able to tell people who will be able to help other children.

Is there another sort of treatment I can have instead?

As well as having magnesium sulphate or placebo, you will also be getting other medicines called Salbutamol and Ipratropium Bromide in the nebuliser. These are

the medicines that most children will have for a bad asthma attack, and if you do not have our medicine you will still be able to have these.

Who will know that I am in the study?

The doctors and nurses who normally take care of you will know. So will the study nurse and pharmacist.

How will the information about me be kept private?

Everything you tell us is private. The only time we would ever tell somebody what you have said is if something made us worry about you. All information collected for this study will be kept safely on computers or paper records. Of course, you can tell your family and friends about the study if you want to.

We cannot promise that the project will help you, but the information we collect might help treat other young people who have problems with asthma. We hope to write about this project in special reports to let other people know what we found out.

What happens if there is a problem with the study?

If you think there are any problems with the study or if you have any worries about it you can tell your parents. You can also tell the study nurse and they will do their best to answer your questions. If you are still worried, your parents will probably be the best people to talk to.

What if I don't want to do the study anymore?

If you would like to stop at any time, just tell your parents, doctor or nurse. They will not be cross with you and will not change the way you are looked after. Your doctor will choose which treatment is best to use instead.

What will happen to the results of the study?

We will write reports for the doctors and nurses who see children with asthma problems. The results will be written in special magazines (scientific journals).

What shall I do now?

Now you have read about the study you need to think about whether you want to join in or not.

Who can I contact for more information?

If you have any questions at all, at any time, please contact <<contact details>>

Thank you for reading; we hope the information was useful

Assent Form for Children (aged 5-10): 18/01/2008, V2.0
(to be completed by the child and their parent/guardian)

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

ISRCTN81456894

Child (or if unable, parent on their behalf)/young person to circle all they agree with:

Have you read information (or had it read to you) about this project?	***Yes / No***
Has somebody else explained this project to you?	***Yes / No***
Do you understand what the project is about?	***Yes / No***
Have you asked all the questions you want?	***Yes / No***
Have you had your questions answered in a way you understand?	***Yes / No***
Do you understand it's OK to stop taking part at any time?	***Yes / No***
Are you happy to take part?	***Yes / No***

If any answers are 'no' or you **don't** want to take part, do not write your name

If you **do** want to take part, please write your name and today's date below. Your parent or guardian must also write their name here to if they are happy for you to do the project. The doctor or nurse who explained this project needs to sign as well. Thank you.

Your Name	Date	
Parent's Name	Signature	Date
Researcher	Signature	Date

When completed, 1 copy for MCRN CTU; 1 for researcher site file; 1 for patient, 1 (original) to be kept in medical notes.

Young Person (11-15) Information and Assent Form: 18/01/2008, V2.0

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

ISRCTN81456894

Information Sheet for a Young Person with a Bad Asthma Attack

We are inviting you to take part in some research. Before you decide if you want to join it's important to understand why the research is being done and what it will mean for you. Please read this leaflet carefully and if you can, talk it over with your family, or the doctor or nurse.

Please ask us if there is anything that is not clear or if you would like more information. Thank you for reading this.

Why are we doing this research?

Children and young people with bad asthma attacks are treated with a medicine called salbutamol (ventolin) mixed with ipratropium bromide (atrovent) through a nebuliser, which helps them to breathe more easily. The nebuliser is explained in more detail later.

Adding another medicine called magnesium sulphate to the salbutamol nebuliser may also help. We would like to know whether adding magnesium sulphate to the nebuliser is better that a placebo medicine. A placebo is a medicine that looks like the active medicine (in this case magnesium sulphate) but doesn't actually contain any medicine.

What is the medicine being tested?

The medicine we are testing is called magnesium sulphate. Magnesium is normally found in your body and is helpful in a number of ways. One of the ways is that it can help to relax muscle. We would like to see if the magnesium will help to relax the muscle in your airways that tightens up during an asthma attack.

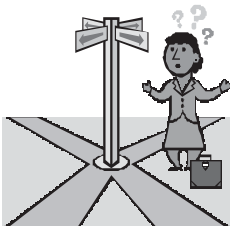
The magnesium sulphate used in this project has been especially made. Half the children will be given the magnesium and half will be given the placebo medicine. You will not be able to choose which medicine you take and will not know which medicine you are taking. Your doctor and nurse will not know which medicine you are given, but they can find out if they need to.

We would like your help with this study. You will receive nebulised salbutamol and ipratropium as usual. However instead of mixing the salbutamol and ipratropium with normal saline (salt water), in this study it may be mixed with magnesium sulphate.

Why have I been asked to take part?

You have been chosen because you are having a bad asthma attack. This project will involve around 500 children in the UK.

Do I have to take part?

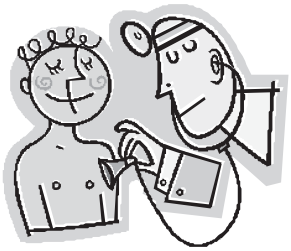


No- not at all. We only want people to take part if they would like to. If you decide not to, don't worry, it won't change how you are looked after. If you decide to take part and then change your mind, that's OK as well- you can stop at any time and don't have to say why if you don't want to.

If you agree, we will ask you to write your name on a form called an 'assent form'. This is to say you understand the project and what will happen. You will be given your own copy to keep as well.

What will happen to me if I take part?

If you take part, the magnesium sulphate or placebo medicine will be added to the nebuliser, along with the other medicines we mentioned earlier. The nebuliser is a machine that turns the medicines into a mist that you can breathe through a mask or mouthpiece. After about 20 minutes, a doctor or nurse will do a quick exam of your chest to see if you have gotten any better. You will then receive the nebuliser twice more in the same way. After the final nebuliser we will keep checking on you to see if you get better. You may keep getting other nebulisers or medicines, but these will not have the extra medicine from this project.



What will I be asked to do?

Taking part in the study is very simple. Nearly all children who come to hospital with a bad asthma attack will have medicine through a nebuliser. The only difference is that for this project, the nebuliser will have magnesium sulphate or the placebo medicine in as well. Each nebuliser will last for around 10-15 minutes.

What other treatment could I have instead?

All children who come to hospital with a bad asthma attack are treated depending on their age and how bad the attack is. If you do not take part in the study, you will get the same treatment as anyone else.

What are the side-effects of the medicines and might I have some if I take part in the research?

Other projects have shown us that magnesium sulphate is safe to have through a nebuliser. We know that when some people have extra magnesium in their body, their face may go a little bit red and feel warm. We don't expect this to be a problem for most children in this project, but if it does happen, you don't need to worry- the effect will wear off quickly.

Is there anything else to be worried about if I take part?

We don't think so. We would like you to have all three nebulisers of the project medicine even if you get a little better or a little worse. If you do not feel better after the nebulisers, you might need to have some different medicine. The doctor and nurses will decide if you need this and take good care of you.

How will the information about me be kept private?

If you decide to take part in the project, you will be given a number that tells us who you are. We will not need to use your name, and so no-one will know the information is about you. We would like to give your name to people who are helping to run the project as they will want to ask your parents some more questions, if that is OK. They would also like to send you a questionnaire about your asthma to fill in.

What are the possible benefits of taking part?

We cannot promise that the project will help you, but the information we collect might help treat other young people who have problems with asthma. We hope to write about this project in special reports to let other people know what we found out.

If you ask any questions at all, please ask <<contact details>>

Thank you for reading; we hope the information was useful

Assent Form for Children (aged 11-15): 18/01/2008, V2.0
(to be completed by the child and their parent/guardian)

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

ISRCTN81456894

Child (or if unable, parent on their behalf)/young person to circle all they agree with:

Have you read information (or had it read to you) about this project?	***Yes / No***
Has somebody else explained this project to you?	***Yes / No***
Do you understand what the project is about?	***Yes / No***
Have you asked all the questions you want?	***Yes / No***
Have you had your questions answered in a way you understand?	***Yes / No***
Do you understand it's OK to stop taking part at any time?	***Yes / No***
Are you happy to take part?	***Yes / No***

If any answers are 'no' or you **don't** want to take part, do not write your name

If you **do** want to take part, please write your name and today's date below. Your parent or guardian must also write their name here to if they are happy for you to do the project. The doctor or nurse who explained this project needs to sign as well. Thank you.

Your Name	Date	
Parent's Name	Signature	Date
Researcher	Signature	Date

When completed, 1 copy for MCRN CTU; 1 for researcher site file; 1 for patient, 1 (original) to be kept in medical notes

Appendix 9 Health economics questionnaire

MAGnesium NEbuliser Trial In Children (MAGNETIC)

MAGNETIC TRIAL NUMBER:

Relationship to patient (e.g. mother/father):

Recently you went to hospital with your child who was having problems with their asthma. During the visit to hospital you gave permission for your child to take part in the MAGNETIC study. As part of the study, we would be very grateful if you could fill in this questionnaire. Your answers are important and the information that you give us will be treated confidentially.

The questionnaire asks you to think about the health and other care your child has received since that visit to hospital. It also asks about some of the expenses you may have incurred because of your child's asthma.

Thank you for allowing your child to take part in our study. If you have any concerns about this questionnaire, please feel free to telephone Mr John Lowe on 0151 282 4522 (Monday to Friday). Please return this questionnaire to the MAGNETIC Co-ordinating Centre in the freepost envelope provided.

Section1: Costs of attending hospital with a child having problems with their asthma

The questions in this section relate **only to the day (or night)** when you went to hospital with your child who was having problems with their asthma on 05/03/2009.

1.1 What would you have been doing if you had not taken your child to hospital?

Paid employment	☐	Study time	☐
Looking after children or relatives	☐	Voluntary work	☐
Housework	☐	Sleeping	☐
Leisure activities	☐	Other	☐

If other, please specify: _____

1.2 Did anyone else, such as your partner, relatives or friends go with you to the hospital or meet you there?

No ☐ Yes ☐

If yes, what would they have been doing if they had not gone to the hospital?

Paid employment	☐	Study time	☐
Looking after children or relatives	☐	Voluntary work	☐
Housework	☐	Sleeping	☐
Leisure activities	☐	Other	☐

If other, please specify: _____

1.3 How much time did you or anyone else, such as your partner, relatives or friends spend at the hospital?

	Time spent at hospital (hours)
You	
Partner	
Relatives or friends	

1.4 Did you spend any money on travel when you went to the hospital?

No ☐ Yes ☐

If yes, please estimate the total (to and from) travel costs for yourself and your child.

	Total costs (£)
Car park fees	
Petrol/fuel costs	
Public transport fares	
Taxi fares	
Other (please specify):	

1.5 Did anyone else, such as your partner, relatives or friends, spend any money on travel to be with you and your child at the hospital?

No ☐ Yes ☐

If yes, please estimate the total (to and from) travel costs for your partner, relatives or friends.

Costs to partner (£)	**Costs to relatives/friends (£)**

Car park fees		
Petrol/fuel costs		
Public transport fares		
Taxi fares		
Other (please specify):		

1.6 Did you or anyone else, such as your partner, relatives or friends incur any other expenses because of this hospital visit?

No ☐ Yes ☐

If yes, please estimate the expenses incurred by you, your partner, relatives or friends.

Expenses incurred	**Total costs (£)**		
	Costs to you	**Costs to partner**	**Costs to relatives/ friends**
Lost pay (due to travel/attending hospital)*			
Child care costs (due to hospital visit)			
Expenses in hospital (e.g. snacks/gifts)			
Other costs (please specify): _____ _____			

*Please do not record if annual or compassionate leave was taken or the time taken off work was made up at a later point.

Section 2: Health and social care use in the last four weeks

The questions in this section relate to the **four week period** since you went to hospital with your child who was having problems with their asthma on 05/03/2009.

2.1 Please list the prescribed inhalers that your child has used to help with asthma or breathing problems since the visit to hospital four weeks ago on 05/03/2009.

Name of inhaler*	**Dose**	**Number of puffs per day**	**Number of days of inhaler use**
***EXAMPLE ONLY**: Child is given BECLOMETHASONE (100mcg) to be taken twice a day for four weeks*			
BECLOMETHASONE	100mcg	2	28
1.			
2.			
3.			

* Sometimes the name of the inhaler is written ON the inhaler. If you are unsure of the name of the inhaler, please write the colour of the inhaler instead (e.g. brown, orange, blue).

2.2 Please list any other prescribed medicines (e.g. painkillers, antibiotics or anti-inflammatory drugs) that your child has used to help with asthma or breathing problems since the visit to hospital four weeks ago on 05/03/2009:

Name of medicine/drug	**Dose**	**Tablets or liquid**	**How many times per day**	**Number of days of treatment**
***Example ONLY**: Child is given a course of AMOXYCILLIN tablets (250mg) to be taken three times a day for five days for a lower respiratory tract infection*				
AMOXYCILLIN	250mg	Tablets	3	5
1.				
2.				

3.				
4.				
5.				

2.3 Please list any medicines (e.g. painkillers, heat or massage oils, herbal or complimentary remedies) that you have bought for your child from the chemist or other shops to help with asthma or breathing problems since the visit to hospital four weeks ago on 05/03/2009:

Medicines/preparations bought	**Cost (£)**

2.4 Has your child had any contact with non-hospital health or social care professionals for advice about asthma or breathing problems since the visit to hospital four weeks ago on 05/03/2009?

No ☐ Yes ☐

If yes, please complete the following table:

Health and social care professional	**Number of contacts**	**Type of contact (e.g. surgery visit, home visit, telephone call)**	**Typical length of contact (minutes)**
Family doctor			
Nurse linked to family doctor			
Community asthma nurse			
Other (specify):_____			
Other (specify):_____			

2.5 Has your child attended a hospital outpatient department for advice about asthma or breathing problems since the hospital visit four weeks ago on 05/03/2009?

No ☐ Yes ☐

If yes, please complete the following table:

Hospital outpatient department	**Total number of visits**	**Typical length of visit (minutes)**
Accident and Emergency Department		
Children's Assessment Unit		
Other (specify):		
Other (specify):		
Other (specify):		

2.6 Did your child stay in hospital overnight because of the visit to hospital four weeks ago on 05/03/2009?

No ☐ Yes ☐

If yes, please complete the following table:

Hospital stay	**Name of hospital and ward**	**Reason for hospital stay**	**Number of nights in hospital**
Hospital visit four weeks ago ended in overnight stay			

2.7 Has your child stayed in hospital overnight because of asthma or breathing problems **since** the initial visit to hospital four weeks ago on 05/03/2009?

No ☐ Yes ☐

If yes, please complete the following table:

Hospital stay	**Name of hospital and ward**	**Reason for hospital stay**	**Number of nights in hospital**
1st hospital stay:			
2nd hospital stay:			

Section 3: Time lost from school, work and other usual activities in the last four weeks

All of the questions in this section relate to the **four week period** since you went to hospital with your child who was having problems with their asthma on 05/03/2009.

3.1 How many full days (or half days) has your child been absent from school because of asthma or breathing problems (e.g. attending hospital or seeing the family doctor) since the visit to hospital four weeks ago on 05/03/2009:

	Full days
	Half days

3.2 Have you, your partner, relatives or friends had to reduce the amount of time spent on usual activities (e.g. paid work, leisure time, studying) over the last four weeks as a result of your child's recent asthma or breathing problems?

No ☐ Yes ☐

If yes, please estimate how much time (total hours) had to be given up for each usual activity over the last four weeks as a result of your child's recent asthma or breathing problems.

Usual activity	**You (hours)**	**Your partner (hours)**	**Relatives/ friends (hours)**
Paid work			
Study time			
Caring for children/relatives			
Voluntary work			
Housework			
Sleep			
Leisure activities			
Other (please specify): _____			

Section 4: Extra costs to you, your partner, relatives or friends

The questions in this section relate to the **four week period** since you went to hospital with your child who was having problems with their asthma on 05/03/2009.

4.1 Have you, your partner, relatives or friends had to incur any other expenses because of your child's asthma or breathing problems since the day of the hospital visit four weeks ago on 05/03/2009?

No ☐ Yes ☐

If yes, please estimate the extra costs over the last four weeks.

Costs	**Extra costs over the last four weeks (£)**		
	Cost to you	**Cost to partner**	**Cost to relatives/ friends**
Costs resulting from visits to family doctor:			
Travel costs			
Lost earnings*			
Child care costs			
Other expenses			
Costs resulting from visits to hospital since 05/03/2009:			
Travel costs			
Lost earnings*			
Child care costs			
Other expenses			
Other costs:			

Help with housework			
Telephone bills			
Special equipment for child			
Other expenses			

*Please do not record if annual or compassionate leave was taken or the time taken off work was made up at a later point.

4.2 Is there anything else that you would like to tell us about the health or other care received by your child since the hospital visit four weeks ago on 05/03/2009?

No ☐ Yes ☐

If yes, please give details in the box below.

Please return this questionnaire in the envelope provided.

Thank you very much for your time and help.

Appendix 10 Protocol

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: 20 - 25 sites throughout the United Kingdom. Site details are listed in Appendix C

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.

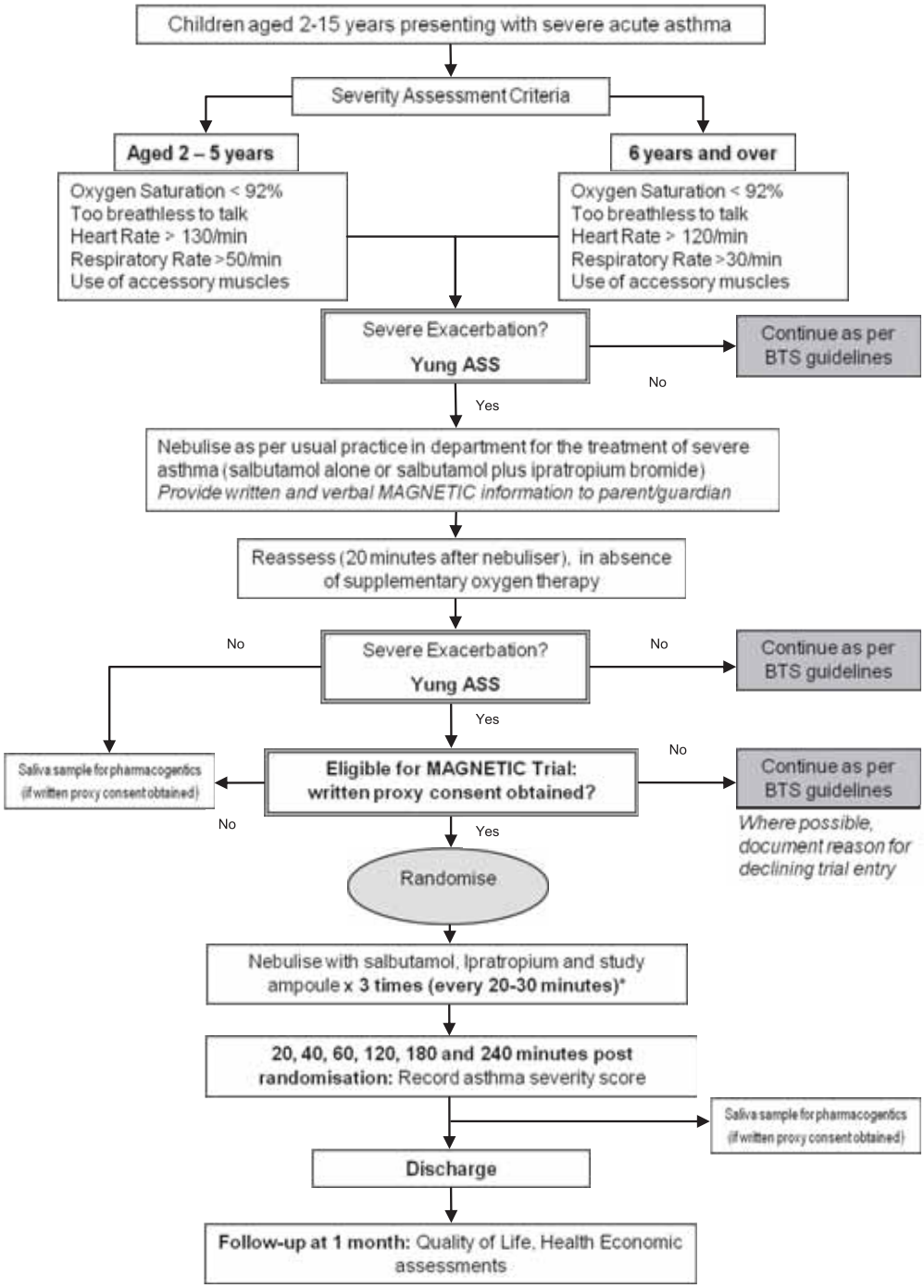
Objectives:

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™ 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)
- Collection of demographic information including:
    - Age of asthma onset
    - Use of inhaled corticosteroids, long acting beta-2 agonist and oral steroids
    - Frequency of short acting beta-2 agonist use in the last 24 hours
    - 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. 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. Two sets of kits will be available for children, one for ages 2-5 years and one for children 6 years and over. 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 Quality Control North West (QCNW), Stepping Hill Hospital, Stockport, who will provide labelled and blinded treatment kits following randomisation lists provided by the MCRN CTU. Each will contain three 5ml vials with 2.5ml magnesium sulphate solution or isotonic saline (placebo) in each vial. These will be received by the site pharmacy and dispensed in batches to the A+E department where they will be stored in a locked cabinet at <25°C. The cabinet will contain a maximum/minimum thermometer to monitor storage conditions. This should be checked daily and the results recorded on the log provided. Should the temperature fall outside of range the site will contact the CTU who will advise on the course of action. In the event a discrepancy is detected out of hours, the kits should not be used until support is available. Kits will have an expiry date of two years after manufacture. 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. 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.

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 at <25°C.

At closure of the trial, all used and unused treatment kits will be returned to the pharmacy for shipment to QCNW 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, with 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. Completion of ASS score (record time of assessment)
    b. Review of adverse events and concomitant medications
    c. Begin second nebuliser treatment (as for first dosing)

3) 40mins post randomisation:
    a. Completion of ASS score (record time of assessment)
    b. Review of adverse events and concomitant medications
    c. Begin third nebuliser treatment (as for first dosing)

4) 60mins post randomisation:
    a. Completion of ASS score (record time of assessment)
    b. Review of adverse events and concomitant medications
    c. Treat as per usual practice

5) 120mins post randomisation:
    a. Completion of ASS score (record time of assessment)
    b. Review of adverse events and concomitant medications
    c. Treat as per usual practice

6) 180mins post randomisation:
    a. Completion of ASS score (record time of assessment)
    b. Review of adverse events and concomitant medications
    c. Treat as per usual practice

7) 240mins post randomisation:
    a. Completion of ASS score (record time of assessment)
    b. Review of adverse events and concomitant medications
    c. Treat as per usual practice

8) 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

9) 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	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
Study Intervention**			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)		
Assessment of Adverse Events				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.

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 and respiratory rate 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 meter 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 and age category (age 2-5 years, 6 years and over).

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

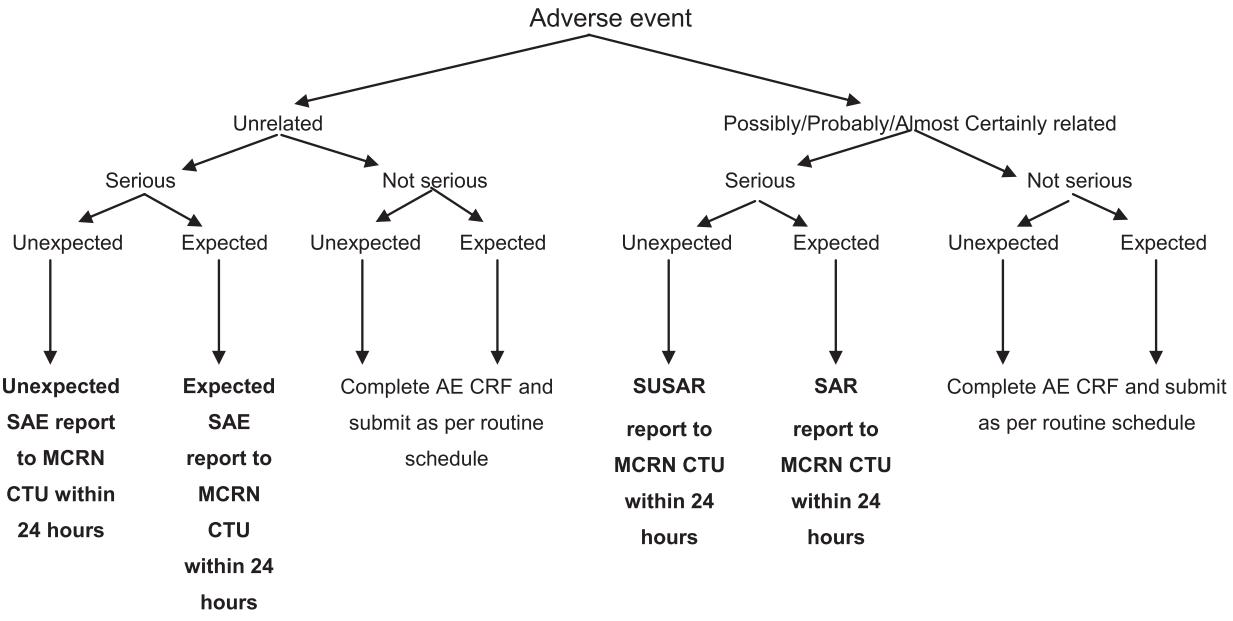
All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the MCRN CTU in the first instance. A flowchart is given below to aid in determining reporting requirements. 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) 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 and MREC. 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 and the MREC. 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 2-5 years, 6-10 years and for those aged 11-15 years and assent will be obtained when possible.

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.

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. Both 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).

These parameters will be marked Ø in the CRF. Source documents for Ø marked sections in the CRF should be identified prior to the clinical phase of the trial for each participating trial site.

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 Monitoring 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. If any such problems are identified, a photocopy of the problematic CRF(s) will be returned to the local site by post or fax for checking and confirmation or correction, as appropriate – any data which are changed should be crossed through with a single line and initialled (see section 13.3.1). The amended version should be returned to CTU and a copy retained at site. CTU will send reminders for any overdue and missing data.

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.

Weekly 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 1 (23/11/2007)

Original Approved version

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)

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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)

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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

MAGNETIC PROTOCOL – SUMMARY OF AMENDMENTS

Version 6.1 (18/01/2010)

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SAP January 27, 2011

MAGNETIC: MAGnesium NEbuliser Trial In Children

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

Statistical Analysis Plan

Contents

1. Introduction

The Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the main, pre-planned analyses for the study "MAGnesium NEbuliser Trial In Children (MAGNETIC) – A randomised, placebo controlled study of nebulised magnesium in acute severe asthma in children". This study is 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.

These planned analyses will be performed by the trial statistician. The analysis results will be described in a statistical analysis report, to be used as the basis of the primary research publications according to the study publication plan.

All analyses are performed with standard statistical software (R or SAS). More specialised software in R will be used in the joint analysis of longitudinal and time to event data The final analysis datasets, programs and outputs are archived following good clinical practice guidelines (ICH E9). The testing and validation of the statistical analysis programs will be performed following the relevant Standard Operation Procedure.

2. Design

2.1 Study design

This is a multi-centre, randomised, placebo controlled study involving 20 - 25 sites throughout the United Kingdom that plans to recruit 500 children, 250 into each of the study arms. All patients recruited into the study will have standard treatment as per BTS guidelines plus either nebulised magnesium sulphate (2.5ml of isotonic nebulised magnesium sulphate) or placebo (2.5ml of isotonic nebulised saline). Each site randomises patients to one of two treatment arms in a 1:1 ratio.

2.2 Study objectives

The main objective is to compare the asthma severity score (ASS) at an hour of children with acute severe asthma given nebulised magnesium sulphate when used as an adjunct to nebulised salbutamol and ipratropium bromide to those given nebulised salbutamol, ipratropium bromide and placebo. 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.

Secondary objectives are:
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;
b) Length of stay in hospital;
c) Patient outcomes in terms of quality of life, time off school and healthcare resource usage over the following month;
d) Parent outcomes in terms of time off work over the following month;
e) Overall cost to the NHS and society.

2.3 Primary and Secondary outcomes

Primary outcome

Asthma Severity Score (ASS) after 60 minutes of treatment.

Secondary outcomes

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™ 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)

2.4 Inclusion/exclusion criteria

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

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

2.5 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.

2.6 Recruitment

The date first patient recruited was 03/01/2009. Expected date of end of recruitment and expected date of end of follow-up will be 31/10/2010 and 31/12/2010 respectively There are 30 sites recruiting patients into the trial and the proposed recruitment targets are given in table 1.

Table 1: Planned recruitment targets at each centre

Recruiting Centre	Minimum Target Accrual per centre
Royal Devon and Exeter Hospital	20
Leicester Royal Infirmary	20
Royal Albert Edward Infirmary, Wigan	20
St Thomas' Hospital	20
Whiston Hospital	10
Blackpool Victoria Hospital	20
Countess of Chester Hospital	10
Birmingham Heartlands Hospital	20
Bristol Royal Hospital for Children	20
Birmingham Childrens Hospital	20
Royal London Hospital	20
Royal Preston Hospital	20
Derbyshire Children's Hospital	20
Wythenshawe Hospital	20
Queens Hospital, Burton on Trent	20
Ormskirk District General Hospital	10
Queens Medical Centre, Nottingham	20
Leighton Hospital Hospital	10
Sheffield Children's Hospital	20
Macclesfield District General Hospital	10
Singleton Hospital, Swansea	10

Royal Aberdeen Children's Hospital	20
Royal Hospital for Sick Children, Glasgow	20
Fairfield Genernal Hospital	20
Tameside General Hospital	10
Craigavon Area Hospital	10
North Staffordshire	20
University Hospital of Wales	20
Altnagelvin Area Hospital	10
Antrim Area Hospital	10

3. Description of study population

3.1 Representativeness of study sample and patient throughput

Details of patients assessed for eligibility, those who meet the study inclusion criteria, those who are eligible and randomised, those who are eligible but not randomised (with reasons as far as possible), those who withdraw from the study after randomisation (with reasons as far as possible) and those who are lost to follow-up (with reasons as far as possible) will be summarised in a CONSORT flow diagram. Eligible patients who are randomised will be described with respect to demographic details and history (gender, age at randomisation, age of asthma onset, current asthma medication, allergy history, previous admission for asthma, duration of the most recent asthma attack, treatment/nebulisers received pre-admission and asthma severity score (ASS), SaO2, blood pressure, respiratory rate, oxygen therapy at baseline). The number of ineligible patients randomised will be reported.

3.2 Baseline comparability of randomised groups

Patients in each treatment group (Magnesium and Placebo) will be described separately with respect to gender, age at randomisation, age of asthma onset, current asthma medication, allergy history, previous admission for asthma, duration of the most recent asthma attack, treatment/nebulisers/steroids received pre-admission and asthma severity score (ASS), SaO2, blood pressure, respiratory rate, oxygen therapy at baseline. Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted.

3.3 Follow-up assessments and losses to follow-up

The number (and percentage) of patients with scheduled follow-up assessments at 20, 40, 60, 120, 180 and 240 minutes post randomisation will be reported by treatment group. The number lost to follow-up within each treatment group will be reported and reasons where known will be documented in the CONSORT flow diagram. Any deaths and their causes will be reported. Any unblinded events will be reported. The rate of patient and parent outcome questionnaires return at one month will be reported by treatment group.

3.4 Description of compliance with therapy

In this study, treatment should be directly observed. Deviations from intended treatment (e.g. withdrawals from randomised treatment) will be summarised for each treatment group. The distribution of timing of treatment administration will be summarised by treatment groups.

4. Trial monitoring

4.1 Internal Pilot

The standard deviation that was used for the original sample size calculation will be checked after approximately 30 patients have been randomised.

The only outcome data that will be analysed within the interim analyses will be the primary outcome of the study which is defined in the protocol as the Asthma Severity Score (ASS) after 60 minutes of treatment.

This blinded internal pilot will not have any significant impact on the final analysis (Friede and Keisser 2006).

4.2 Interim Analysis Plan

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. 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

If the trial is stopped early then the analysis will contain all the patients that have been randomised up until that point. The procedures that are described in the Statistical Quality Assurance standard operating procedure will all be implemented before and after the interim analyses.

5. Unblinding of randomisation treatments

The number of patients who were unblinded will be reported for each treatment group and the reasons as to why they were unblinded will be recorded. Unblinding envelopes for the remaining patients will be checked to ensure they were not opened or tampered with.

6. Patients groups for analysis

6.1 Intention to treat (ITT) analysis of efficacy outcomes

To provide a pragmatic comparison of the policies of the different drug treatments, the principle of invention to treat, as far as is practically possible, will be the main strategy of analysis adopted for the primary end point. These analyses will be conducted on all patients who have primary outcome data, assigned to the two treatment groups Magnesium or Placebo as randomised, regardless of the study treatment or non-study treatment received. A sensitivity analysis will be applied for any missing primary outcome data (see section 7.4 below).

6.2 Analysis of safety outcomes

For the analysis of safety outcomes, all patients who have received at least one dose of the study drug and were available for follow-up will be included. Patients will be included in the treatment group they actually received.

7. Data Analysis

7.1 Analysis of primary efficacy outcome

The primary endpoint is the Asthma Severity Score (ASS) at T60.

The primary analysis will follow intention to treat (ITT) approach. The hypothesis of no difference between the two treatment arms will be tested using analysis of covariance (ANCOVA). A p-value of 0.05 (5% level) will be used to declare statistical significance and 95% confidence intervals of the estimated effects will be reported. The primary analysis using ANCOVA will not adjust for any missing data. However, reasons for missing outcome data will be reported and a sensitivity analysis will be undertaken (see Section 7.4).

The assumptions that are made when using ANCOVA (i.e. normality of ASS at treatment levels, homogeneity of variance, homogeneity of regression slopes, linear regression) will be assessed. Histogram of ASS will be plotted for checking normality and a suitable transformation (e.g. square root, log) will be considered to correct non-normally distributed data. Levene's test will be used to test the assumption of homogeneity of variance. Assumptions of linear regression (magnitude of the scatter of the points is the same throughout the length of regression line) and homogeneity of regression slopes (direction and strength of this relationship must be similar in each treatment group) will be detected by examining simple scatter plots between ASS and covariates. If unequal variances, nonlinearity and/or non-parallel slopes are present, a suitable transformation of ASS will be employed to improve the linearity and to promote equality of the variances.

Randomisation is stratified by centre, however due to the large number of small centres, centre will not be included in the model as a covariate and this is due to the fact that including a large number of small centres may lead to unreliable estimates of the treatment effect and p-values that may be too large or too small (EMEA 2003). To test the robustness of ignoring the centre effect in the primary analysis, sensitivity analyses will be performed. A GLM type II analysis will be carried out with treatment, centre, and treatment by centre interaction and baseline measurement included as covariates. Centre will be treated as both fixed and random in separate analyses to assess if there is any effect of this assumption. If the sensitivity analysis suggests the results are not robust to how centre is handled in analysis, centre characteristics (e.g. university hospital, DHS, specialist centre) will be explored further.

All longitudinal ASS data collected will be used in a secondary analysis, with a resulting increase in power. Longitudinal ASS data will be summarised by the area under the curve (AUC). The AUC is a summary measure that integrates repeated assessments of a patient's endpoint over the duration of the treatment. AUC measures preserved discriminant validity in treatment comparisons and reported more precise treatment effect estimates (Pham et al 1999, Matthews, 1990). Since the study drug is aimed to lower the ASS over 3 time intervals, AUC is the most appropriate measure for the treatment comparison.

7.2 Analysis of secondary efficacy clinical outcomes

The five clinical secondary outcomes of interest are:

- '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)

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 arms using a chi-square test. Since these are centre specific outcomes, a sensitivity analysis will be undertaken to account for centre characteristics.

The mean (standard deviation) or median (inter-quartile range) of number (frequency) of additional salbutamol administrations will be computed depending on whether it is skewed or not, and compared across treatment groups using a t-test or Mann Whitney U test.

Summaries of length of stay in hospital will be presented as means (standard deviations) or medians (inter-quartile ranges) depending on whether it is normally distributed or not, and compared across treatment groups.

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

A P-value of 0.05 (5% level) will be used to declare statistical significance and 95% confidence intervals of the estimated effects will be reported.

7.3 Analysis of secondary outcomes of Quality of Life and Health Economic measures at one month

There are four patient/parent secondary outcomes at 1 month follow-up of interest:

- Paediatric quality of life (PedsQL™ 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)

Independent-sample *t*-tests will be used to test for differences in resource use, costs, utility scores (generated by the EQ-5D multi-attribute utility measure), and QALYs between treatment groups. All statistical tests will be two-tailed and considered statistically significant at P-value<0.05.

Handling missing health economic data
The ICE command within Stata (Version 10.0) will be used to impute missing data for economic outcomes. Following the methods of Briggs et al. (2003) for handling missing data, five imputed datasets will be generated through multiple imputation using non-parametric bootstrapping (Efron and Tibshirani 1993) in Microsoft Excel (Office 2003) and the results will be combined using equations described by Briggs et al. (2003) to calculate standard errors around mean costs and effects that incorporate uncertainty around imputed values as well as sampling variation. Standard errors will be used to calculate 95% confidence intervals around total and incremental costs and QALYs based on Student's *t*-distribution.

Cost-effectiveness acceptability curves (CEACs) (Briggs and Gray 1999) showing the probability that nebulised magnesium sulphate is cost-effective relative to placebo at a range of ceiling ratios will be generated based on the proportion of bootstrap replicates (across all five imputed datasets) with positive incremental net benefits (Stinnett and Mullahy 1998). Incremental net benefit can be defined as the incremental QALY gain multiplied by the ceiling ratio minus the incremental cost (Stinnett and Mullahy 1998), where the ceiling ratio (or threshold) represents the maximum society is willing or able to pay for each additional QALY. All statements about cost-effectiveness will be

based on a £20,000 per QALY gained threshold. The probability of nebulised magnesium sulphate being less costly or more effective will be based on the proportion of bootstrap replicates that have negative incremental costs or positive incremental benefits, respectively. No discounting will be applied to costs and health effects as the time horizon for the economic evaluation will be less than one year.

A series of multi-way and probabilistic sensitivity analyses will be performed to explore the implications of uncertainty surrounding variables with a degree of uncertainty.

7.4 Analysis of missing primary outcome data

Three nebulised study treatments will be given at T0, T20 and T40. The primary analysis will be of the Asthma Severity Score (ASS) at T60. To investigate how sensitive the results of the primary analysis are to missing data a number of strategies will be used. These sensitivity analyses will involve joint modelling as well as imputing values for missing ASS at T60.

These sensitivity analyses will be carried out as secondary analyses of the study data. The results of these analyses will be compared to assess the relative effect of missing data on the conclusions of the primary analysis.

7.4.1 Description of missing data

The proportion of patients with missing outcome data will be reported by treatment arm together with reasons for missingness. .

Further descriptions of the missing outcome data will be reported in terms of:

- Differences in key baseline characteristics between treatment arms in those with observed ASS T60.

This description will be used to assess whether the patients with missing outcomes affect the randomisation balance (Wood et al, 2004).

- Differences in key baseline characteristics between patients with observed and missing ASS T60.

This description will be used to assess the plausibility of the MCAR (missing completely at random) assumption (Wood et al, 2004).

7.4.2 Imputation

If missingness is due to an administrative reason (e.g. staff involved were called to an emergency), missing ASS at T60 will not be imputed. Such values are missing for reasons unrelated to any inference we wish to draw about the intervention and hence MCAR. Otherwise, missing values will be imputed depending on the reason for the data being missing.

(1) Impute with worst-case value: If the reason for missingness is related to the patient's poor condition (e.g. death, study withdrawal due to severity by clinician), the missing ASS at T60 will be replaced by the worst possible score for the ASS. ASS is measured on a scale between 0 and 9 (where severity increases with score); hence a missing value would be replaced with a 9.

(2) Impute with best-case value: If missingness is due to study withdrawal by parent/self discharge (e.g. parent felt child was well enough to go home), the missing value is replaced by the lowest score that the patient experiences at T0, T20 and T40.

(3) Model-based imputation: If the reason for missingness is not available, missing values will be (multiply) imputed by MICE (Multivariate Imputation by Chained Equations, van Buuren and Oudshoorn, 1999) algorithm conditional on all available values at T0, T20 and T40. MICE iterates through values at each time point, modelling each conditional on the others. The imputations themselves are predicted values from a regression model, with the appropriate random error included. MICE is available as an stand alone package (WinMICE), and also in R (mice library) and SAS. Since ASS is a numerical score, imputations can be generated using predictive mean matching (pmm) method.

Both (1) and (2) are *ad hoc* approaches, so rarely lead to unbiased estimates of the treatment effects (Unnebrink and Windeler 1999; Wood et al 2004; 2005). Approach (3) is based on the MAR (missing at random) assumption (Wood et al, 2004).

7.4.3 Joint modelling

The problem of non-ignorable missing ASS data will be addressed through a more advanced analysis of joint modelling of the longitudinal data and the time to dropout from the study (Henderson et al 2000). In this analysis, patients who did not dropout from the study will be censored at the time of discharge from hospital. Dropout due to reasons related to treatment will be treated as potentially informative, and dropout due to other reasons as a censored follow-up time.

Mean profile plots will be drawn which provide a visual representation of the variation patients may experience in terms of their ASS over time. By reversing the time-axis, variation in ASS of an individual prior to informative dropout from the study will be examined.

8. Description of safety outcomes

8.1 Safety Analysis

All adverse events (AEs) and serious adverse events (SAEs) reported by the clinical investigator will be presented, identified by treatment group. AEs will be grouped according to a pre-specified AE coding system and tabulated. The number (and percentage) of patients experiencing each AE/SAE will be presented for each treatment arm categorised by severity. For each patient, only the maximum severity experienced of each type of AE will be displayed. The number (and percentage) of occurrences of each AE/SAE will also be presented for each treatment arm. No formal statistical testing will be undertaken.

Dummy AE table:

No.	Adverse Event (Expected/Unexpected)	Severity	Arm		Total number of patients
			Treatment A n (%)	Treatment B n (%)	
1	Facial flushing (E)	Mild Moderate Severe			
2	Tachycardia (U)	Mild Moderate Severe			

Dummy SAE/SUSAR table:

No.	Treatment		Description	Severity	Relationship to study drug	Expectedness	Cause	Outcome	Patient status	Unblinded
	A	B								
1										
2										

9. Reporting protocol deviations

Protocol deviations will be classified according to the following table and summarised for each treatment group. They will be compared across treatment groups and any imbalance will be investigated.

Protocol specification	Potential deviation(s)	Impact	Justification (in terms of whether bias is likely in the assessment of response,
Inclusion criteria			
For children **6 years and older** severe asthma is based on at least one of the following criteria being met: f. Oxygen saturations less than 92% while breathing room air g. Too breathless to talk h. Heart rate greater than 120 bpm i. Respiratory rate greater than 30 breaths/min j. Use of accessory neck muscles	None of the specified severe asthma criteria	Major	The severity of asthma is likely to influence response
For children aged **2-5 years of age**, severe asthma is based on at least one of the following criteria being met f. Oxygen saturations less than 92% while breathing room air g. Too breathless to talk h. Heart rate greater than 130 bpm i. Respiratory rate greater than 50 breaths/min j. Use of accessory neck muscles	None of the specified severe asthma criteria	Major	The severity of asthma is likely to influence response
Exclusion criteria			

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Patient suffering from life threatening symptoms	Patient suffering from life threatening symptoms	Major	Likely to influence response.
Patient has co-existing severe renal or liver disease	Patient has co-existing severe renal or liver disease	Major	Patient may not be able to metabolise drug effectively thus affecting response
Patient known to have had a previous reaction to magnesium	Patient known to have had a previous reaction to magnesium	Major	May affect efficacy of study drug and potentially increase incidence of adverse events
Patient known to be pregnant	Patient known to be pregnant	Major	True effect of magnesium on foetus is not known
Patient have co-existing respiratory disease (except asthma)	Patient have co-existing respiratory disease (except asthma)	Major	Co-existing disease may adversely affect efficacy of study drug
Patient been involved in a trial of a medicinal product within last three months	Patient been involved in a trial of a medicinal product within last three months	Major	Cannot be sure of effect of potential drug interactions on efficacy and/or safety of study drug
Patient previously been randomised into the MAGNETIC trial	Patient previously been randomised into the MAGNETIC trial	Minor	May affect the way of patient response in patient-reported outcomes, which may introduce bias and affect generalisability of results
Patient 16 years or over	Patient 16 years or over	Minor	Arbitrary cut-off level, no physiological reason
Treatment regime			
Allocation	Patient did not receive full trial treatment as per protocol	Major	May affect ASS and outcome data
Timing	Deviations outside acceptable timing window (T=60+15mins) without explanation	Minor	May shorten or lengthen treatment period. TMG to review cases blind to allocation to determine whether minor/major deviation.

Primary outcome data				
Assessment of ASS at T60	Deviation in the method of assessment	Major	Introduce bias in the assessment of response	
Secondary outcome data				
'Stepping down' of treatment at one hour Number and frequency of additional salbutamol administration Requirement for intravenous bronchodilator treatment Intubation and/or admission to a paediatric intensive care unit (PICU)	Deviation in the method of assessment	Major	Introduce bias in the assessment of response	
Length of stay in hospital				
Patient and parental outcomes at 1 month follow-up	If the questionnaire is returned too long after one month and we are not comident that the data relate to one month	Major	Introduce bias in the assessment of response	

10. Setting results in context of previous research

We will integrate the results of this trial within the context of an up-to-date systematic review of relevant evidence from other trials (Clarke et al 2007). We will refer the results of this trial to the latest existing systematic review of nebulised magnesium in children with asthma (currently Mohammed and Goodacre (2007)). This review concluded that further trials of nebulised magnesium sulphate in children were needed. More recent trials not included in this review will be identified and reviewed.

Acknowledgments

References

Briggs A, Clark T, Wolstenholme J, Clarke P. Missing... presumed at random: cost-analysis of incomplete data. Health Econ 2003;12(5):377-92.

Brigg A H, Gray A M. Handling uncertainty when performing economic evaluation of healthcare interventions. Health Technol Assess 1999;3(2):1-134.

Carpenter J, Kenward M: **Missing Data.** [http://www.lshtm.ac.uk/msu/missingdata/]

Clarke M, Hopewell S, Chalmers I. Reports of clinical trials should begin and end with up-to-date systematic reviews of other relevant evidence: a status report. *JRSM* 2007; 100: 187-190

Efron B, Tibshirani R. An introduction to the bootstrap. New York: Chapman and Hall, 1993.

National Institute for Health and Clinical Excellence (NICE). Guide to the methods of technology appraisal. NICE: London, 2007.

EMEA. Points to consider on adjustments for baseline covariates. The European Agency for the Evaluation of Medical Products. 2003. http://www.emea.europa.eu/pdfs/human/ewp/286399en.pdf

Friede T and Keisser M. Sample size recalculation for binary data in internal pilot study designs: A Review. Biometrical Journal 2006; 48: 537-555.

Henderson R, Diggle P, Dobson A. Joint modelling of longitudinal measurements and event time data. Biostatistics 2000; 1: 465–480.

Matthews J N S, Altman D G, Campbell M J, Royston P. Analysis of serial measurements in medical research. British Medical Journal 1990; 300 (6719): 230-235

Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis. Emergency Medicine Journal 2007;24:823-830.

Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG. (1976) Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part I: Introduction and design. British Journal of Cancer 34:585-612

Pham B, Cranney A, Boers M, Verhoeven A C, Wells G, Tugwell P. Validity of area-under-the-curve analysis to summarize effect in rheumatoid arthritis clinical trials. J. Rheumatol. 1999; 27: 712-716.

Stinnett A A, Mullahy J. Net health benefits: A new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making 1998;S65-S80.

Unnebrink K, Windeler J. Sensitivity analysis by worst and best case assessment: is it really sensitive? Drug Information Journal. 1999;33:835–39.

van Buuren S, Oudshoorn K. Flexible Multiple Imputation by MICE. Technical Report PG/VGZ/99.054, TNO Prevention and Health.1999. http://www.multiple-imputation.com/.

Wood A M, White I R, Hillsdon M, Carpenter J. Comparison of imputation and modelling methods in the analysis of a physical activity trial with missing outcomes, International Journal of Epidemiology.2005; 34. 89-99.

Wood A M; White I R; Thompson S G. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. Clinical trials. 2004;1(4):368-76.

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

SAP January 27, 2011

Appendix

Approval of MAGNETIC Protocol Deviations table

This MAGNETIC Protocol Deviations table (Version 1, 09/07/2009) has been completed and approved by the following personnel:

Trial statistician

Print Name: R Kolamunnage-Dona **Date:** 4/3/11

Signature: RKolamy

Supervising statistician (PP PRW)

Print Name: CARROL GAMBLE **Date:** 4/3/11

Signature:

Chief Investigator

Print Name: Colin Powell **Date:** 4/3/11

Signature:

Chair of Trial Steering Committee

Print Name: **Date:**

Signature:

Chair of Independent Data Safety Monitoring Committee

Print Name: D R Jones **Date:** 4 March 2011

Signature:

EME
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