MAGNESIUM TRIAL IN CHILDREN (MAGNETIC): A Randomised, Placebo Controlled Trial and Economic Evaluation of Nebulised Magnesium Sulphate in Acute Severe Asthma in Children

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

[1]School Of Medicine, Cardiff University; [2]Department of Biostatistics, University of Liverpool; [3]Liverpool Reviews and Implementation Group, University of Liverpool; [4]Warwick Medical School, University of Warwick, [5]Chidren's Hospital for Wales

Correspondence to: Dr Colin Powell, Department of Child Health, Institute of Molecular and Experimental Medicine, School of Medicine, Cardiff University, University Hospital of Wales, Cardiff, CF14 4XW; powellc7@cardiff.ac.uk

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1. no financial support for the submitted work from anyone other than their employer;
2. no financial relationships with commercial entities that might have an interest in the submitted work;
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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

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Objectives

Does the use of nebulised magnesium sulphate (MgSO4) when given as an adjunct to standard therapy in acute severe asthma in children, result in a clinical improvement when compared to standard treatment alone?

Design

Patients were randomised to receive three doses of MgSO4 or placebo, each combined with salbutamol and ipratropium bromide, for one hour. The Yung Asthma Severity Score (ASS) was measured at baseline, randomisation, and at 20, 40, 60 (T60), 120, 180 and 240 minutes following randomisation.

Setting

Emergency Departments and Children's Assessment Units at 30 hospitals in the UK

Participants

Children aged 2-15 years with a acute severe asthma

Interventions

Patients were randomised to receive nebulised salbutamol 2.5mg (aged 2-5) or 5mg (aged 6 and over) and ipratropium bromide 0.25mg mixed with either 2.5ml of isotonic MgSO4 (250mmol/L, tonicity 289 mOsm; 151mg per dose) or 2.5ml of isotonic saline on three occasions at approximately 20 minute intervals

Main outcome measures

The primary outcome measure was the ASS after one hour of treatment. Secondary measures included: 'stepping down' of treatment at one 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, time off work were collected one month after randomisation.

Results

508 children were recruited into the study; 252 received MgSO4 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 MgSO4 [0.25 (95%CI 0.02-0.48) p=0.034] and this difference was sustained up to

240 minutes (0.20 (95%CI; 0.01-0.40 p=0.042). Assessing treatment-covariate interactions there is evidence for 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 secondary outcomes measured. Adverse events were reported in 19% of children in the magnesium group and 20% in the placebo group. There were no clinically significant serious adverse events in either group. 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. 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.

Conclusion

This study supports the use of nebulised isotonic MgSO4 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. There is no harm 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.

Word count 600

List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ASS	Yung Asthma Severity Score
AUC	Area under the curve
BTS	British Thoracic Society
CAU	Children's Assessment Unit
CEA	Cost effectiveness analysis
CEACS	Cost effectiveness acceptability curves
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit (refers to MCRN CTU)
CUA	Cost utility analysis
ED	Emergency Department
FEV1	Forced Expiratory Volume in one second
GMP	Good Manufacturing Practice
GLM	Generalised linear models
GM	General paediatric ward
HDU	High dependency care
IB	Investigator's Brochure
ICER	Incremental cost effectiveness ratio
IDSMC	Independent Data and Safety Monitoring Committee
IMP	Investigational Medicinal Product
LRN	Local research networks
MCAR	Missing completely at random
MCRN CTU	Medicines for Children Clinical Trials Unit
MREC	Multi-centre Research Ethics Committee
NHS	National Health Service
PEFR	Peak Expiratory Flow Rate
PI	Principal Investigator
PIC	Patient Information and Consent form
PICU	Paediatric intensive care unit
QALY	Quality adjusted life year
QoL	Quality of life
R&D	Research & Development
RCT	Randomised controlled study
ROC	Receiver Operation Characteristics
RP	Research Practitioner
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard deviation
SMD	Standard mean difference
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

MAGNESIUM TRIAL IN CHILDREN (MAGNETIC): A Randomised, Placebo Controlled Trial and Economic Evaluation of Nebulised Magnesium Sulphate in Acute Severe Asthma in Children

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Background:

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.

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, 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 $ß_2$ 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 $ß_2$ 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.

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 magnesium sulphate. The two paediatric studies, including 62 and 20 children respectively, of nebulised magnesium sulphate demonstrated equivocal results.

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.

Objectives:

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

Methods:

Population

Children aged 2-15 years suffering from acute severe asthma exacerbations as defined by the British Thoracic Society (BTS) guidelines

Setting

Emergency Departments and Paediatric Assessment units at 30 hospitals in the UK

Inclusion criteria:

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

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

Patients were identified on presentation to Emergency Departments (ED)/Paediatric assessment units (PAU) and assessed again 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 practise) and informed proxy consent obtained following consultation with a trained member of the study team. Following the initial nebuliser, patients no long meeting one or more of the inclusion criteria were excluded.

Interventions:

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

The ASS was collected after each nebuliser (at approximately 20, 40 and 60 minutes post-randomisation), and for the following 3 hours (approximately 120, 180 and 240 minutes post-randomisation). Adverse events 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 over 5 years) were contacted to complete a set of postal questionnaires, collecting data for the quality of life and health economic measures. The 1-month follow up postal questionnaire collected QoL (PedsQL^{TM} Asthma Module and EQ-5D questionnaires) and health economics (NHS and non-NHS) data from discharge to 1-month post-randomisation.

Results: 508 children with acute severe asthma exacerbations were recruited into the study; 252 were randomised to receiving magnesium sulphate 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%CI 0.02-0.48) p=0.034] and this difference was sustained up to 240 minutes (0.20 (95%CI; 0.01-0.40 p=0.042). These differences are likely to be of minimal clinical significance. Assessing treatment-covariate interactions there is evidence for 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. Adverse events were reported in 19% of children in the magnesium group and 20% in the placebo group. There were no clinically significant serious adverse events 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 QALY gained respectively.

Conclusions There are sufficient data in this study to support the use of nebulised isotonic magnesium sulphate 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. The cost effectiveness of adding this treatment to the standard treatment regimen has been demonstrated.

Implications for health care: This is the largest study of nebulised magnesium sulphate 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 (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. The cost effectiveness of adding this treatment to the standard treatment regimen has been demonstrated.

Recommendations for research: Further studies of 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:

a) exploration of the relationship between ASS and the BTS definition of acute severe asthma

b) assessment of the value of the area under the curve analysis of ASS

c) 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.

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Contents

Chapter 1 – Introduction

1.1 Background

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 of children with asthma (Sennhauser 2005). The Department of Health has targeted respiratory disease as an area for improved management (www.dh.gov.uk). The British Thoracic Society and Scottish Intercollegiate Guideline Network (BTS/SIGN) (BTS 2011) 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 (younger than 16 years old) differs markedly from that for adults (16 years and older) 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 $ß_2$ agonists and ipratropium and systemic corticosteroids. This is similar to the initial management in adults. 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 $ß_2$ agonists. For children over 5 years of age who do not respond to initial treatment, 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 the guideline recognises that intravenous Magnesium sulphate (MgSO4) is a safe treatment for patients with acute asthma, with no side effects up to doses of 100mg/kg, it concedes that its place in management is not yet established. MgSO4 is not recommended for children aged 5 years and younger. The BTS

guidelines recommend intravenous MgSO4 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 (BTS 2011). There are no current paediatric recommendations concerning nebulised MgSO4.

There is clear evidence that MgSO4 has bronchodilator effects in acute asthma (Mohammed 2007). The BTS guidelines state that experience suggests that intravenous and the nebulised routes are both safe ways of administering MgSO4 in adults. Further trial results are awaited in adults (e.g. 3Mg study ongoing by Goodacre 2012). A single dose of intravenous MgSO4 of a dose of 1.2g - 2g 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 MgSO4 in doses of 135mg - 1152mg in combination with $ß_2$ agonists show a trend towards reduction in the number of hospital admissions and is mentioned as a possible treatment in adults (Blitz 2005, Blitz 2005). In marked contrast to the paediatric recommendations, intravenous aminophylline and intravenous $ß_2$ agonists have limited use in adults with recommendations that these interventions are reserved for ventilated patients and those *in extremis* (BTS 2011). The final recommendation from BTS/SIGN is that more studies are needed regarding the route, frequency and dose in adults for MgSO4 (BTS/SIGN 2011). The recommendations from the Cochrane review of 2005 (Blitz 2005) and the 2007 systematic review by Mohammed and Goodacre (Mohammed 2007) are that more studies are needed in both adults and children to identify exactly how MgSO4 (intravenous or inhaled) should be used.

1.2 Rationale

1.2.1 Mechanisms

The use of MgSO4 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 (BTS 2011). There are a number of proposed mechanisms for its actions. In vitro studies demonstrate an inhibitory effect of MgSO4 on contraction of bronchial smooth muscle, and the release of acetylcholine in cholinergic nerve terminals, and of histamine from mast cells (Blitz 2005). There is evidence that MgSO4 may act as an anti-inflammatory agent by inhibiting the

neutrophil respiratory burst in adults with asthma (Cairns 1996). The main effect of MgSO4 is that it blocks the calcium ion influx to the smooth muscles of the respiratory system (Gourgoulianis 2001) and bronchodilatation occurs.

1.2.2 Clinical evidence for Mg SO4 as a bronchodilator

1.2.2.1 Intravenous magnesium sulphate

The Acute Asthma and Magnesium Study Group has demonstrated the efficacy of intravenous MgSO4 in severe acute asthma in adults (Silverman 2002). In a multicentre randomised placebo controlled trial of 248 adults with acute asthma and a forced expiratory volume in one second (FEV1) below 30% predicted, intravenous administration of 2mg of MgSO4 as an adjunct to the standard therapy resulted in significant benefit in FEV1 of nearly 5%. The effect appeared greatest in those with the most severe asthma, with a difference of 10% in FEV1 between MgSO4 and placebo treated groups; thus the recommendations set out in the BTS guidelines (BTS 2011). A Cochrane review of intravenous treatment with MgSO4 (Rowe 2004) supports this evidence and recommendation. Intravenous administration of MgSO4 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 MgSO4 in acute asthma.

1.2.2.2 Nebulised magnesium sulphate

Nebulised MgSO4 does not appear to act as a bronchodilator in stable chronic asthma (Hill 1995, Zandsteeg A 2009). However, in acute exacerbations, nebulised MgSO4 appears to have a bronchodilator response of similar magnitude to salbutamol when examining subjects between the age of 12 and 60 years with moderate to severe acute asthma as defined by changes in PEFR (Mangat 1998).

Initial therapeutic trials of nebulised MgSO4 administered as an adjunct to nebulised salbutamol gave conflicting results in adults. In a small study of 35 adults, Nannini demonstrated a significantly greater improvement in peak expiratory flow (PEFR) rate at 20 minutes after administration in patients receiving nebulised MgSO4 in addition to nebulised salbutamol, compared to nebulised isotonic saline and salbutamol (Nannini Jr 2000). A report in adults with severe acute asthma with an FEV1 of less than 30% of predicted, 30

minutes after initial administration of salbutamol via a nebuliser, demonstrated a significant benefit in FEV1 for those receiving MgSO4 compared to isotonic saline (Hughes 2003). In contrast, Bessmertny could show no evidence of benefit in 74 adults with moderately severe asthma (Bessmertny 2002).

The most recent Cochrane review of nebulised MgSO4 examined only six randomised controlled trials (RCTs) involving a total of 296 patients (Blitz 2005). Four studies compared nebulised MgSO4 with β2-agonist to β2-agonist and placebo (Hughes 2003, Nannini 2000, Bessmertny 2002, Mahajan 2004) and two studies compared MgSO4 to β2-agonist alone (Mangat 1998, Meral 1996). Three of the six studies involved adults exclusively: Bessmertny 2002 (18-65 years), Hughes 2003 (16-65 years) and Nannini Jr 2000 (> 18 years). Of the remaining three studies, one included a mix of adults and paediatric patients aged 12-60 years (Mangat 1998) and there were two paediatric studies which included children from aged 5 years up to the age of 17 years (Mahajan 2004, Meral 1996).

The two paediatric studies that used nebulised MgSO4 both have methodological deficits (Meral 1996, Mahajan 2004). However, the results of the studies show that nebulised MgSO4 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 (Meral 1996). There appears to be an additive effect when inhaled MgSO4 is combined with salbutamol (Mahajan 2004).

Meral 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 either received 2 ml of MgSO4 (280 mmol/L, 258 mOsm, pH 6.7) nebulised over 15 to 20 minutes or inhaled salbutamol (NB, no salbutamol was given in the MgSO4 group). Clinical score and peak expiratory flow rate (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 (Meral 1996). This study had an unclear randomisation and blinding procedure, had a questionable outcome measure (due to the lack of reproducibility and reliability of PEFR) and unclear inclusion and exclusion criteria (Costello 2004).

Mahajan included 62 patients, aged 5-17 years with severe acute asthma, in a double blind randomised, placebo controlled trial. 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 MgSO4 (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 MgSO4 and albuterol combined (Mahajan 2004).

The overall conclusions from this review were that the use of nebulised inhaled MgSO4 in addition to ß2 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% CI: -0.03 to 0.50; 4 studies) (Blitz 2005). 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 MgSO4 treatment was safe (Blitz 2005). Thus conclusions regarding treatment with nebulised MgSO4 were difficult to draw.

Mohammed and Goodacre completed a systematic review in 2007 and they identified three more studies involving nebulised MgSO4 (Mohammed 2007). There were no new exclusively paediatric publications. There was one new adult study by Kokturk in 2005 (18-60 years) and two studies with mixed adult and older teenage adolescents: Aggarwal 2006 (13-60 years) and Drobina 2006 (12-60 years). These three studies contributed a further 236 patients bringing the overall total to 532.

Kokturk 2005 examined 26 patients (18-60 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 MgSO4 (2.5 mls of 6.3%) and salbutamol (2.5 mls) to saline as placebo and salbutamol. This small study suggested there was no benefit gained from adding MgSO4 to salbutamol in terms of PEFR or number of hospital admissions (Kokturk 2005).

Aggarwal 2006 went on to study 100 patients (13-60 year olds). The mean age of the groups studied was 46 years in the intervention group and 46 years in the control group, which would suggest the study, was unlikely to have contained many adolescents. They 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) to nebulised MgSO4 (1 ml of 500mg), three doses in one 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 showed no difference in outcomes between the two groups and concluded that there was no therapeutic benefit gained from adding MgSO4 to the standard treatment regimen (Aggarwal 2006). Drobina 2006 (published in abstract only) examined 110 patients (12-60 year olds) with mild to severe asthma, again using PEFR and admissions as the primary outcomes. The intervention group received 150 mg of MgSO4 (0.3 mls of 50% MgSO4) to each nebulised dose of medication. The control group received nebulised treatments of albuterol 0.5% (5 mg/mls) combined with 0.5 mg of ipratropium bromide 0.02% inhalation solution. This study showed no evidence of an effect of adding MgSO4 on the above outcomes (Drobina 2006).

These further three papers with 236 patients thus showed no evidence of an effect. The reviewers therefore concluded along with the other six studies that nebulised MgSO4 was associated in adolescents and adults with weak evidence of an effect upon respiratory function (SMD: 0.17; 95% CI -0.02 to 0.36; p = 0.09), and 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 (Blitz 2005). The reviewers felt able to make 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 MgSO4 to standard treatment upon 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 (Blitz 2005). Assessment of the risk of outcome reporting bias in the latest systematic review (Mohammed 2007) led to a sensitivity analysis adjusting for the suspected bias; the results suggested that the conclusions of the review were robust to this problem (Dwan 2010).

1.2.3 Risks and Benefits

1.2.3.1 Risks

All six studies reported in the Cochrane review showed no serious adverse events (SAEs) in either arm (Blitz 2005). The risk of SAEs was low in (i) the studies comparing MgSO4 to β_2-

agonists (Risk Difference (RD): 0.00; 95% CI: -0.11 to 0.11) and (ii) those comparing MgSO4 with β_2-agonist to β_2-agonist alone (RD: 0.00; 95% CI: -0.03 to 0.03). The risk of less SAEs was low and appeared to be less likely in patients treated with MgSO4 - 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 (Mohammed 2007), Aggarwal 2006 and Kokturk 2005 reported no significant adverse events, Drobina 2006 made no comment (see Appendix 1, Table 2).

A systematic review (not published) of the adverse effects of inhaled MgSO4 in children was undertaken by the University of Liverpool for this study and identified two studies (Rolla 1987, Rolla 1988), not included in the Cochrane review (Blitz 2005) containing at most 18 further children. There were no reported AEs (Table 1). These extra studies were not randomised controlled studies of MgSO4 during an acute asthma attack but they did report the effects of administering nebulised MgSO4, thus AEs could be examined (Rolla 1987, Rolla 1988).

In the MAGNET pilot study (Ashtekar 2008, EudraCT number: 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. There were seven patients randomised to active treatment and ten patients randomised to placebo. MAGNET showed there were no differences between the two groups when comparing the median asthma severity score (ASS) (Conway 1985, Bishop 1992, Yung 1996) after three nebulised treatments and the area under the curve of the ASS for the six time points (Ashtekar 2008). There were insufficient numbers to make a significant comment about the efficacy of nebulised MgSO4 from the pilot study where the main aim was to test recruitment, administration and outcome assessment feasibility.

Two children (both of whom received MgSO4) had mild AEs. 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 (Ashtekar 2008).

1.2.3.2 Benefits

As described in detail above, five studies showed a benefit to using nebulised MgSO4 in some preparation (Merel 1996, Mangat 1998, Nannini 2000, Hughes 2003, Mahajan 2004) whereas four studies showed no benefit (Bessmetry 2002, Kokturk 2005, Aggarwal 2006, Drobina 2006). There was heterogeneity between trials regarding study design, dose given, intervention comparison, primary outcomes and exclusion criteria (see Appendix 1, Tables 1-3), There was a non-statistically 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 hospitalisations were similar between the groups (RR: 0.69; 95% CI: 0.42 to 1.12; 3 studies). Subgroup analyses demonstrated statistically significant differences in lung function improvements with nebulised MgSO4 in addition to ß2-agonist in patients with severe exacerbations of their asthma (SMD: 0.55; 95% CI: 0.12 to 0.98).

However, only one study reported the effect of three doses of MgSO4 nebulised with salbutamol in patients with severe asthma. In the study reported by Hughes, three MgSO4 mixed with salbutamol nebulised treatments were given at 30 minute intervals in adults with severe asthma, and resulted in a two-fold greater increase in FEV1 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 had used nebulised ipratropium bromide as well as salbutamol as standard treatment (Drobina 2006), which is certainly the current recommendation from the BTS for children and for adults (BTS 2011).

The Liverpool University systematic review also investigated the efficacy of nebulised MgSO4 in children. The findings are summarised in Table 1.1.

Table 1.1: 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) - one transient hypotension (spontaneously resolved); no hyporeflexia	Patients treated with nebulised MgSO4 improved in terms of bronchodilation and Fischl score (Fischl 1981). 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

At the beginning of recruitment to MAGNETIC this was the current published evidence. We are currently completing a further update of the Cochrane review (Blitz 2005) using the Cochrane review methodology (Powell 2012) and this will be published in the near future. 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 MgSO4 and 399 who were controls in studies). The seven studies published since Mohammed 2007 or earlier studies not included in Mohammed's systematic review are: three studies involving adults exclusively (Abreu-Gonzalez 2002, Gaur 2008, Gallegos-Solórzano 2010); one study including adults and pediatric patients (Neki 2006); two studies that enrolled pediatric patients (Ashtekar 2008, Khashabi 2008) and, in the remaining study, the age of participants was not stated (Dadhich 2005). The data from these studies will be discussed in Chapter 5 of this report. The features of these 16 studies are presented in Appendix 1 in three tables but they are clearly heterogeneous in study design, population examined, intervention administered and outcomes measured.

Thus there is a need for a large study examining the addition of nebulised MgSO4 in children with acute severe asthma compared to standard treatment in a placebo controlled double blind randomised manner. MAGNETIC is a randomised placebo controlled multicentre trial of the use of nebulised MgSO4 in severe acute asthma in childhood in patients who show a poor response to maximal conventional aerosol treatment.

1.3 Objective

1.3.1 Primary objective

Does nebulised MgSO4 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?

1.3.2 Secondary objectives

Does nebulised MgSO4 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) Costs and cost-effectiveness for the NHS and personal social services and, more broadly, for society.

Chapter 2 - Methods

2.1 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 when compared to standard treatment alone.

2.2 Design

This was designed as a prospective, controlled, double-blind, multicentre, randomised controlled trial comparing the effects of nebulised MgSO4 versus placebo for children presenting to secondary care with an acute severe asthma exacerbation.

2.3 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 Medicines for Children Research Network 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:

2.3.1 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 (BTS 2011). 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 (BTS 2011).

For children **6 years and older** severe acute 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 beats per minute (bpm)
d) Respiratory rate greater than 30 breaths per minute
e) Use of accessory neck muscles

For children aged **2-5 years of age**, severe acute 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 per minute
e) Use of accessory neck muscles

2.3.2 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 to be pregnant
e) Known to have had a reaction to magnesium previously
f) Parents who are unable or unavailable 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

2.4 Interventions

Patients were 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 MgSO4 (250mmol/L, tonicity 289 mOsm; 151mg per dose) or 2.5ml of isotonic saline on three occasions at approximately 20 minute intervals. There is currently no specific agreed dose of MgSO4 for use in children (Mohammed 2007). The MgS04 dose for this study was chosen based on the doses described in the published paper by Hughes in 2003 as they were shown to be effective and safe in acute asthma in an adult population (Hughes 2003). The magnesium solution needs to be isotonic as hypertonic and hypotonic solutions may cause bronchoconstriction (Hughes 2003). The doses used in the published paediatric studies were both isotonic [Meral 1996; 2 mls of isotonic MgS04 (280 mmol/L, tonicity 258 mOsm; 116 mg/dose) and Mahajan 2004; 2.5 mls of isotonic (6.3%) MgS04; 145mg/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 (BTS 2011) with the MgSO4 or placebo added. Use of various doses is described in the clinical effectiveness literature (see Appendix 1 and Chapter 5 discussion).

2.5 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 (BTS 2011), the Yung Asthma Severity Score (ASS) was recorded (Yung 1996). 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 (BTS 2011) were met and informed consent had been obtained from the parent and if appropriate assent from the child.

Patients were randomised to receive either 2.5ml of isotonic MgSO4 (250mmol/L, tonicity 289 mOsm; 151mg per dose) or 2.5ml of isotonic saline via nebuliser on three occasions at approximately 20 minute intervals. Each nebuliser also contained salbutamol 2.5mg (children aged 2-5 years) or 5mg (children aged 6 years and over) and ipratropium bromide 0.25mg 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 1st treatment nebuliser), 40 (T40, after 2nd treatment nebuliser), 60 (T60, after 3rd treatment nebuliser), 120, 180 and 240 minutes post-randomisation. Adverse events, 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 5 and over) were contacted by the research team and asked to complete postal questionnaires one month after their hospital visit in order to collect health related quality of life (QoL) and health economics data. The schedule of study procedures is shown in Table 2.1 below.

Table 2.1: Schedule of study procedures

Procedures		Screening	Randomisation*	20 minutes post Randomisation	40 minutes post Randomisation	60 minutes post Randomisation	120 minutes post Randomisation	180 minutes post Randomisation	240 minutes post Randomisation	During Admission	Before discharge	1 month follow-up	Premature Discontinuation
Signed consent form			X										
Assessment of eligibility criteria		X	X										
Yung Asthma Severity Score (ASS)		X	X	X	X	X	X	X	X				
Assignment to study treatment			X										
Review of medical history		X	X										
Review of concomitant medications		X	X	X	X	X	X	X	X	X	X		X
Study intervention**			X	X	X								
Blood pressure, SaO_2, respiration rate		X	X	X	X	X	X	X	X				
PedsQL™ Asthma Module												X	
EQ-5D												X	
Health economics questionnaires												X	
Physical exam	Complete	X											X
	Symptom-directed		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		
Assessment of adverse events				X	X	X	X	X	X	X	X		X

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

2.6 Procedures for assessment

2.6.1 Efficacy

Asthma severity was assessed using a validated score, the Yung Asthma Severity Score (ASS) (Conway 1985, Bishop 1992, Yung 1996) which comprises three clinical signs: wheezing, accessory muscle use and heart rate. Each component has a minimal score of zero and a maximum of three. The total score is a sum of each component, giving a minimum score of zero and a maximum of nine. 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 (Bishop 1992) with good inter-observer agreement and correlates well with oxygen saturation and FEV_1 (Yung 1996). 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.

2.6.2 Safety

Patient status was monitored for four 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 – e.g. facial flushing. Adverse events were followed up until discharge from hospital.

2.6.3 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 (PedsQL^{TM} Asthma Module and EQ-5D questionnaires) and health economics (NHS and non-NHS) data from discharge to 1-month post-randomisation (see Appendix 2 and Appendix 9).

2.7 Outcomes

The choice of a primary outcome in acute asthma studies is variable and many (Rafai 2012). There are no agreed core outcomes for use in acute asthma studies both in adult and paediatric studies and so there is huge variation in primary and secondary outcomes reported (Blitz 2005, Mohammed 2007). In the nebulised MgSO4 literature there are numerous variable outcomes (see Appendix 1, Table 2) reported. Measuring lung function in children during an acute attack or those who have never had their lung function measured previously is too unreliable to use accurately (Gorelick 2004). Thus an asthma severity score 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 twenty asthma severity scores (van der Windt 1994, Birken 2004, Rafai 2012) all with different qualities. We chose the most validated and easiest to use, the Yung ASS (Yung 1996). The choice of the ASS is discussed further in Chapter 5. As there was evidence that the response to inhaled MgSO4 is within the first hour of treatment (Merel 1996, Blitz 2005, Goodacre 2007), 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 which we collected based on the most common secondary outcomes measured in acute asthma studies (Rafai 2012). 'Stepping down' of treatment at one hour describes the decision to change from nebulisers to spacers, a proxy for the treating clinician making a judgment that the child is getting better having presented with severe exacerbation. In a study of 36 emergency departments 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 one hour after treatment was started, thus potentially able to change from nebulisers to spacers (Kelly 2004).

2.7.1 Primary outcome

The primary endpoint was the Asthma Severity Score (ASS) after 60 minutes of treatment. It was defined as ASS at T60.

2.7.2 Secondary outcomes

Clinical (during hospitalisation)

- 'stepping down' of treatment at one hour

  (The 'stepping down' of treatment at one hour is defined by the change to MDI/ spacer combination only or no further treatment until discharge)
- 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 (one 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 for the child
- Health care resource usage (e.g. GP visits, additional prescribing)
- Time off work (related to child's illness)

2.8 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 (Yung 1996). The SD was estimated from the Cardiff pilot study (EudraCT number: 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 nine. A difference of 0.5 was deemed by the research and trial management group 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 one hour of treatment from 50% to 63% with 80% power at a 5% significance level. Sample size calculations were undertaken using NQuery Advisor software: version 4.0 (Elashoff J. D. nQuery Advisor

Version 4.0 User's Guide. Statistical Solutions, 2000. Los Angeles, CA; http://statistical-solutions-software.com/wp-content/uploads/nQ70_version2_manual.pdf).

2.9 Randomisation and blinding

Randomisation lists were generated in STATA Statistical Software: Release 9 (StataCorp. 2005. College Station, TX: StataCorp LP) 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 2.5ml $MgSO_4$ or placebo, manufactured and quality controlled and QP released by St Mary's Pharmaceutical Unit, Cardiff, UK [MA (IMP) 35929]. Centres used their own stock of salbutamol and ipratropium bromide.

2.10 Data management

The data were recorded on standardised CRFs designed collaboratively by the Trial Management Group (TMG). These were returned to the MCRN CTU and the data entered onto a validated electronic study database (Infer Med Macro 2008) 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, 'length of stay', 'admission to paediatric intensive care unit (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 data as possible were collected about the reasons for missing data.

2.11 Statistical methods

2.11.1 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 standard deviation 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.

2.11.2 Interim analysis

In order to estimate the effect of nebulised MgSO4 for the primary efficacy outcome, a single interim analysis adopting the Haybittle-Peto (Peto 1976) 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.

2.11.3 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) (SAS 2011), 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 (http://cran.r-project.org/). The software for joint modelling (JoineR library) 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 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 (IQR: inter quartile range) depending on the degree of skewness, and categorical variables presented in terms of numbers (%) per category. The intention to treat 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 standard deviations 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 (Appendix 5). The Chief Investigator (CI) classified the information on the reason for missing ASS data, 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 (Appendix 5) to assess whether missingness affects the randomisation balance and plausibility of the MCAR (missing completely at random) assumption respectively. Sensitivity analysis was also performed to examine a centre effect Appendix 6).

All continuous secondary outcomes which 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-square test.

The CI 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 one hour, and AEs and SAEs, blind to treatment group allocation. A statistical test comparing the % 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.

2.11.4 Protocol amendments

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

2.12 Health economics analysis plan

The economic evaluation aimed to assess the cost effectiveness of nebulised magnesium sulphate 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 quality of life (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 focussed on the short and medium-term costs and consequences of nebulised magnesium sulphate 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 magnesium sulphate.

The primary analysis (base-case) took the perspective of the NHS and Personal Social Services (NICE, 2008) 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 while the second comprised a cost-utility analysis (CUA) calculating the incremental cost per quality adjusted life year (QALY) gained through treatment.

2.12.1 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 (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 whilst 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 readmissions (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 data base with in-built safeguards against inconsistent entries and then verified by dual coding.

2.12.2 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 employed followed recent guidelines on costing health and social care services as part of an economic evaluation (Drummond 2005, NICE 2008). 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 (Curtis 2010). Some costs were valued using the NHS Reference Costs (2009-10), a catalogue of costs compiled by the Department of Health in England (Department of Health 2010). Drug costs were obtained from the British National Formulary (BNF 2010). 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). 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 earning were not valued if annual or compassionate leave was taken as a result of the child's health state. All costs were expressed in pound sterling and valued at 2009-2010 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.

2.12.3 Calculation of utilities and quality adjusted life years

Parents of children aged ≥5 years were asked to describe their children's QoL at one month after participation in the MAGNETIC trial using the proxy version of the EuroQol EQ-5D instrument (Kind 1999). The EQ-5D is the generic, multi-attribute, preference based measure preferred by NICE for broader cost effectiveness comparative purposes (NICE 2008). The EQ-5D consists of two principal measurement components. The first is a descriptive system, which defines health-related quality of life 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 one month for each child (Dolan 1995). 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 (Dolan 1995). Resulting utility scores range from scores -0.59 to 1.0, with zero representing death and one representing full health. Utilities values below zero 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 zero (worst imaginable health state), was not included in MAGNETIC.

There is limited evidence of the psychometric properties of the EQ-5D in young children (Petrou 2003). Consequently, analyses were conducted to 'map' or 'cross-walk' responses to the Pediatric Quality of Life Inventory™ (PedsQL) Asthma Module onto EQ-5D utility scores. These mapping models were developed on the basis of data collected for 5-16 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 2-4 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 (Brazier 2010, Longworth 2011).

Model 1: Ordinary Least Squares (OLS) 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: OLS using the PedsQL Sub-scales

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 sub-scales; 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 sub-scales 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 sub-scale 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 sub-scale 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 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 (http://www.pedsql.org).

Model 3: OLS using the PedsQL Sub-scales 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 sub-scale scores, squared sub-scale scores and interaction terms derived using the product of sub-scale scores. The dependent variable (EQ-5D utility

score) was measured on its natural scale and the PedsQL sub-scale scores were measured on a (0-100) scale. The model was defined as:

$$y_i = \alpha + \beta x_{ij} + \theta r_{ij} + \delta z_{ij} + \varepsilon_{ij}$$

Where i = 1,2,..., n represents individual respondents and j = 1,2,..., 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 which 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 2-4 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 (MSE) (a recommended measure of predictive ability) was calculated for each model (Brazier 2010).

Baseline utility data was 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. In order 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 onto EQ-5D health states from which baseline utility scores were estimated. In the base-case analysis, ASS scores of 1-3 were mapped onto an EQ-5D health state of 11111; ASS scores of 4-6 were mapped onto an EQ-5D health state of 22222; and ASS scores of 7-9 were mapped onto 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 one 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, whilst 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.

2.12.4 Missing data

Multiple imputation was used to impute missing data and avoid biases associated with complete case analysis (Briggs 2003). Missing data was a particular issue for costs and utility scores collected at the 1-month follow-up. The MICE algorithm within R statistical software version 2.13 (R Development Core Team; http://cran.r-project.org) 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 was 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 datasets were generated.

2.12.5 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 cost-utility analysis (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 less than 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 datasets generated through multiple imputation were bootstrapped separately in Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA) and the results were subsequently combined (Briggs 2003) to calculate standard errors around mean costs and effects that incorporate uncertainty around imputed values as well as sampling variation. Standard errors were used to calculate 95% confidence 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 datasets) with positive incremental net benefits (Briggs 1999; Stinnett and Mullahy, 1998). 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 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) 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) 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 onto EQ-5D health states with lower utility scores than in the baseline analysis (ASS scores of 1-3 mapped onto an EQ-5D health state of 11222; ASS scores of 4-6 mapped onto an EQ-5D health state of 22333; and ASS scores of 7-9 were mapped onto an EQ-5D health state of 33333); 4) assuming baseline ASS mapped onto EQ-5D health states with higher utility scores than in the baseline analysis (ASS of 1-3 mapped onto an EQ-5D health state of 11111; ASS of 4-6 mapped onto an EQ-5D health state of 22111; and ASS of 7-9 were mapped onto 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

3.1 Participant flow and recruitment

Five hundred and eight children were randomised from 30 centres UK-wide (1 centre in Wales, 2 in Scotland, 2 in Northern Ireland, 25 in England).

The first child was recruited on 14/12/2008 and the last child was randomised on 21/03/2011. Table 3.1 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; Morriston Hospital, Swansea; Royal Hospital for Sick Children Belfast) but did not randomise any children.

3.1.1 Screening data

Sites were requested to prospectively record each potentially eligible child on a screening log, and return this to the CTU on a monthly basis. The log recorded the time and date of presentation, whether the child was screened, eligible, and whether they were 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 where the logs were received, they were often sent sporadically and were poorly completed, not recording children who were missed for trial eligibility assessment.

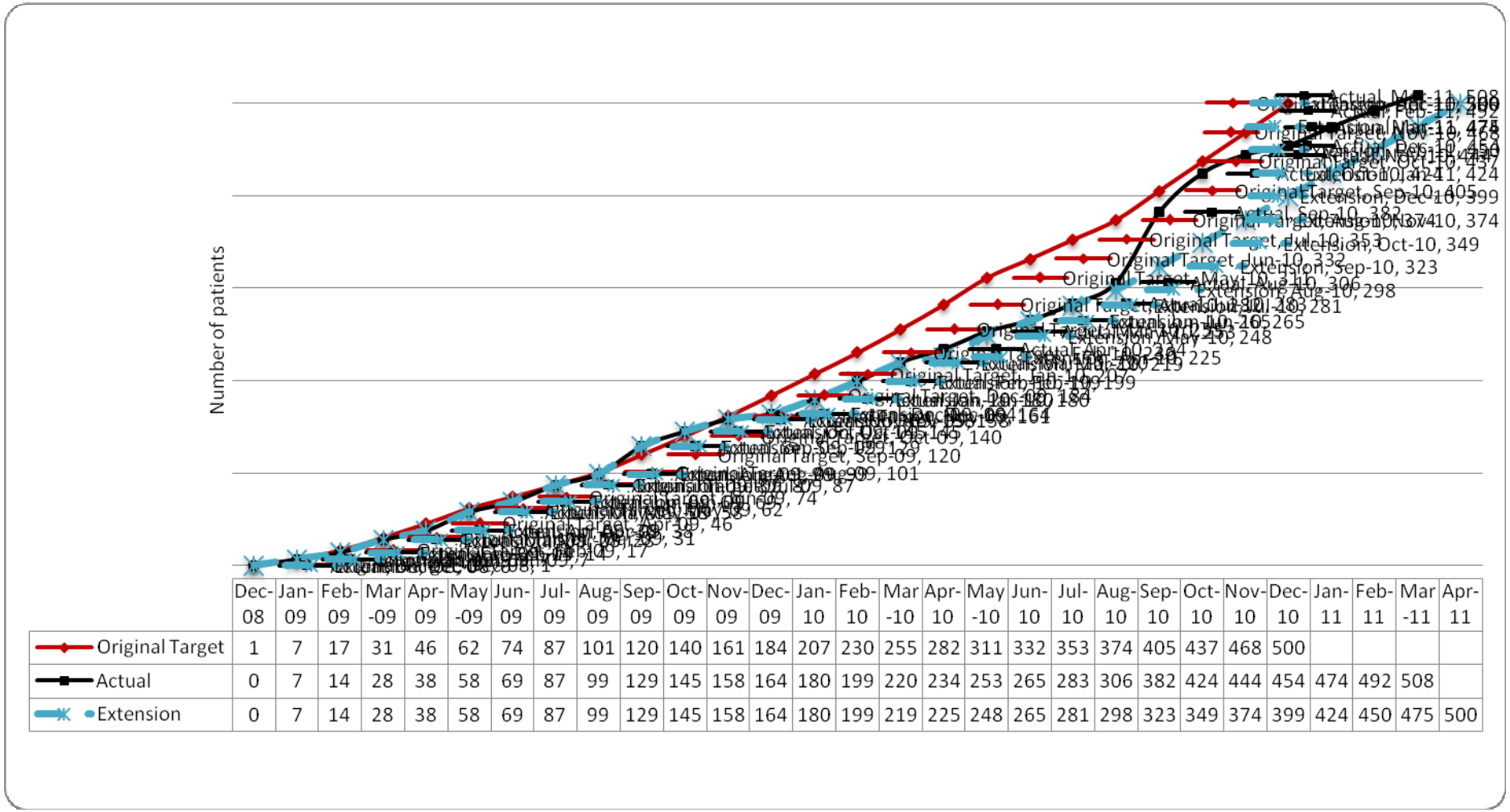
Efforts were regularly made to encourage return (supported on one occasion by the MRCN LRNs), as screening information was the primary way to objectively assess barriers to recruitment in under-performing sites. Another option given was to record the information retrospectively by review of departmental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

3.1.2 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 3.1 below), 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, GCP 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 five months in August 2010 and recruitment rates improved following intervention of the MCRN Local Research Networks 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.

Figure 3.1: Expected versus actual recruitment rates



	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

TABLE 3.1: Recruitment by centre

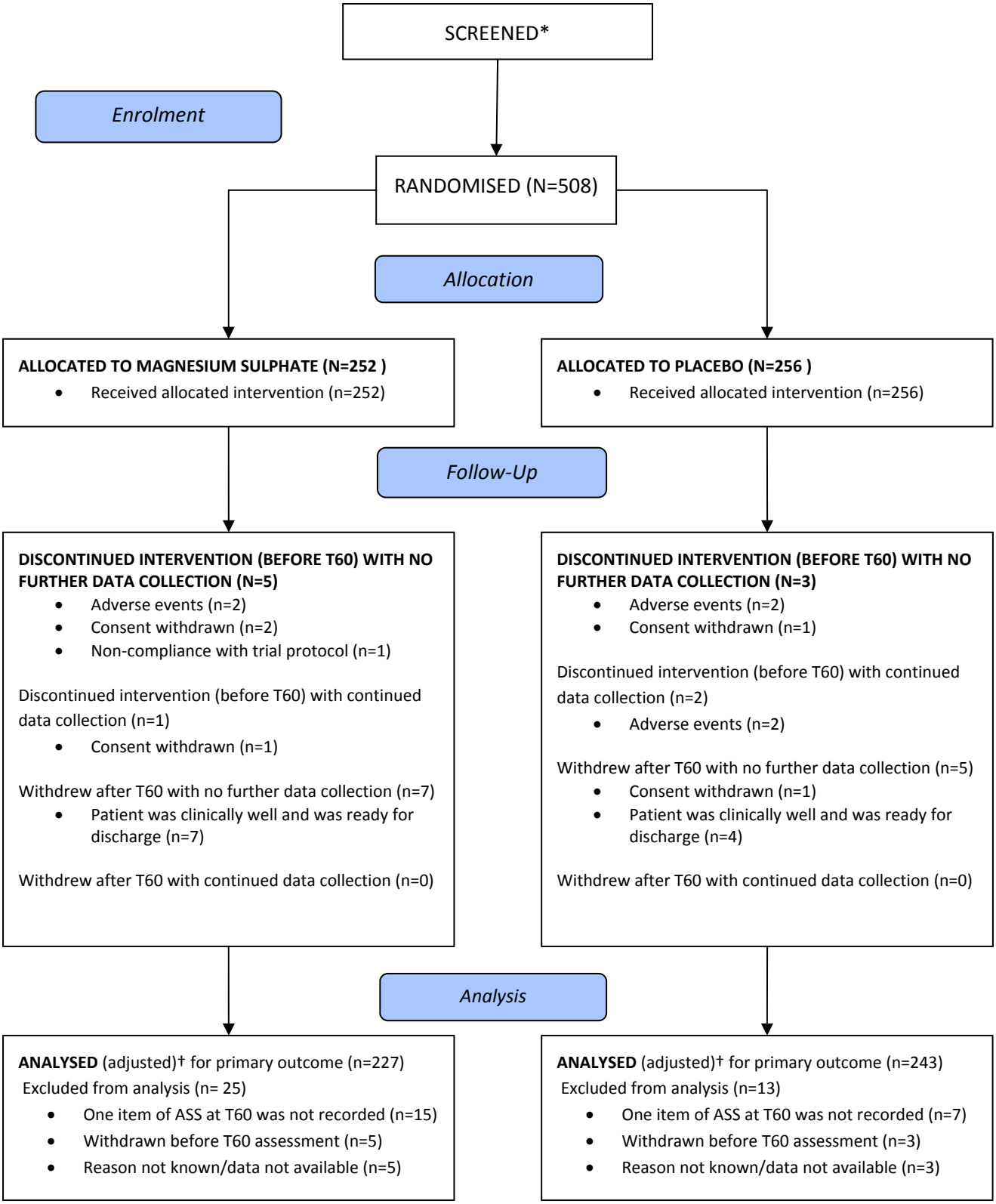
Centre	Date site initiated	Target recruitment	Number randomised	Date of first randomisation	Date of final randomisation
St Thomas Hospital	04/12/2008	30	26	02/01/2009	17/03/2011
Royal Devon and Exeter Hospital	04/12/2008	30	33	05/01/2009	20/03/2011
Derbyshire Children's Hospital	17/12/2008	20	21	20/02/2009	17/01/2011
Tameside General Hospital	17/12/2008	10	3	14/01/2009	27/10/2009
Leicester Royal Infirmary	09/01/2009	20	20	23/07/2009	08/07/2010
Royal Albert Edward Infirmary, Wigan	09/01/2009	18	20	02/03/2009	25/02/2011
Queens Hospital, Burton	09/01/2009	20	21	13/02/2009	14/11/2010
University Hospital of Wales	09/01/2009	25	31	05/02/2009	18/01/2011
Royal London Hospital	09/01/2009	12	11	02/04/2009	21/11/2010
Countess of Chester Hospital	21/01/2009	16	26	30/07/2009	15/03/2011
Macclesfield District General Hospital	21/01/2009	25	28	17/02/2009	05/03/2011
Royal Hospital for Sick Children, Glasgow	29/01/2009	30	22	14/04/2009	21/12/2010
Sheffield Children's Hospital	29/01/2009	20	14	28/05/2009	19/11/2010
Preston Royal Infirmary	29/01/2009	14	12	04/08/2009	06/02/2011
Bristol Royal Children's Hospital	16/04/2009	30	37	27/04/2009	15/03/2011
QMC Nottingham	06/05/2009	20	20	29/06/2009	22/11/2010
Victoria Hospital Blackpool	06/05/2009	17	7	26/06/2009	01/02/2011
Ormskirk and District Hospital	12/05/2009	20	30	05/06/2009	09/06/2011
Wythenshawe Hospital	16/09/2009	10	3	15/12/2009	06/12/2010
Birmingham Children's Hospital	02/10/2009	15	14	28/11/2009	23/02/2011
University Hospital of North Staffordshire	03/11/2009	18	19	28/01/2010	09/02/2011
Craigavon Area Hospital	14/11/2009	13	9	29/01/2010	24/01/2011
Birmingham Heartlands Hospital	18/01/2010	15	4	28/03/2010	11/05/2010
Royal Aberdeen Children's Hospital	01/04/2010	16	11	08/06/2010	27/01/2011
University Hospital North Tees	30/04/2010	18	17	22/05/2010	06/03/2011
University Hospital Lewisham	30/04/2010	15	14	30/05/2010	07/03/2011
Altnagelvin Area Hospital	09/06/2010	10	14	15/08/2010	02/02/2011
Southampton General Hospital	02/07/2010	10	6	29/07/2010	14/10/2010
Royal Manchester Children's Hospital	23/08/2010	10	10	27/08/2010	28/01/2011
Royal Cornwall Hospital	07/12/2010	8	5	09/02/2011	16/03/2011

3.1.3 The flow of children

The flow of children through the trial is represented in the CONSORT flow diagram in Figure 3.2. Five hundred and eight (508) children were randomised; 339 patients from Emergency Departments; 169 from Paediatric Assessment Units; 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, ten 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.

Figure 3.2: Consort flow diagram



*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.

† Analysed unadjusted for baseline ASS

3.2 Baseline comparability of randomised groups

Table 3.2 shows that the baseline characteristics of the 508 randomised participants were comparable, 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 of 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 9am and 5pm. 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.

Table 3.2: Baseline characteristics of the study population

Baseline Characteristic	Magnesium (n=252)	Placebo (n=256)	Total (n=508)
Age (in 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 of asthma onset (years)	(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 24hrs	162 (64)	162 (64)	324 (64)
For the last 6hrs or less	35 (14)	38 (15)	73 (15)
Current asthma medication, n(%) (can be more than one)			
Undiagnosed	79	76	155
Diagnosed	173	180	353
None	7 (2)	1 (0)	8 (1)
Short acting beta-2-agonists	196 (51)	207 (53)	403 (52)
Inhaled corticosteroids	106 (28)	109 (28)	215 (28)
Long acting beta-2 agonists	11 (3)	19 (5)	30 (4)
LABA/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*	8 (2)	7 (2)	15 (2)
Nothing ticked (V1 CRF) **	5 (1)	6 (1)	11 (1)

Allergy history, n(%) (can be more than one)			
None/Nothing ticked	118 (40)	123 (39)	241 (39)
Hayfever	38 (13)	61 (19)	99 (16)
Eczema	97 (33)	91 (29)	188 (31)
Food allergy	41 (14)	42 (13)	83 (14)
Treatment received pre-admission			
Steroids only	21 (8)	25 (10)	46 (9)
Nebulisers only	68 (27)	72 (28)	140 (27)
Both steroids & nebulisers	47 (19)	55 (21)	102 (20)
Yes, but neither steroids or 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			
salbutamol+ipratropium	106 (42)	101 (40)	207 (41)
not given	144 (58)	150 (59)	294 (58)
	0 (0)	3 (1)	3 (1)
SaO2, Mean(SD), range	(n=250) 93.8 (3.5), 84-100	(n=253) 93.4 (3.4), 81-100	(n=503) 93.6 (3.4), 81-100
Blood pressure, Mean(SD), range			
Systolic	(n=210) 109.5 (14.1), 62-163	(n=211) 112.7 (12.5), 70-172	(n=421) 111.1 (13.4), 62-172
Diastolic	(n=210) 65.5 (11.6), 30-105	(n=211) 66.3 (12.7), 34-123	(n=421) 65.9 (12.2), 30-123
Respiratory rate, Mean(SD), range	(n=247) 43.2 (10.5), 20-72	(n=250) 42.5 (10.9), 20-70	(n=497) 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)

* Other drugs: Ipratroprium Bromide, Desloratadine, Cetrizine, Erythromicin, Sodium Cromoglycate

**Version 1 of the CRF did not include a category 'None' and only listed the various medications

3.3 Timing of treatment administration

Each child was 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. 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.

Table 3.3 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 one 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 1st and 3rd treatments should be 40 minutes but an allowance of an additional 15 minutes would be tolerable. Therefore if the above timing was greater than 55 minutes, this was defined as a deviation outside the acceptable window (Table 3.4). There were 53 children who received their third treatment more than 55 minutes after randomisation. Note that this is a change to the proposed deviation outlined in the SAP, and was made prior to un-blinding and any comparative analysis (see Appendix 3 for more details).

Table 3.3: Treatment details for ALL randomised children

	Magnesium Prescribed Time (min)			Placebo Prescribed Time (min)			Total Prescribed Time (min)		
	First*	**Second****	**Third*****	**First***	**Second****	**Third*****	**First***	**Second****	**Third*****
Number treated	252	248	246	255	252	250	507	500	496
Timing of treatment Mean (SD) Range	5.3 (8.4) 0-65	23.6 (5.9) 10-65	23.7 (6.8) 10-65	6.4 (8.1) 0-40	23.1 (5.1) 5-40	23.0 (5.5) 14-60	5.8 (8.3) 0-65	23.4 (5.5) 5-65	23.3 (6.2) 10-65

* Time from randomisation to prescription of first nebulised treatment

** Time from prescription of first treatment to prescription of second treatment

*** Time from prescription of second treatment to prescription of third treatment

3.4 Un-blinding of randomised treatments

The treatment allocation for two children was un-blinded during the course of the trial (one in the magnesium group and one in the placebo group, Table 3.12). One child (magnesium group) was un-blinded 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 un-blinded after resolution of a SAE as parents wished to be notified of their child's treatment allocation.

3.5 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 3.4 and summarised for each treatment group. There is no imbalance across treatment groups.

Table 3.4 Protocol Deviations (post randomisation)

Protocol specification	Number of deviations (%)	
	Magnesium	Placebo
Inclusion criteria Two children aged 15 and 23 months were recruited	0*	2 (1%)
Exclusion criteria One child was recruited twice	0*	2 (1%)
Treatment regime		
Allocation (Did not receive full trial treatment as per protocol)	7 (3%)	12 (5%)
Timing ** (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

* Data not available for one child

** Where the child has received <3 treatments, they were not included and hence not included in the denominator when looking at rates

3.6 Internal pilot and interim analysis

To ensure the appropriateness of the standard deviation (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 standard deviation estimated from a sample of 26 patients with complete ASS data at T60 (ranging from 2 to 7) was 1.4. Since there were ten patients with missing ASS at T60, and these could plausibly include both extremes of the possible ASS range (0 to 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 who did have ASS at T60, 25 had T40 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 the missing observations would have a substantial impact on the standard deviation 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.

Further a blinded interim analysis was undertaken after 262 children had been randomised. ANCOVA adjusted for baseline ASS and an independent samples t-test were performed, and the mean differences and 99.9% confidence intervals were reported in the closed section of the IDSMC report; blinded results as presented to the IDSMC are shown in Table 3.5.

Table 3.5 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* (-0.922, 0.308)	-0.356 (-0.923, 0.211)

*Treatment difference < 0 favours treatment

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.

3.7 Analysis of primary outcome

The results for the final analysis of the primary outcome are presented in Table 3.6. 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, -0.02) 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.

Table 3.6: Primary outcome results

	Magnesium n_m=228	Placebo n_p=244	Estimate (95% CI), p-value	
	T60 mean (sd), range	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

Key baseline characteristics for those with observed ASS at T60 are presented in Appendix 5 Table C-1, 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 (Appendix 5, Table C-2), indicating plausibility of the MCAR (missing completely at random) assumption.

The reasons for missing primary outcome data are provided in Appendix 5 (Section C.1) with the results of the sensitivity analyses (Section C.2). The problem of non-ignorable missing ASS data is addressed through joint modelling of the longitudinal data and the time to dropout from the study (Appendix 5, Section C.2.3). 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.

3.8 Analysis of secondary outcomes

3.8.1 Area under the curve (AUC) for ASS over three time intervals

The results for the area under the curve (AUC) analysis for ASS at 20, 40 and 60 minutes are presented in Table 3.7. Figure 3.3 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) lower in the magnesium group. However, the difference between the treatment groups was not statistically significant.

Table 3.7: Area Under the Curve for primary outcome

	Magnesium	Placebo	Estimate (95% CI), p-value
	AUC mean (sd), range	AUC mean (sd), range	Difference in Mean
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

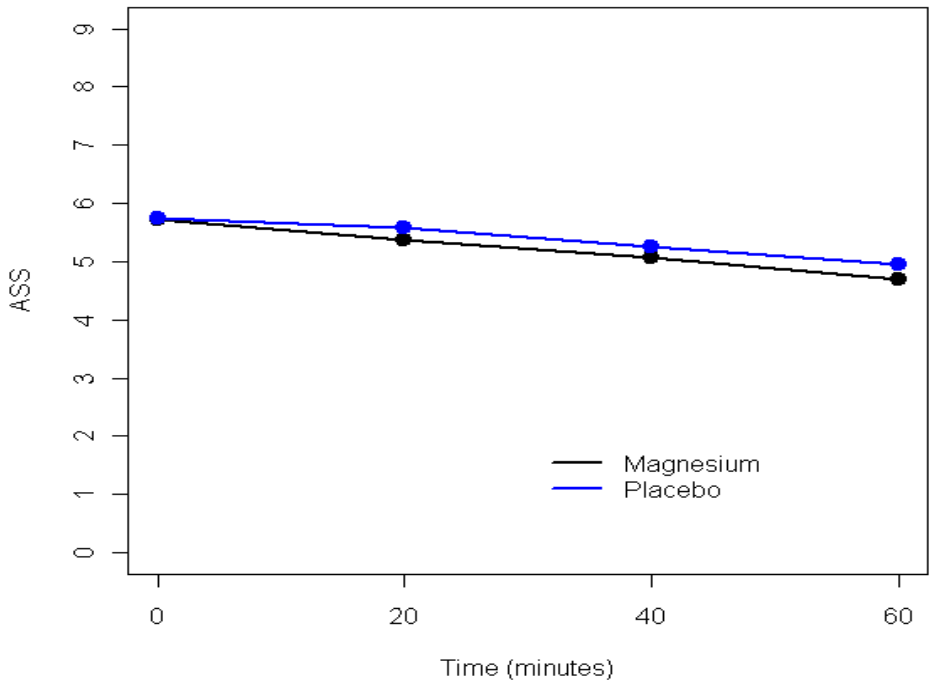


Figure 3.3 Mean longitudinal profiles

3.8.2 Analysis of secondary efficacy clinical outcomes

There were five secondary efficacy clinical outcomes; 'stepping down' of treatment at one hour, number 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 (PICU). Results are shown in Table 3.8.

The 'stepping down' of treatment at one hour was defined by the no treatment or MDI spacer only until discharge. The proportion of child stepping down at one 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.

The length of stay in hospital was defined by the time from randomisation to trial treatment to discharge from hospital. The median length of stay for children in magnesium group is 26 hours while 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 paediatric intensive care unit (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 magnesium group showed favourable secondary outcomes compared to the placebo group, none of the differences reached statistical significance. As presented in Appendix 6, since there is no evidence that the treatment effect varies by centre, no sensitivity analyses for the centre specific outcomes ('stepping down' of treatment at one 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.

Table 3.8: Secondary outcome results

Secondary outcome	Magnesium	Placebo	Estimate (95% CI) p-value
Proportion (%) stepping down treatment at one hour n_m=248, n_p=253	82/248 (33%)	76/253 (30%)	0.03 (-0.05 to 0.11) p=0.527
Number 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

Length of stay in hospital (in hours): median (IQR) n_m=251, n_p=254	26.3 (17.4 to 44.8)	27.1 (19.2 to 47.6)	-1.8 (-4.8 to 0.7) 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* n_m=251, n_p=254	22/251 (9%)	15/254 (6%)	0.03 (-0.02 to 0.07) p= 0.283

* Thirty five children were admitted to Paediatric Intensive Care for escalation of treatment and further closer observations due 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

3.9 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 (Blitz 2005, Goodacre 2007). Our hypothesis would be that the effect of the addition of magnesium would be greater in those with more severe disease. We thus took SaO2 at presentation to be the best marker of severity to examine as a treatment covariate (BTS 2011). Secondarily, 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 compared to the later more inflammatory response (Turner 2011), 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 SaO2. 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 3.9, and predicted treatment-covariate interactions are shown graphically in Figures 3.4 and 3.5. 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. Since both ASS and SaO2 are measures of severity, we have also investigated a second model for SaO2 excluding baseline ASS. Both models indicate that magnesium appears beneficial for lower SaO2 (more severe) but no difference for higher SaO2 (less severe).

Table 3.9: Treatment –Covariate interaction effects

	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, 3.17), p<0.0001	2.52 (1.94, 3.10), p<0.0001
Magnesium	-0.28 (-0.51 to -0.04) , p=0.020	0.01 (-0.48, 0.51), p=0.955
ASS at baseline	0.40 (0.32, 0.49), p<0.0001	0.40 (0.31, 0.48), p<0.0001
For the last 6hrs or less vs For the last few days	-0.34 (-0.74 to 0.06), p=0.099	0.03 (-0.51, 0.57), p=0.920
For the last 24hrs 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, 0.64), p=0.250
For the last 6hrs or less vs For the last few days* Magnesium		-0.79 (-1.58, -0.00), p=0.049
For the last 24hrs vs For the last few days* Magnesium		-0.28 (-0.85, 0.30), p=0.346, Marginal effect of attack duration*Magnesium p=0.143
SaO2 (model 1)		
Intercept	5.28 (2.01, 8.56), p=0.002	8.70 (4.16, 13.24), p<0.001
Magnesium	-0.23 (-046 to 0.01), p=0.055	-7.11 (-13.49, -0.74), p=0.029
ASS at baseline	0.38 (0.29, 0.46), p<0.0001	0.37 (0.28, 0.46), p<0.0001
SaO2	-0.03 (-0.06 to 0.01), p=0.124	-0.06 (-0.11, -0.02), p=0.010
SaO2* Magnesium		0.07 (0.01 to 0.14), p=0.034
SaO2 (model 2: without ASS at baseline)		
Intercept	8.24 (4.82, 11.66), p<0.0001	12.19 (7.39, 16.98), p<0.0001
Magnesium	-0.21 (-0.46, 0.04), p=0.095	-8.17 (-14. 99, -1.36), p=0.019
SaO2	-0.04 (-0.07, 0.00), p=0.058	-0.08 (-0.13, -0.03), p=0.003
SaO2* Magnesium		0.08 (0.01 to 0.16), p=0.022

Figure 3.4: Predicted scores for treatment - duration of the most recent asthma attack interaction effect

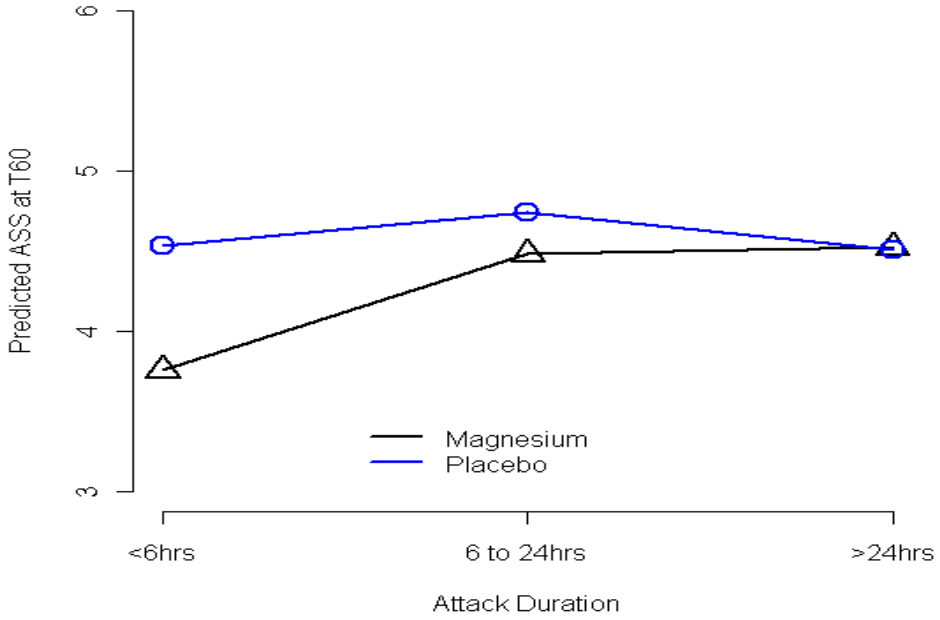
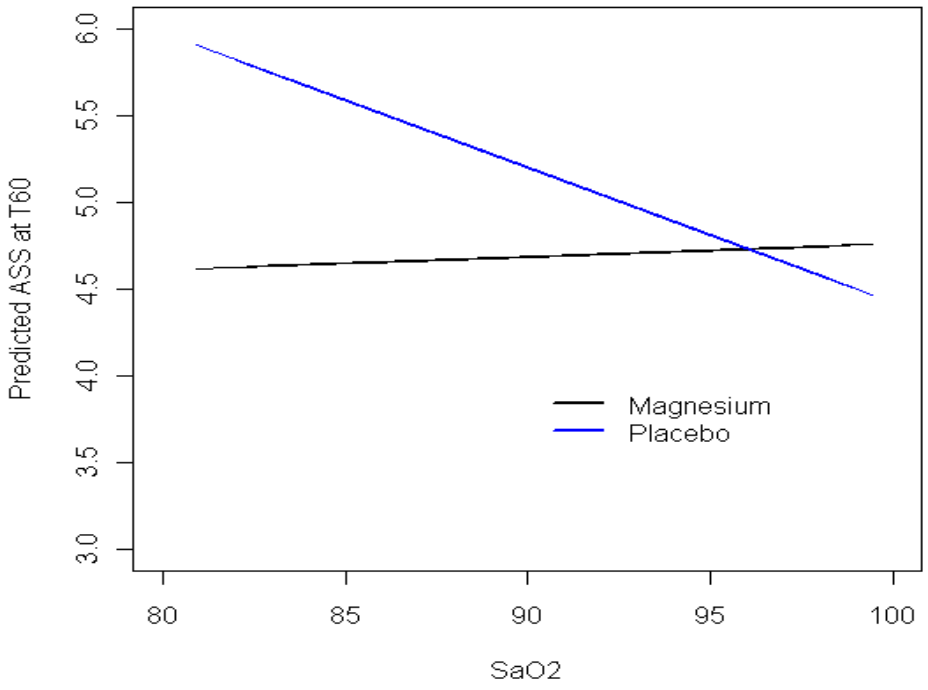


Figure 3.5: Predicted scores for treatment - SaO2 interaction effect



3.10 Safety outcomes

Adverse effects were assessed during follow up checks at 2, 3 and 4 hours following 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.

3.10.1 Adverse events (AE)

The number (and percentage) of children experiencing each AE is presented for each treatment arm in Table 3.10. Serious AEs were not included in this section but will be discussed in more detail in the next section. Table 3.10 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 in out upfront before the blind has been broken.

The results in Tables 3.10 and 3.11 do not appear to suggest there are any important increases in any event in either of the treatment groups.

Table 3.10: Adverse events by number of participants and number of events

Event	Magnesium	Magnesium	Placebo	Placebo	Total	Total
	Children (%) n=47/252 (19%)	Events n=47	Children (%) n=52/255 (20%)	Events n=59	Children (%) n=99/507 (19%)	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	1 (0.4)	1	1 (0.2)	1
Blood *per rectum*	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	1 (0.4)	1	1 (0.2)	1
Dizziness	1 (0.4)	1	0 (0)	0	1 (0.2)	1
Drowsiness	1 (0.4)	1	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	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	1 (0.4)	1	1 (0.2)	1
Itchy face	0 (0)	0	1 (0.4)	1	1 (0.2)	1
Jitteriness	1 (0.4)	1	0 (0)	0	1 (0.2)	1
Nausea	4 (1.6)	4	2 (0.8)	2	6 (1.2)	6
Sleep*	0 (0)	0	1 (0.4)	1	1 (0.2)	1
Teeth whitening	0 (0)	0	1 (0.4)	1	1 (0.2)	1
Urticarial rash	0 (0)	0	1 (0.4)	2	1 (0.2)	2
Vacant episode	0 (0)	0	2 (0.8)	2	2 (0.4)	2
Vomiting	21 (8.3)	21	24 (9.4)	29	45 (8.9)	50

* "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 3.11: Adverse events by severity

Event	Severity ‡	Number of Events			Number of children †		
		Magnesium	Placebo	Total	Magnesium (%) n=47/252 (19%)	Placebo (%) n=52/255 (20%)	Total (%) n=99/507 (19%)
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)
Asymptomatic hypotension	Mild	1	1	2	1 (0.4)	1 (0.4)	2 (0.4)
	Moderate	0	1	1	0 (0)	1 (0.4)	1 (0.2)
Back pain	Mild	0	1	1	0 (0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0)	0 (0)	0 (0)
Blood *per rectum*	Mild	0	1	1	0 (0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0)	0 (0)	0 (0)
Chest pain	Mild	1	2	3	1 (0.4)	1 (0.4)	2 (0.4)
	Moderate	0	1	1	0 (0)	1 (0.4)	1 (0.2)
Diarrhoea	Mild	0	1	1	0 (0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0)	0 (0)	0 (0)
Dizziness	Mild	1	0	1	1 (0.4)	0 (0)	1 (0.2)
	Moderate	0	0	0	0 (0)	0 (0)	0 (0)
Drowsiness	Mild	1	0	1	1 (0.4)	0 (0)	1 (0.2)
	Moderate	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)	2 (0.8)	2 (0.4)
Feet cramp	Mild	0	1	1	0 (0)	1 (0.4)	1 (0.2)
	Moderate	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)	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)
Hypokalaemia	Mild	0	1	1	0 (0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0)	0 (0)	0 (0)
Itchy face	Mild	0	1	1	0 (0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0)	0 (0)	0 (0)
Jitteriness	Mild	1	0	1	1 (0.4)	0 (0)	1 (0.2)
	Moderate	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)
Sleep	Mild	0	1	1	0 (0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0)	0 (0)	0 (0)
Teeth whitening	Mild	0	1	1	0 (0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0)	0 (0)	0 (0)
Urticarial rash	Mild	0	2	2	0 (0)	1 (0.4)	1 (0.2)
	Moderate	0	0	0	0 (0)	0 (0)	0 (0)
Vacant episode	Mild	0	1	1	0 (0)	1 (0.4)	1 (0.2)
	Moderate	0	1	1	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)

† Each child recorded once in the highest severity category

‡no AE was listed as severe.

3.10.2 Serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSARs)

There were 15 SAEs (three on magnesium, 12 on placebo) but no SUSARs during the course of the trial. Increased bronchospasm was reported by the same child on two occasions during follow-up. One child who was admitted to PICU was subsequently admitted to hospital twice due 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 3.12.

Table 3.12: Serious adverse events

	Treatment allocation	*Description*	*Seriousness*	*Severity*	*Relationship*	*Expectedness*	*Cause*	*Outcome*	*Child Status*	*Unblinded*
1	Placebo	Low SaO2 (<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 >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

	Treatment allocation	*Description*	*Seriousness*	*Severity*	*Relationship*	*Expectedness*	*Cause*	*Outcome*	*Child Status*	*Unblinded*
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	Bronchiectatsis	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	Readmitted to hospital	Required hospitalisation	Mild	Unlikely	Unexpected	Disease under study	Resolved with sequelae	Continuing in trial	No
13	Placebo	Readmitted 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 IV drugs	Medically significant / important	Moderate	Unlikely	Expected	Disease under study	Resolved	Continuing in trial	No

3.11 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 Table 3.13 and Table 3.14 by time point. The number in brackets is the number of occurrences for each reason.

Table 3.13: 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					x(2)	x(5)	
Placebo	Child was clinically well and was ready for discharge					x(2)	x(2)	
Placebo	SAE (Low SaO2 (<86%)/Silent Chest /Cyanosis)			X				
Magnesium	AE (Hypotension)			X				
Placebo	AE (Sleep)		x					
Placebo	Mother withdrew consent (Child's father not present, mother was tired, tearful and unsure)	x						
Placebo	Self-discharged (Parent felt they could provide required treatment at home)					x		
Magnesium	Child did not like the taste of nebuliser		x					
Magnesium	Child not tolerating nebulisers, becoming distressed		x(2)					
Magnesium	Non-compliance with protocol		x					

Table 3.14: 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)			X				
Placebo	AE (Vacant episode)		x					
Placebo	AE (Vomiting)		x					

Chapter 4 - Results of economic evaluation

4.1 Analysis of resource use and costs

Table 4.1 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 4.2a), whilst initial hospital admissions represented the most costly resource category (£765.20 and £748.93 for the magnesium and placebo groups respectively (Table 4.2a). 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 of the experimental intervention. Table 4.2b 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). 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). 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). 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.

Table 4.1: Resource use values by resource item and allocation group

NHS and social care resources: from randomisation to discharge

Resource use based on complete case data (N= 252 for magnesium and 256 for placebo)

	Magnesium	Placebo	p-value*
Initial hospital inpatient admissions	232 (92%)	245 (96%)	0.097
Chest x-ray	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 112 for placebo)

	Magnesium	Placebo	p-value*
Hospital re-admissions (asthma)	8 (7%)	8 (7%)	1.0
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

Days off school

Days off school based on complete case data (N=89 for magnesium and 80 for placebo)

	Magnesium		Placebo		Difference		
	Mean	SE*	Mean	SE	Mean	SE	p-value**
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	-.492	0.933

*P-values were calculated in SPSS using chi-square

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

Table 4.2a: NHS and social service costs by cost category and allocation group

NHS and social care costs: from randomisation to discharge Costs (£) based on complete case data (N= 252 for magnesium and 256 for placebo)							
	Magnesium		**Placebo**		**Difference**		
	Mean	**SE***	**Mean**	**SE**	**Mean**	**SE**	**P***
(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
Adverse events 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 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 one-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

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

Table 4.2b: Broader societal costs (£) by category and allocation group

Non-NHS costs up to 4 weeks post randomisation Costs (£) based on complete case data (N= 118 for magnesium and 112 for placebo)							
	Magnesium		**Placebo**		**Difference**		
	Mean	**SE***	**Mean**	**SE**	**Mean**	**SE**	**P***
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

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

4.2 Results of the cost-effectiveness analysis

4.2.1 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 4.3 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 4.3 differ from those presented in Table 4.5 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 36.60% 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 4.1. 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, cost-effectiveness acceptability curves (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 4.2. The CEAC shown in Figure 4.2 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 (Szefler 2011). 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 4.4). 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 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, 678) includes negative values, i.e. there is a possibility of a net monetary loss associated with adopting magnesium (Table 4.3). 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, 3058).

Sensitivity analyses were conducted to determine the impact of changing particular parameter values or assumptions on the size of the ICER (Tables 4.3 and 4.4 and Figure 4.2). 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 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. Cost-effectiveness acceptability curves generated following each sensitivity analysis are shown in Figure 4.2. Estimates of net monetary benefits for notional cost-effectiveness thresholds per unit decrement in ASS are shown in Table 4.4 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).

Table 4.3: Cost-effectiveness ratios for the CEA base-case analysis and sensitivity analyses – Complete case analyses

	Mean costs (95% CI)				Mean effects (95% CI)						Probability magnesium is			
Analysis[1]	Magnesium(£)	Placebo (£)	Difference (£)		Magnesium(£)	Placebo (£)	Difference(£)		ICER (£)		More effective* (%)	Less costly* (%)	Cost-effective* (%)[2]	Cost-effective* (%)[3]
Base-case	908(764, 1052)	863(752, 975)	45(-138, 227)		4.72(4.54, 4.90)	4.95(4.78, 5.13)	0.24§(-0.02, 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, 918)	794(718, 871)	18(-111, 148)		4.72(4.54, 4.90)	4.95(4.78, 5.13)	0.24(-0.02, 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, 1227)	950(790, 1109)	77(-179, 333)		4.72(4.54, 4.90)	4.95(4.78, 5.13)	0.24(-0.02, 0.49)		327		89.20	32.60	68.30	85.90
Exact LOS used	783(649, 917)	753(651, 855)	30(-139, 198)		4.72(4.54, 4.90)	4.95(4.78, 5.13)	0.24(-0.02, 0.49)		126		89.50	42.60	81.00	87.50
LOS rounded up to full days	1019(867, 1172)	964(844, 1084)	56(-139,250)		4.72(4.54, 4.90)	4.95(4.78, 5.13)	0.24(-0.02 0.49)		233		88.90	35.00	74.70	86.70
NHS Reference costs used to value A&E visit	876(732, 1020)	831(719, 942)	45(-136, 227)		4.72(4.54, 4.90)	4.95(4.78, 5.13)	0.24(-0.02, 0.49)		193		87.70	36.70	76.50	85.40
NHS Reference costs used to value stay on GM ward	943(797, 1090)	900(787, 1013)	43(-142, 228)		4.72(4.54, 4.90)	4.95(4.78, 5.13)	0.24(-0.02, 0.49)		184		90.30	38.50	78.10	88.70

§ 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

[1] Complete case analysis included placebo N=244; magnesium N=228

[2] Magnesium was considered to be "cost-effective" if it had positive net benefit at a £1000 cost-effectiveness threshold

[3] Magnesium was considered to be "cost-effective" if it had positive net benefit at a £5000 cost-effectiveness threshold

* Based on 1000 bootstrap replicates of the dataset

CI, confidence interval; LOS, length of stay

Table 4.4: Net benefits for the CEA base case and sensitivity analyses – Complete case analyses

Analysis[1]		Mean monetary net benefit (95% CI)						
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 visit (£)**	**NHS Reference costs used to value stay on GM ward (£)**
£0		-54(-347, 214)	-21(-247,184)	-87(-493, 303)	-26(-280, 233)	-59(-353,229)	-49(-346, 217)	-49(-332, 217)
£500		58(-321, 412)	102(-223, 391)	31(-398, 514)	93(-254, 427)	55(-300, 416)	65(-307, 421)	76(-285, 416)
£1000		170(-362, 678)	225(-260, 686)	149(-391, 779)	211(-298, 688)	169(-312, 690)	179(-358, 687)	201(-295, 693)
£1500		282(-410, 977)	349(-320, 988)	267(-406, 1073)	329(-360, 992)	282(-363, 1022)	293(-403, 957)	326(-326, 988)
£2000		394(-499, 1263)	472(-383, 1284)	385(-464, 1344)	447(-415, 1316)	396(-428, 1332)	407(-470, 1228)	450(-371, 1302)
£2500		506(-570, 1554)	595(-451, 1596)	503(-493, 1635)	565(-470, 1617)	510(-524, 1629)	521(-525, 1512)	575(-418, 1637)
£3000		618(-648, 1845)	718(-516, 1922)	621(-571, 1928)	684(-560, 1922)	624(595, 1962)	635(-588, 1813)	700(-468, 1956)
£3500		730(-708, 2139)	842(-584, 2232)	739(-641, 2250)	802(-650, 2228)	737(-675, 2302)	749(-655, 2100)	825(-524, 2273)
£4000		842(-807, 2438)	965(-629, 2546)	857(-709, 2541)	920(-731, 2558)	851(-754, 2634)	863(-721, 2402)	950(-579, 2588)
£4500		954(-874, 2734)	1088(-680, 2867)	975(-784, 2889)	1038(-811, 2888)	965(-830, 2949)	977(-796, 2726)	1075(-634, 2904)
£5000		1066(-945, 3058)	1212(-767, 3174)	1092(-864, 3184)	1156(-898, 3198)	1079(-908, 3273)	1091(-868, 2999)	1199(-689, 3228)

[1]Complete case analysis included placebo N=244; magnesium N=228
CI, [bootstrap] confidence interval; LOS length of stay; GM general medical ward
Based on 1000 bootstrap replicates of the dataset

Figure 4.1: Cost-effectiveness plane for CEA base-case analysis: complete case analyses

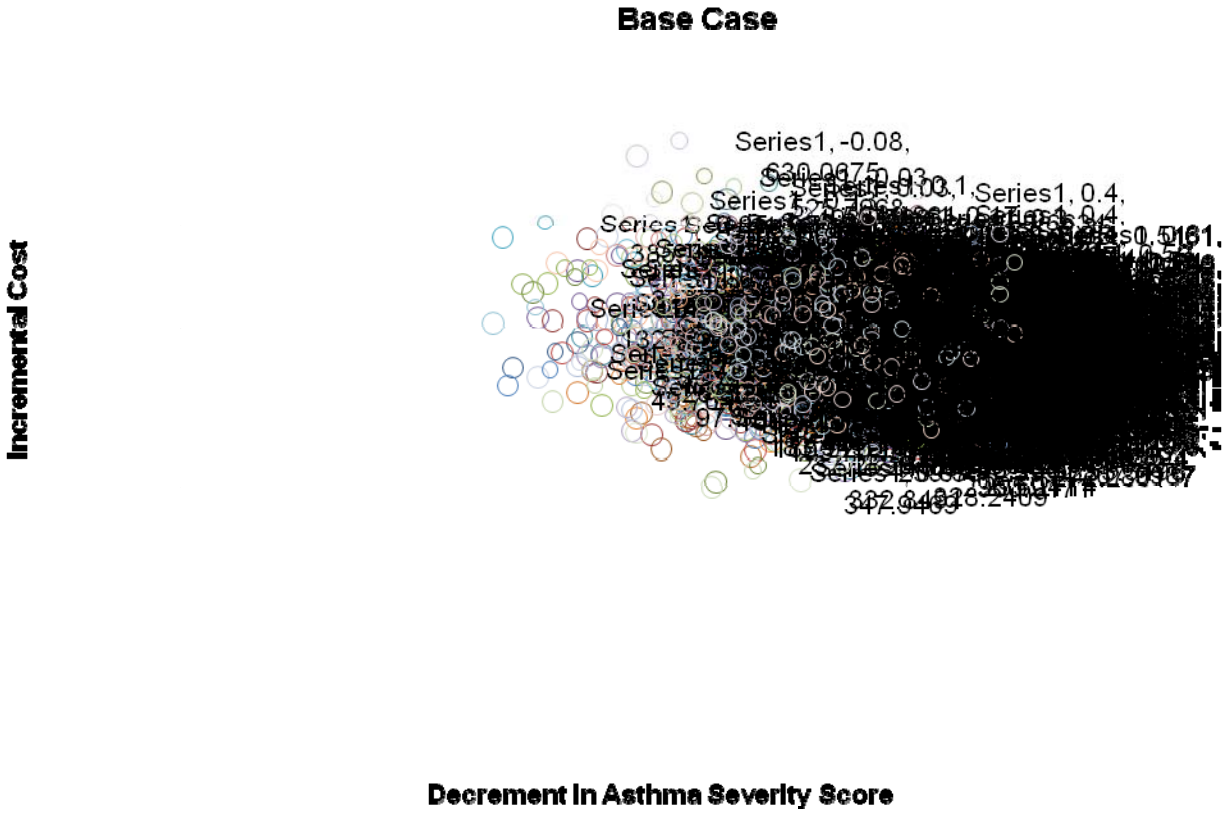
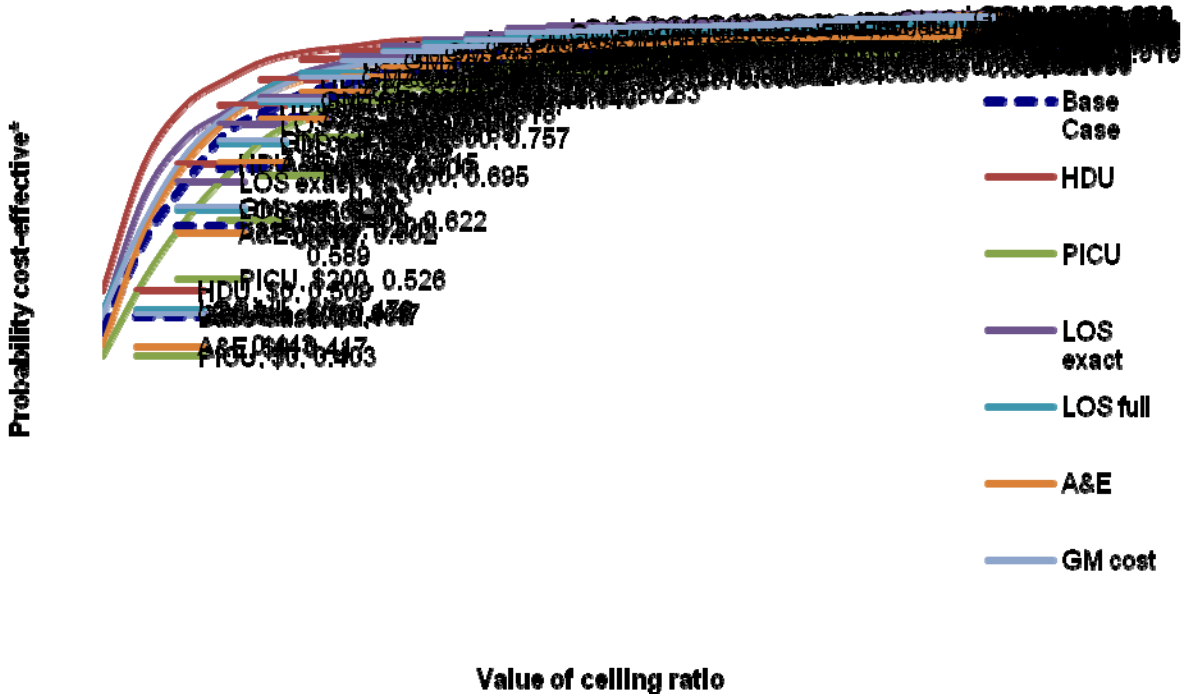


Figure 4.2: CEACs for CEA base cases analyses and sensitivity analyses: complete case analyses



* 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. HDU denotes a lower per diem cost applied to higher level care; PICU denotes a higher per diem cost applied to higher level care; LOS exact denotes part of a day spent by a child in an inpatient ward equated to a proportional period for costing purposes; LOS full denotes part of a day spent by a child in an inpatient ward equated to a full 24 hour period for costing purposes; A&E denotes a lower NHS reference cost applied to A&E attendances; GM denotes a higher per diem cost applied to general medical ward care.

4.2.2 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 4.5. 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 4.3. The CEAC shown in Figure 4.4 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 4.6). 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, 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, 3440).

Finally, sensitivity analyses were conducted to determine the impact of changing particular parameter values or assumptions on the ICER (Tables 4.5 and 4.6 and Figure 4.4). 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 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. Cost-effectiveness acceptability curves generated following each sensitivity analysis are shown in Figure 4.4. Estimates of net monetary benefits for notional cost-effectiveness thresholds per unit decrement in ASS are shown in Table 4.6 for each sensitivity analysis.

Table 4.5: 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[1]		**Magnesium(£)**	**Placebo (£)**	**Difference (£)**		**Magnesium(£)**	**Placebo (£)**	**Difference(£)**		**ICER (£)**		**More effective*** **(%)**	**Less costly*** **(%)**	**Cost-effective*** **(%)**[2]	**Cost-effective*** **(%)**[3]
Base-case		897(762, 1031)	882(768, 995)	15(-161, 191)		4.66(4.49, 4.83)	4.95(4.78, 5.12)	0.29§(0.05, 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, 900)	802(726, 879)	-1(-125, 123)		4.66(4.49, 4.83)	4.95(4.78, 5.12)	0.29(0.05, 0.53)		-2		93.0	51.90	89.70	92.50
Higher level inpatient care valued using NHS cost for paediatric intensive care (£2225)		1015(827, 1202)	980(816, 1144)	35(-214, 283)		4.66(4.49, 4.83)	4.95(4.78, 5.12)	0.29(0.05, 0.53)		119		92.40	40.90	78.90	90.80
Exact LOS used		773(649, 898)	769(666, 873)	4(-158, 166)		4.66(4.49, 4.83)	4.95(4.78, 5.12)	0.29(0.05, 0.53)		14		93.30	47.70	86.50	92.90
LOS rounded up to full days		1005(861, 1148)	985(862, 1108)	20(-169, 208)		4.66(4.49, 4.83)	4.95(4.78, 5.12)	0.29(0.05, 0.53)		68		92.90	48.30	85.50	91.40
NHS Reference costs used to value A&E visit		865(730, 999)	849(736, 962)	16(-159, 192)		4.66(4.49, 4.83)	4.95(4.78, 5.12)	0.29(0.05, 0.53)		55		93.80	42.00	85.50	92.20
NHS Reference costs used to value stay on GM ward		931(794, 1068)	918(804, 1032)	14(-165, 192)		4.66(4.49, 4.83)	4.95(4.78, 5.12)	0.29(0.05, 0.53)		47		92.90	47.50	85.70	92.70

§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

[1]Imputed case analysis included placebo N=256; magnesium N=252

[2] Magnesium was considered to be "cost-effective" if it had positive net benefit at a £1000 cost-effectiveness threshold

[3] Magnesium was considered to be "cost-effective" if it had positive net benefit at a £5000 cost-effectiveness threshold

* Based on 1000 bootstrap replicates of the dataset

CI, confidence interval; LOS, length of stay; GM general medical ward

Table 4.6: Net benefits for the CEA base case and sensitivity analyses – Analyses following multiple imputation

Analysis[1]		Mean monetary net benefit(95% CI)						
(Rc)		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 visit (£)	NHS Reference costs used to value stay on GM ward (£)
£0		-23(-310, 249)	-1(-200, 191)	-42(-441, 366)	-3(-284, 260)	-12(-318, 285)	-26(-312, 251)	-13(-307, 261)
£500		121(-266, 493)	142(-162, 413)	97(-379, 562)	142(-187, 491)	134(-230, 510)	120(-250, 473)	133(-237, 492)
£1000		266(-275, 805)	284(-189, 693)	235(-364, 842)	288(-184, 794)	279(-224, 799)	266(-266, 763)	279(-237, 799)
£1500		410(-304, 1135)	426(-211, 993)	374(-350, 1128)	434(190, 1112)	425(-229, 1,014)	412(-280, 1066)	426(-274, 1135)
£2000		554(-338, 1473)	569(-255, 1315)	512(-387, 1452)	579(-223, 1435)	570(-259, 1,413)	557(-303, 1393)	572(-311, 1459)
£2500		699(-362, 1797)	711(-285, 1635)	651(-444, 1778)	725(-254, 1775)	715(-299, 1,722)	703(-348, 1719)	718(-343, 1793)
£3000		843(-400, 2125)	853(-311, 1957)	790(-485, 2075)	871(-287, 2120)	861(-325, 2,030)	849(-397, 2039)	864(-385, 2125)
£3500		987(-422, 2463)	996(-354, 2278)	928(-554, 2393)	1016(-315, 2452)	1006(-376, 2,357)	995(-442, 2382)	1011(-422, 2457)
£4000		1132(-465, 2774)	1138(-386, 2597)	1067(-619, 2731)	1162(-325, 2764)	1152(-422, 2,678)	1141(-478, 2725)	1157(-460, 2789)
£4500		1276(-494, 3095)	1280(-413, 2903)	1206(-678, 3070)	1308(-373, 3087)	1297(-468, 2,999)	1287(-529, 3057)	1303(-496, 3142)
£5000		1420(-523, 3440)	1423(-440, 3229)	1344(-736, 3384)	1453(-395, 3416)	1442(-514, 3,315)	1433(-583, 3390)	1449(-530, 3501)

[1]Imputed case analysis included placebo N=256; magnesium N=252
CI, [bootstrap] confidence interval; LOS length of stay; GM general medical ward
Based on 1000 bootstrap replicates of the dataset

Figure 4.3: Cost-effectiveness plane for CEA base-case analysis: analyses following multiple imputation

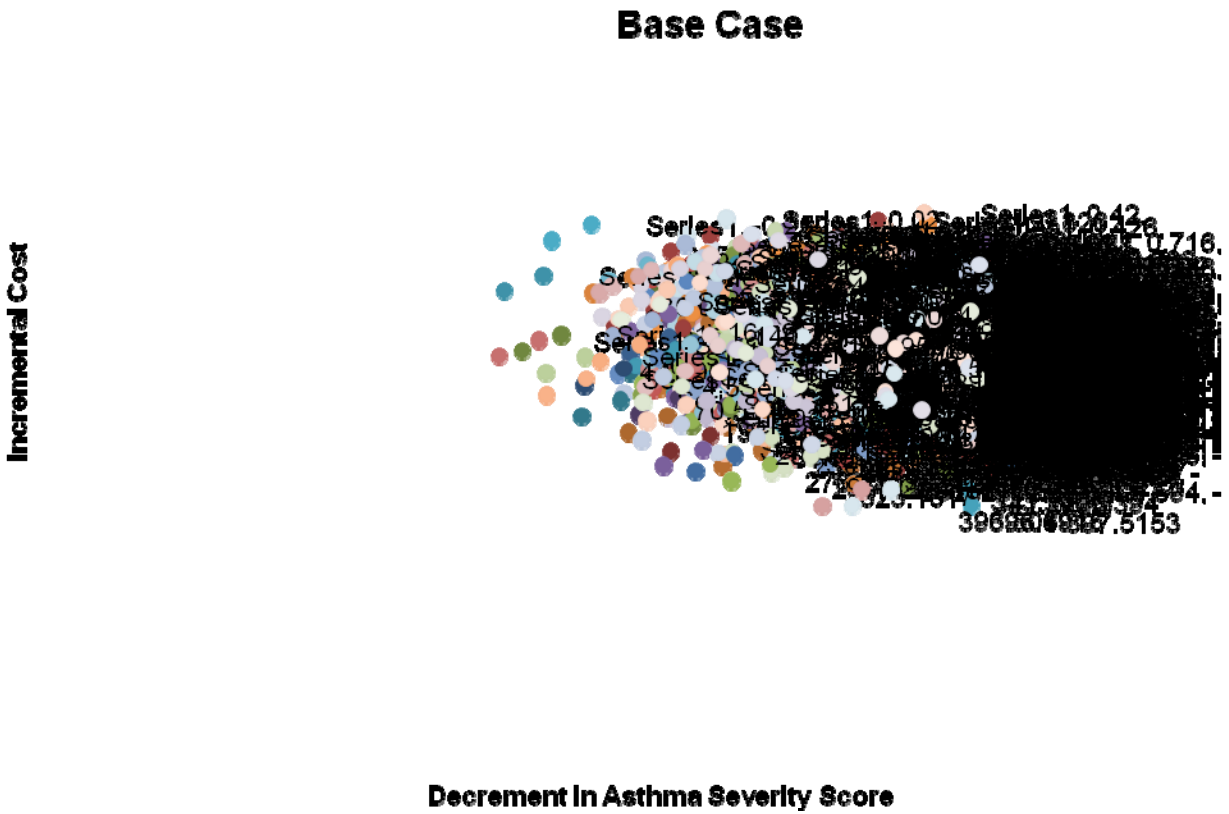
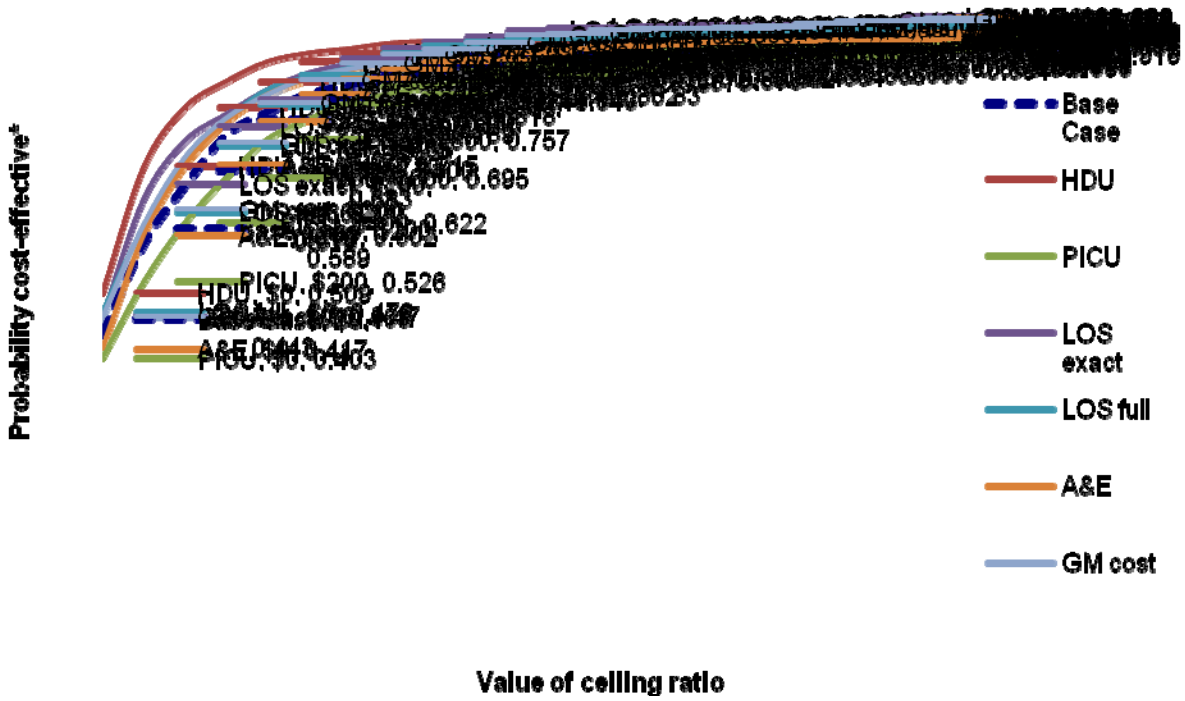


Figure 4.4: CEACs for CEA base cases analyses and sensitivity analyses: analyses following multiple imputation



* 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. HDU denotes a lower per diem cost applied to higher level care; PICU denotes a higher per diem cost applied to higher level care; LOS exact denotes part of a day spent by a child in an inpatient ward equated to a proportional period for costing purposes; LOS full denotes part of a day spent by a child in an inpatient ward equated to a full 24 hour period for costing purposes; A&E denotes a lower NHS reference cost applied to A&E attendances; GM denotes a higher per diem cost applied to general medical ward care.

4.2.3 Analysis of health-related quality of life and utility measures

Parents were asked to describe the QoL of their children at one month using the Pediatric Quality of Life Inventory™ (PedsQL™) Asthma Scales. In addition, children aged ≥5 years were asked to describe their own health-related quality of life at one 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 quality of life designed for childhood, such as the KIDSCREEN and Child Health Questionnaire, the PedsQL™ has been validated for use in children under the age of five years (Eiser 2001). The PedsQL™ Asthma Scales comprise parallel child self-report [ages 5-7 (young child), 8-12 (child) and 13-18 (adolescent)] and parent proxy-report [ages 2-4 (toddler), 5-7 (young child), 8-12 (child) and 13-18 (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 (3 items) and communication (3 items). A 5-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 3-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 sub-scale 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 sub-scales 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 4.7). 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 sub-scale and total scores across quartiles of the relevant scales are shown in Table 4.8. A total of 52 (45%) children in the magnesium arm had a total parent-reported PedsQL™ asthma score ≥76 compared to 38 (34%) in the placebo arm.

Table 4.7: Sub-scale descriptives for the PedsQL™ Asthma Module (parent proxy-report*)

		Magnesium (N= 116)			Placebo (N=112)			
Sub-scale	**No of items**	**N**	**Mean**	**[SE]**	**N**	**Mean**	**[SE]**	**P value†**
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

***** The study population includes all children for whom there was some parent completed PedsQL™ data available
† Comparisons between trial arms carried out using Student t-tests for continuous variables

Table 4.8: Distribution of scores for the PedsQL™ Asthma Module (Parent proxy-report*) by sub-scales

	Magnesium (N= 116)				Placebo (N=112)			
	Score				***Score***			
PedsQL subscale/ total scale scores	***0- <26***	***26- <51***	***51- <76***	***76-100***	***0- <26***	***26- <51***	***51- <76***	***76-100***
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
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)

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

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 sub-scales 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 4.9). 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 sub-scale and total scores across quartiles of the relevant scales are shown in Table 4.10. A total of 14 (30%) children in the magnesium arm had a total child-reported PedsQL™ asthma score ≥76 compared to 11 (24%) in the placebo arm.

Table 4.9: Sub-scale descriptives for the PedsQL™ Asthma Module (Child self-report*)

		Magnesium (N= 47)			Placebo (N=46)			
Subscale	**No of items**	**N**	**Mean**	**[SE]**	**N**	**Mean**	**[SE]**	**p-value†**
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

* The study population includes all children for whom there was some PedsQLTM data available
† Comparisons between trial arms carried out using Student t-tests for continuous variables

Table 4.10: Distribution of scores for the PedsQL™ Asthma Module (Child self-report*) by sub-scales

	Magnesium (N= 47)				Placebo (N=46)			
	Score				***Score***			
PedsQL subscale/ total scale scores	***0- <26***	***26- <51***	***51- <76***	***76- 100***	***0- <26***	***26- <51***	***51 - <76***	***76- 100***
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
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)

*Study population includes all children for whom there were some PEDSQL ™ data

Ordinary least squares (OLS) regressions were conducted using the total child-reported PedsQL^{TM} asthma score (model 1) and total parent-reported PedsQL^{TM} asthma score (model 2) as the dependent variables (Table 4.11). Potential confounders replicated the covariates incorporated into the main clinical analyses. Robust standard errors were estimated to account for potential heteroskedasticity 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^{TM} asthma score (P=0.734) and a 4.84 increase in the total parent-reported PedsQL^{TM} asthma score (P=0.043). In model 2, no other clinical or sociodemographic covariate was a significant predictor of the total PedsQL^{TM} asthma score. We do not consider there to be a clinically plausible reason why there may be a relationship between PedsQL^{TM} and late night admission.

Table 4.11: Ordinary least squares of marginal effects for PedsQL™ total scores

Variable (unit)	Self-reported PedsQL™ (child completed[1])			Proxy PedsQL™ (parent completed[2])		
	Fully Adjusted β [Robust SE]	P>|t|	[95% Conf. Interval]	Fully adjusted β [Robust SE]	P>|t|	[95% Conf. Interval]
Trial Arm (Referent= Placebo)						
Magnesium	1.336 [3.911]	0.734	[-6.455, 9.126]	4.836 [2.372]	0.043	[0.156, 9.515]
Age (years)	0.598 [0.569]	0.296	[-0.534, 1.731]	-0.648 [0.414]	0.119	[-1.464, 0.169]
Gender (Referent= Female)						
Male	9.200 [4.219]	0.032	[0.796, 17.603]	3.584 [2.408]	0.138	[-1.167, 8.335]
Duration of most recent asthma attack (Referent= last 6 hours or less)						
For the last few days	-10.738 [4.616]	0.023	[-19.933, -1.543]	-0.539 [3.294]	0.870	[-7.038, 5.959]
For the last 24 hours	-11.611 [5.927]	0.054	[-23.417, 0.196]	-1.615 [3.956]	0.684	[-9.419, 6.190]
SA O2 (value)	0.472 [0.601]	0.435	[-0.726, 1.670]	0.290 [0.342]	0.398	[-0.385, 0.964]
Assessment at baseline (Severity score)	2.188 [1.561]	0.165	[-0.922, 5.299]	1.619 [1.027]	0.117	[-0.407, 3.645]
Respiratory rate	0.206 [0.194]	0.291	[-0.180, 0.591]	0.006 [0.160]	0.971	[-0.311, 0.322]
Oxygen therapy required (Referent= No)						
Yes	-0.401 [3.910]	0.919	[-8.190, 7.389]	0.952 [2.498]	0.704	[-3.976, 5.880]
Time of day randomisation occurred (Referent= 09:00 – 17:00)						
17:01 – 22:00	4.112 [4.078]	0.317	[-4.013, 12.236]	2.659 [2.400]	0.270	[-2.078, 7.395]
22:01 – 08:59	14.612 [4.815]	0.003	[5.021, 24.203]	4.674 [3.646]	0.201	[-2.519, 11.868]

[1]The study population includes all children for whom there was some PedsQL™ data available

[2]The study population includes all children for whom there was some parent completed PedsQL™ data available

Parents of children aged ≥5 years were asked to describe the QoL of their children at one month using the proxy version of the EuroQol EQ-5D instrument. The EQ-5D is the generic, multi-attribute, preference based measure preferred by NICE for broader cost-effectiveness comparative purposes (NICE 2008). The parents were only asked to complete 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 one month for each child (Dolan 1995).

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 4.12 shows the distribution of functional levels across the five EQ-5D dimensions for the two trial groups. Table 4.13 shows sub-optimal levels of function within EQ-5D dimensions by trial group. There were no significant differences in sub-optimal 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 4.14). 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 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 one 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.

Table 4.12: EQ-5D levels of function by trial arm (children aged 5 and over*)

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)

* The study population includes all children aged 5 and over for whom there was some EQ-5D data available

Table 4.13: Number (%) of patients with sub-optimal levels of function[§] within each EQ-5D dimension (Children aged 5 and over*)

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

§ Sub-optimal levels of function defined as levels 2 or 3 for each EQ-5D dimension

† Calculated using Fisher's exact test for equality of proportions comparing Trial Arm A and Trial Arm B

* The study population includes all children aged 5 and over for whom there was some EQ-5D data available

Table 4.14: Ordinary least squares and Tobit estimator of marginal effects for EQ-5D utility scores (Children aged 5 and over*)

Variable (unit)		OLS		Tobit		
	Fully Adjusted β [Robust SE]	P>|t|	[95% Conf. Interval]	Fully adjusted β [Robust SE]	P>|t|	[95% Conf. Interval]
Trial Arm (Referent= Placebo)						
Magnesium	-0.023 [0.062]	0.705	[-0.146, 0.099]	-0.100 [0.126]	0.430	[-0.351, 0.151]
Age (years)	0.012 [0.011]	0.277	[-0.010, 0.033]	0.011 [0.021]	0.603	[-0.031, 0.053]
Gender (Referent= Female)						
Male	0.074 [0.067]	0.272	[-0.059, 0.207]	0.107 [0.136]	0.433	[-0.164, 0.378]
Duration of most recent Asthma attack (Referent= last 6 hours or less)						
For the last few days	-0.054 [0.048]	0.265	[-0.150, 0.042]	-0.182 [0.197]	0.359	[-0.574, 0.211]
For the last 24 hours	-0.132 [0.076]	0.088	[-0.284, 0.020]	-0.408 [0.211]	0.057	[-0.828, 0.012]
SA O2 (value)	-0.007 [0.006]	0.236	[-0.020, 0.005]	-0.015 [0.017]	0.374	[-0.048, 0.018]
Assessment at baseline (Severity score)	0.036 [0.025]	0.165	[-0.015, 0.086]	0.077 [0.051]	0.135	[-0.025, 0.178]
Respiratory Rate	0.002 [0.002]	0.436	[-0.003, 0.006]	0.006 [0.007]	0.383	[-0.008, 0.020]

Oxygen Therapy required (Referent= No)						
Yes	-0.030 [0.064]	0.636	[-0.158, 0.097]	-0.096 [0.132]	0.468	[-0.358, 0.166]
Time of day that randomization occurred (Referent= 09:00 – 17:00)						
17:01 – 22:00	-0.068 [0.056]	0.227	[-0.043, 0.180]	0.263 [0.147]	0.078	[-0.031, 0.556]
22:01 – 08:59	0.060 [0.077]	0.437	[-0.094, 0.214]	0.210 [0.245]	0.394	[-0.278, 0.697]

* The study population includes all children aged 5 and over for whom there was some EQ-5D data available

A number of mapping models were developed on the basis of data collected for 5-16 year old children for whom both EQ-5D and PedsQL™ responses were available. The best fitting model, in terms of the lowest root mean squared error (MSE) and lowest Akaike Information Criterion (AIC) statistic, was model 3 (described in the method section), 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 2-4 year old children in MAGNETIC for whom the validated toddler module of the PedsQL™ Asthma Scales had been completed; the root mean square error for this preferred model – model 3 – was 0.026 compared to 0.039 for model 1 and 0.038 for model 2.

Following this estimation procedure for health utilities at one 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.

4.3 Results of the cost-utility analysis

4.3.1 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 4.15 for the 230 children (118 receiving magnesium and 112 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 4.15 differ from those presented in Table 4.17 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 4.5. 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 4.6. The CEAC shown in Figure 4.6 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), 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 4.16). 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, 334) includes negative values, i.e. there is a possibility of a net monetary loss associated with adopting magnesium (Table 4.16). 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 (Tables 4.15 and 4.16; Figure 4.6). 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 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 onto 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 onto 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. Cost-effectiveness acceptability curves generated following each sensitivity analysis are shown in Figure 4.6. Estimates of net monetary benefits for notional cost-effectiveness thresholds per QALY gain are shown in Table 4.16 for each sensitivity analysis.

Table 4.15: 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 magnesium is		
Analysis[1]	Magnesium (£)	Placebo (£)	Difference (£)	Magnesium	Placebo	Difference	Incremental cost/QALY	More effective (%)	Less costly (%)	Cost-effective at a £20,000 cost-effectiveness threshold (%)
Base case[1]	1056 (855, 1256)	1126 (904, 1347)	-70 (-369, 228)	0.00133 (0.00098, 0.00169)	0.00173 (0.00131, 0.00216)	-0.0004 (-0.00095, 0.00015)	175,598	8.5	30.9	67.6
Linear *(U)	1056 (855, 1256)	1126 (904, 1347)	-70 (-369, 228)	0.02530 (0.02060, 0.02999)	0.03047 (0.02539, 0.03555)	-0.00517 (-0.01209, 0.00174)	13,607	7.0	32.7	40.6
Lower (U)	1056 (855, 1256)	1126 (904, 1347)	-70 (-369, 228)	0.00236 (0.00198, 0.00275)	0.00268 (0.00225, 0.00312)	-0.00032 (-0.00090, 0.00026)	219,930	14.4	33.6	64.4
Higher (U)	1056 (855, 1256)	1126 (904, 1347)	-70 (-369, 228)	0.00073 (0.00048, 0.00099)	0.00102 (0.00072, 0.00133)	-0.00029 (-0.00069, 0.00011)	240,906	7.6	30.4	68.2
Societal perspective	1145 (937, 1352)	1211 (977, 1443)	-66 (-378, 246)	0.00133 (0.00098, 0.00169)	0.00173 (0.00131, 0.00216)	-0.0004 (-0.00095, 0.00015)	164,303	8.1	35.9	63.2

[1]Complete case analysis included magnesium (n=218) and placebo (212)

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

(U) utility; lower (U) lower utility value; higher (u) higher utility value

Table 4.16: Net benefits for the CUA base case and sensitivity analyses – Complete case analyses

Analysis[1] / Value of threshold	Base case: % cost-effective	Base case analysis: mean net benefit (95%CI)	Linear* (U): % 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, 351)	67.30	69 (-249,362)	66.4	66 (-229, 377)	69.6	79 (-218, 369)	64.1	61 (-247, 360)
10,000	68.20	67 (-217,342)	53.80	17 (-292, 324)	65.5	63 (-230, 372)	69.0	76 (-222,367)	63.8	57 (-248, 353)
20,000	67.60	63 (-219, 334)	40.60	-36 (-354, 293)	64.4	60 (-228, 365)	68.2	73 (-226, 364)	63.20	53 (-249, 347)
30,000	66.20	59 (-219,327)	30.90	-89 (-441,266)	63.8	57 (-231, 360)	67.5	70 (-229, 361)	62.90	49 (-250, 340)
40,000	65.50	55 (-220,321)	23.20	-141 (-548, 250)	63.3	53 (-228, 351)	66.7	67 (-231, 356)	61.9	45 (-251, 333)
50,000	64.80	52 (-221,315)	19.30	-194 (-661, 248)	62.6	50 (-225, 343)	66	64 (-234, 351)	61.10	41 (-252, 327)
60,000	64.10	48 (-223, 309)	16.20	-246 (-771, 234)	62.0	47 (-222, 337)	64.9	61 (-235, 345)	60.0	37 (-257, 323)
70,000	63.60	44 (-224, 303)	14.70	-299 (-872, 233)	61.30	44 (-222, 331)	64.1	58 (-234, 342)	59.3	33 (-257, 320)
80,000	62.20	40 (-227, 299)	12.90	-352 (-978, 259)	60.10	41 (-222, 325)	63	55 (-233, 338)	58.0	29 (-254, 317)
90,000	60.90	36 (-232,296)	11.40	-404 (-1081, 260)	59.80	37 (-222, 317)	62.10	53 (-231, 333)	56.80	25 (-255, 310)
100,000	60.00	32 (-236, 291)	10.80	-457 (-1200, 269)	59.10	34 (-223, 309)	61.4	50 (-232, 329)	55.40	21 (-258, 303)

[1]Complete case analysis included magnesium (n=218) and placebo (212)

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

(U) utility; lower (U) lower utility value; higher (u) higher utility value

Figure 4.5: Cost-effectiveness plane for CUA base-case analysis: complete case analyses

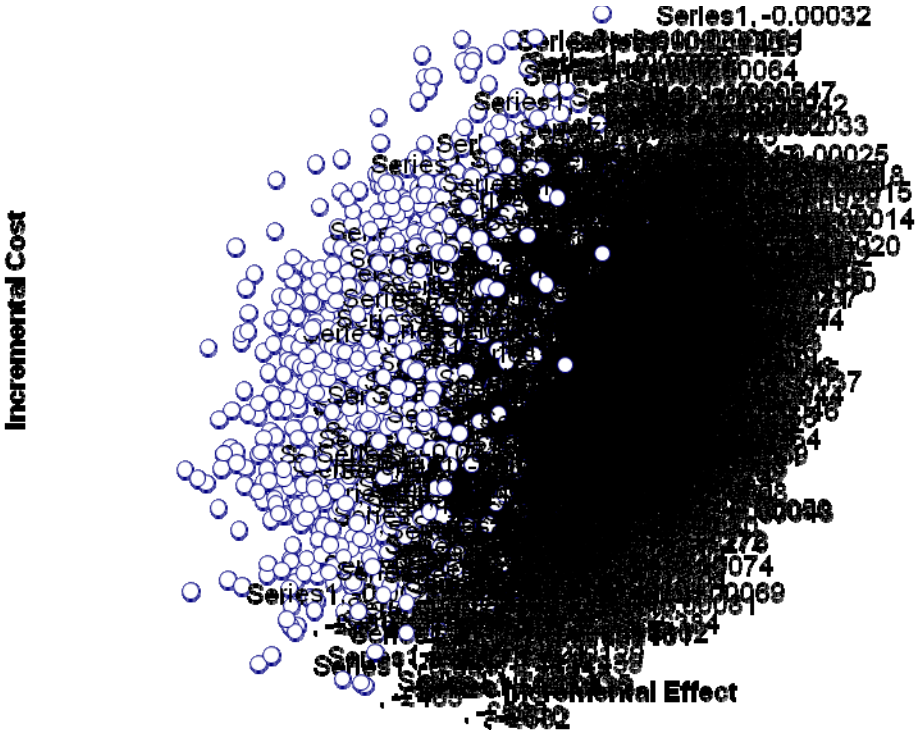
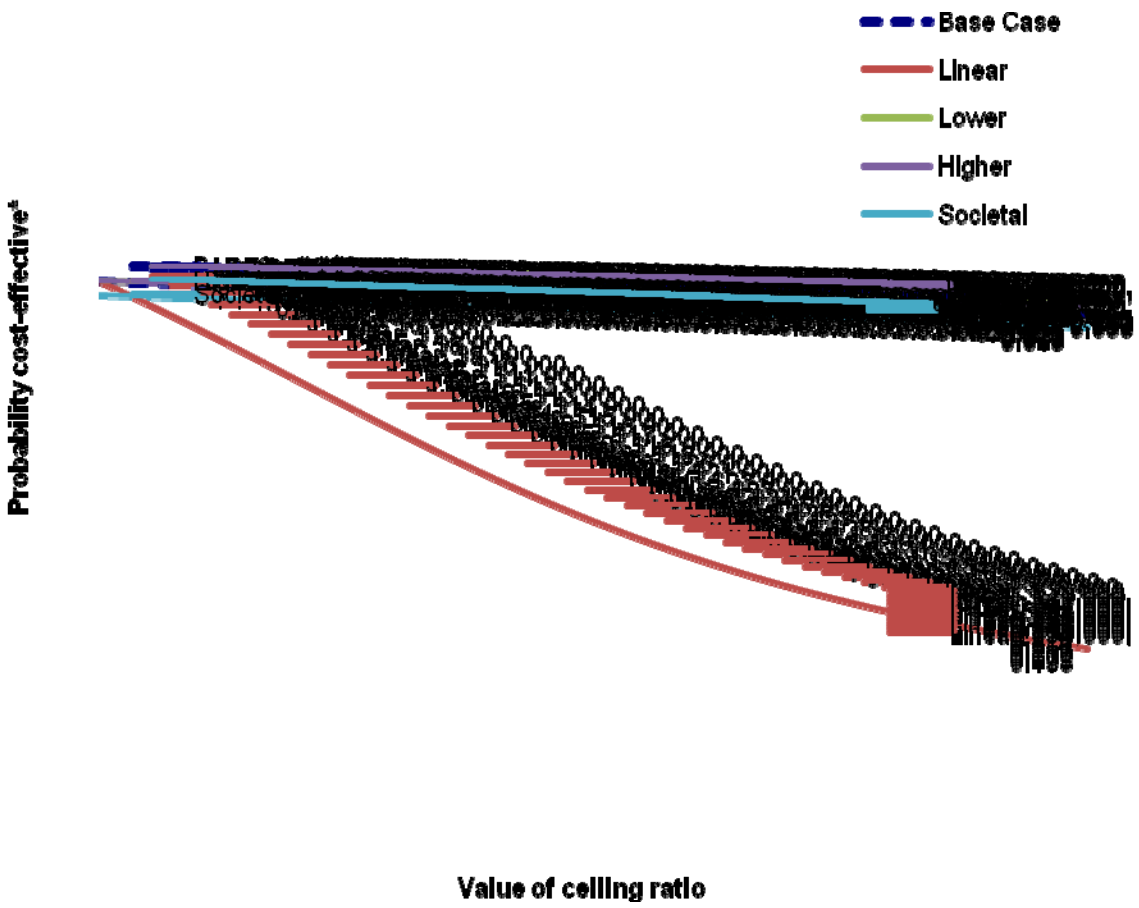


Figure 4.6: CEACs for CUA base cases analyses and sensitivity analyses: complete case analyses



* Each CEAC shows the probability that magnesium is cost effective with changes in the amount that society is willing to pay for a QALY. HDU denotes a lower per diem cost applied to higher level care; PICU denotes a higher per diem cost applied to higher level care; LOS exact denotes part of a day spent by a child in an inpatient ward equated to a proportional period for costing purposes; LOS full denotes part of a day spent by a child in an inpatient ward equated to a full 24 hour period for costing purposes; A&E denotes a lower NHS reference cost applied to A&E attendances; GM denotes a higher per diem cost applied to general medical ward care.

4.3.2 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 4.17. 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 4.7. The CEAC shown in Figure 4.8 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 4.18). 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, 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, 162).

Finally, sensitivity analyses were conducted to determine the impact of changing particular parameter values or assumptions on the ICER (Tables 4.17 and 4.18 and Figure 4.8). 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 onto 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. Cost-effectiveness

acceptability curves generated following each sensitivity analysis are shown in Figure 4.8. Estimates of net monetary benefits for notional cost-effectiveness thresholds per QALY gain are shown in Table 4.18 for each sensitivity analysis.

Table 4.17: 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 magnesium is		
Analysis[1]	**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, 1140)	1014 (895,1131)	-5 (-181, 172)	0.00138 (0.00116, 0.00159)	0.00176 (0.00153,0.00200)	-0.00038 (-0.00070, -0.00007)	11,886	1	49	50.9
Linear (U)	1009 (877, 1140)	1014 (895,1131)	-5 (-181, 172)	0.02458 (0.02161, 0.02755)	0.03018 (0.02709, 0.03326)	-0.00560 (-0.00988, -0.00132)	816	0.8	49.6	14.6
Lower (U)	1009 (877, 1140)	1014 (895,1131)	-5 (-181, 172)	0.00257 (0.00235, 0.00278)	0.00275 (0.00253, 0.00298)	-0.00019 (-0.00050, 0.00013)	24,562	14.2	47	50.6
Higher (U)	1009 (877, 1140)	1014 (895,1131)	-5 (-181, 172)	0.00063 (0.00048, 0.00077)	0.00088 (0.00071, 0.00105)	-0.00025 (-0.00047, -0.00003)	18,088	1.6	48.6	49.6
Societal perspective	1111 (975, 1246)	1112 (987, 1236)	-1 (-185, 183)	0.00138 (0.00116, 0.00159)	0.00176 (0.00153,0.00200)	-0.00038 (-0.00070, -0.00007)	2390	0.7	49.5	48.4

[1]Imputed case analysis included placebo N=256; magnesium N=252

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

(U) utility; lower (U) lower utility value; higher (u) higher utility value

Table 4.18: Net benefits for the CUA base case and sensitivity analyses – Analyses following multiple imputation

Analysis[1] Value of threshold	Base case: % cost-effective	Base case analysis: mean net benefit (95%CI)	Linear *(U): % 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, 177)	54.5	11 (-163, 197)	52.5	2 (-173, 164)	51.2	4 (-169, 172)	51.3	1 (-185, 187)
10,000	52.5	2 (-168, 173)	31	-45 (-223,138)	51.3	0 (-174, 161)	50.3	1 (-171, 169)	49.9	-3 (-186, 182)
20,000	50.9	-2 (-171,168)	14.6	-101 (-291, 89)	50.6	-1 (-175, 159)	49.6	-1 (-173, 166)	48.4	-6 (-188, 178)
30,000	49.4	-6 (-173, 162)	8.3	-158 (-367, 56)	49.8	-3 (-175, 156)	48.7	-4 (-175, 162)	46.7	-10 (-192, 172)
40,000	48.2	-9 (-175, 157)	4.6	-214 (-453,26)	48.6	-5 (-175, 154)	47.8	-6 (-178, 158)	44.5	-14 (-199, 166)
50,000	46.8	-13 (-177, 153)	2.6	-271 (-534, 4)	47.8	-7 (-175, 151)	46.8	-9 (-182, 155)	43.1	-18 (-204, 160)
60,000	45.1	-17 (-179, 151)	1.7	-327 (-621, -27)	47.4	-9 (-175, 148)	45.4	-11 (-184, 153)	40.8	-22 (-205, 154)
70,000	43.3	-21 (-182, 148)	1.2	-384 (-716, -51)	46.3	-11 (-175, 145)	44.2	-14 (-185, 151)	39.1	-25 (-207, 149)
80,000	41.1	-24 (-185, 144)	1.0	-440 (-798, -68)	45.2	-12 (-176, 144)	43.1	-16 (-188, 148)	37.4	-29 (-211, 146)
90,000	38.7	-28 (-188, 140)	0.8	-496 (-903, -90)	44.7	-14 (-177, 143)	41.5	-19 (-190, 146)	36.0	-33 (-213, 141)
100,000	36.7	-32 (-192,136)	0.7	-553 (-1006, -110)	43.5	-16 (-178, 142)	41	-21 (-194, 143)	35.0	-37 (-218, 138)

[1]Imputed case analysis included placebo N=256; magnesium N=252

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

(U) utility; lower (U) lower utility value; higher (u) higher utility value

[1]Imputed case analysis included placebo N=256; magnesium N=252

Figure 4.7: Cost-effectiveness plane for CUA base-case analysis: analyses following multiple imputation

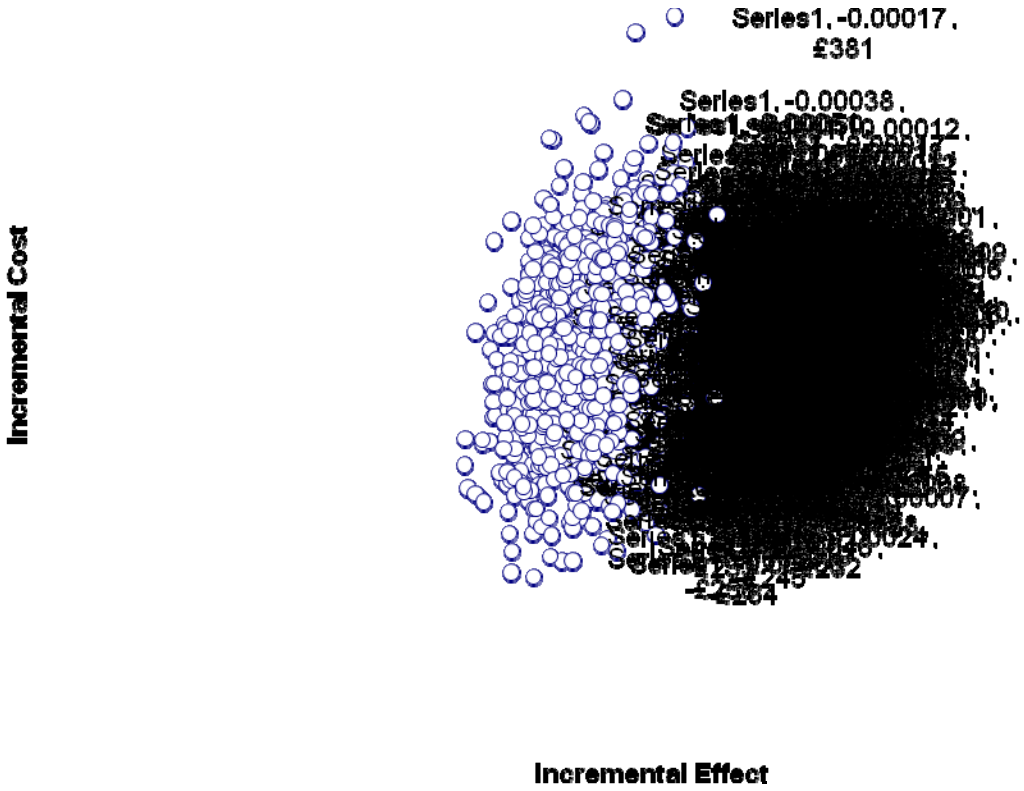
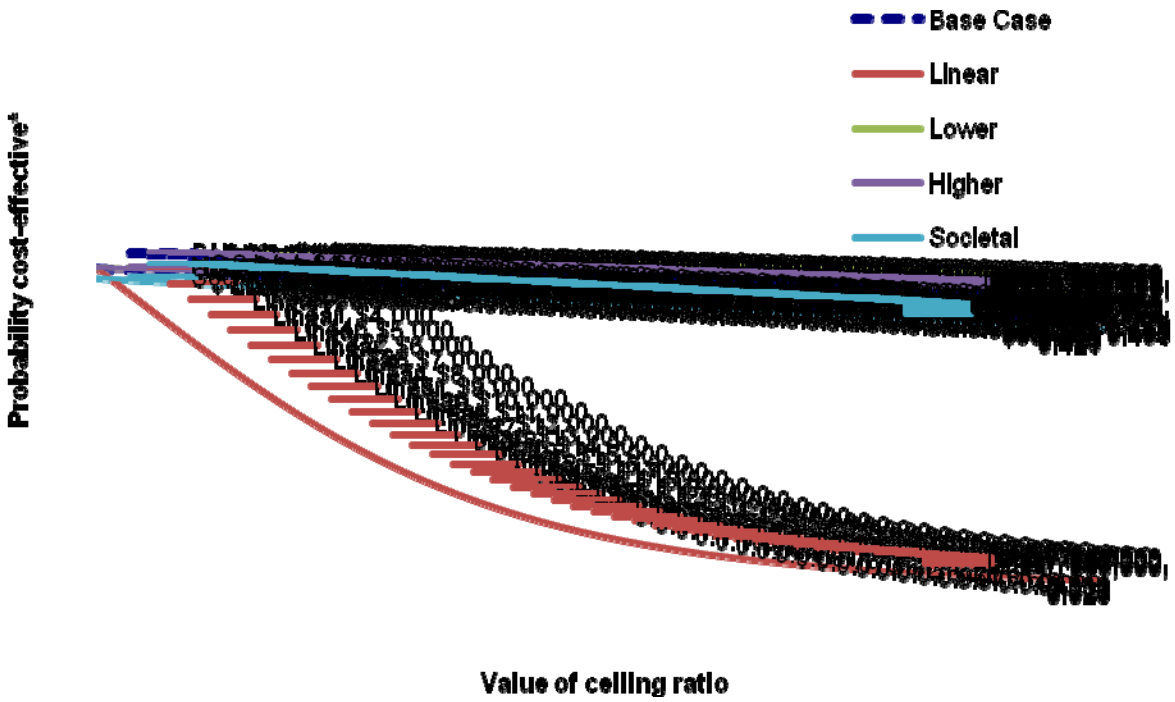


Figure 4.8: CEACs for CUA base cases analyses and sensitivity analyses: analyses following multiple imputation



* Each CEAC shows the probability that magnesium is cost effective with changes in the amount that society is willing to pay for a QALY. HDU denotes a lower per diem cost applied to higher level care; PICU denotes a higher per diem cost applied to higher level care; LOS exact denotes part of a day spent by a child in an inpatient ward equated to a proportional period for costing purposes; LOS full denotes part of a day spent by a child in an inpatient ward equated to a full 24 hour period for costing purposes; A&E denotes a lower NHS reference cost applied to A&E attendances; GM denotes a higher per diem cost applied to general medical ward care.

4.4 Generalised linear model on costs

For the generalised linear models (GLM) 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 4.19 summarises the results of three GLM models that regressed costs on intervention mode as well the pre-specified sociodemographic and clinical covariates. Robust standard errors were estimated to account for potential heteroskedasticity 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 one month acted as the dependent variable, whilst in model 3 societal costs to one 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, whilst increased SaO2 values at baseline are associated with reduced economic costs.

Table 4.19: GLM estimator of marginal effects for costs

Variable (unit)	NHS Costs up to discharge			NHS & PSS Costs to one month			Societal costs to one month		
	Fully Adjusted β [Robust SE]	P>|t|	[95% Conf. Interval]	Fully adjusted β [Robust SE]	P>|t|	[95% Conf. Interval]	Fully adjusted β [Robust SE]	P>|t|	[95% Conf. Interval]
Trial Arm (Referent= Placebo)									
Magnesium	-0.40 [64.33]	0.995	[-126.48, 125.69]	-13.60 [64.83]	0.834	[-140.66, 113.47]	-25.17 [65.90]	0.702	[-154.34, 103.99]
Age (years)	54.35 [13.83]	0.000	[27.25, 81.45]	62.11 14.24]	0.000	[34.20, 90.02]	72.47 [14.64]	0.000	[43.77, 101.17]
Gender (Referent= Female)									
Male	-26.55 [59.99]	0.658	[-144.13, 91.02]	-97.69 [66.65]	0.143	[-228.33, 32.95]	-158.03 [70.49]	0.025	[-296.18, -19.88]
Duration of most recent Asthma attack (Referent= last 6 hours or less)									
For the last few days	2.48 [89.84]	0.978	[-173.59, 178.56]	8.68 [94.81]	0.927	[-177.14, 194.50]	2.87 [93.50]	0.976	[-180.39, 186.13]
For the last 24 hours	42.47 [104.63]	0.685	[-162.62, 247.55]	19.18 [111.55]	0.863	[-199.46, 237.82]	38.40 [111.08]	0.730	[-179.31, 256.11]
SA O2 (value)	-36.84 [9.99]	0.000	[-56.42, -17.26]	-40.66 [10.13]	0.000	[-60.51, -20.81]	-45.37 [10.63]	0.000	[-66.21, -24.54]
Assessment at baseline (Severity score)	50.23 [22.25]	0.024	[6.63, 93.83]	51.84 [24.53]	0.035	[3.77, 99.91]	52.43 [24.40]	0.032	[4.60, 100.26]
Respiratory rate	235.90 [80.91]	0.004	[-1.48, 12.47]	6.41 [3.74]	0.087	[-0.93, 13.74]	6.76 [3.90]	0.083	[-0.88, 14.40]
Oxygen therapy required (Referent= No)									
Yes	-0.030 [0.064]	0.636	[77.32, 394.47]	235.47 [81.69]	0.004	[75.35, 395.58]	267.18 [90.62]	0.003	[89.57, 444.79]
Time of day randomisation occurred (Referent= 09:00– 17:00)									
17:01 – 22:00	-72.40 [53.98]	0.180	[-178.20, 33.40]	-104.17 [57.83]	0.072	[-217.51, 9.17]	-87.17 [60.20]	0.148	[-205.15, 30.82]
22:01 – 08:59	375.15 [276.52]	0.175	[-166.82, 917.11]	246.30 [236.33]	0.297	[-216.90, 709.51]	308.35 [246.70]	0.211	[-175.17, 791.88]

Chapter 5 - Discussion

5.1 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 years and 16 years. The study compares the addition of three doses of nebulised isotonic magnesium sulphate or placebo (isotonic saline) to standard treatment in children aged between 2 years 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 (BTS 2011). 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 (Table 3.6), 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 (Appendix 5; Table C-7) 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 less than six 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 to 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 magnesium sulphate.

We would conclude that in children with acute severe asthma, nebulised isotonic magnesium sulphate may 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.

5.2 Strengths of the study

5.2.1 Study design

The study was a pragmatic study, using the standard British Thoracic Society/ Scottish Intercollegiate Guideline Network guidelines for treating acute asthma (BTS 2011), recruiting patients from 30 centres across the United Kingdom. Although there are data to show that guidelines are not always followed completely (Haby 2002, Babl 2008), 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 +/- 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* 2003 (Hughes 2003) and was noted to be a safe approach to recruiting. Patient status was monitored for safety for four 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 were prompted to check for AEs at each assessment point. Adverse events 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 a low risk of

performance bias. Outcome assessment was also blinded to all so a low risk of detection bias. These data were followed up as much as possible but there was incomplete outcome data especially the one-month health economic data where 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 un-blinded.

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 Local Research Networks of the Medicines for Children Research Network 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 Emergency Departments and Children's Assessment Units - this makes our data more generalisable to the typical clinical situations where 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 Clinical Trials Unit, with a dedicated trials manager, data manager and statistical support improved the quality of data. Finally regular meetings of the Trial Management Group (TMG), Trial Steering Committee (TSC) and Independent Data and Safety Monitoring Committee (IDSMC) ensured regular research governance and guidance for successful completion of the study over the two years of recruitment.

5.2.2 Outcomes

The power of the study was calculated on the basis of the ASS reported by Bishop and Yung (Bishop 1992, Yung 1996) 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 zero and a maximum of nine. Although there are over twenty ASS (van der Windt 1994, Birken 2004, Rafai 2012), the Bishop and Yung score is a well-validated and easy to use and allows comparability with other studies (Yung 1998). The score has been validated as a measure of asthma severity in children, has been demonstrated to be reproducible and reliable (Bishop 1992) with good inter-observer agreement and correlates well with severity as defined by oxygen saturations at presentation and FEV1 at presentation (Yung 1996). 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.

5.2.3 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 (Davies 2008). 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* (Davies 2008) between 1998-2005 and a recent update of this national audit from November 2011 (J Paton, personal communication, March 2012) 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 (Davies 2008) and in this population was slightly lower at 93.6 % (range; 81%-100%), the use of IV bronchodilators as a marker of severity, was 4-5% in the national audit (Davies 2008) and in the same level in November 2011 and in this population was 11% (Table 3.8). 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* (Davies 2008).

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 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.

5.2.4 Treatment-covariate interactions

In the initial SAP (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 (Appendix 3, section A1). Treatment-covariate interactions were investigated for two clinically important baseline covariates, SaO2 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.

5.2.4.1 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 (Blitz 2005, Goodacre 2007, Powell 2012). 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 SaO2 at presentation to be the best marker of severity to examine as a potential treatment effect modifier (BTS 2011). 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.

5.2.4.2 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) (Rodrigo 2000). Definitions used by this prospective study of 403 adults with severe acute asthma (defined as PEFR < 50% predicted at presentation) are that ROAA is less than six hours duration of symptoms and SOAA greater than six 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 (Rodrigo 2000), the latter responding more rapidly to treatment (Woodruff 1998). The incidence of ROAA in this severe group of acute asthma was 11.3% (Rodrigo 2000). Barr *et al* demonstrated in 800 adult patients with acute severe asthma (defined as PEFR < 50% predicted) 14% (95%CI; 11%-16%) had ROAA (Barr 2000). Martin *et al* demonstrated a prevalence of 17% of ROAA in a study of 30 children with near fatal asthma attacks (Martin 1995). Our study recruited 15% of children with an exacerbation with < six hours symptom duration. Three categories (< six hours, <twenty four hours and > twenty four 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 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 to the later more inflammatory phase where the effect is less marked (Turner 2011).

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.

5.2.5 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 four hours after treatment. This is a novel approach to assessing ASS and has not been presented in the acute asthma literature before (Rafai 2012). Longitudinal ASS data were summarised by the area under the curve (AUC). The AUC is a summary measure that integrates repeated assessments over the duration of the treatment.

Figure 3.3 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, Table 3.7). However when we examined the effect over 240 minutes, even accounting for missing values and drop outs we can demonstrate that the statistically significant effect seen at the cross sectional T60 measurement (Table 3.6) is sustained up to 240 minutes (Appendix 5; Figures C-2 and C-3 and Table C-7). Again the clinical significance of this difference is unlikely to be important [treatment effect on ASS 0.2 (95% CI; 0.01 to 0.4)] but it does emphasise that there is a pharmacological effect and 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

5.2.6 Secondary outcomes

We examined secondary outcomes frequently measured in acute asthma studies (Appendix 1, Powell 2012, Rafai 2012): need for intravenous bronchodilator therapy, need for PICU admission and intubation, stepping down of treatment by one 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 show a difference in the two groups 33% in the magnesium group and 30% in the placebo group (p=0.53). Based on the study by Kelly *et al* (Kelly 2004) where in 720 patients (adults and children) presenting to the ED in 36 Australian EDs, 50% were had improved from severe to moderate after an hour of treatment and so could 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; rather than a score, a clinician's subjective impression. However the fact that only a third stepped down at one hour in this study would suggest we have a group of children with more severe acute asthma attacks compared to the mixed population of all levels of severity in those presenting to EDs in the Kelly study (Kelly 2004); 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. The study of Khashabi 2008 (only presented in abstract form) examined 40 children with acute asthma (mean age 3.55 years) showed no difference in an ASS one hour after two doses of either nebulised magnesium and salbutamol compared to salbutamol and placebo but did show a difference in mean duration of supplemental oxygen therapy (not defined in the abstract); 15.2 (95%CI; 9.3-21.5) versus 19.0 (95%CI; 12.4-25.8) (Khashabi 2008). This outcome should be defined and explored further in future studies of acute asthma.

5.2.7 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 D-1).

5.2.8 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 3.3) 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 3.4 has shown that only 53/508 times were considered to be protocol deviations with 10% in the magnesium group and 12% in the placebo group.

5.3 Potential limitations

5.3.1 Dose of magnesium given

We used the same dose of isotonic magnesium sulphate for all ages on each of the three administrations in the first hour (2.5mls of 250 mmol/L, tonicity 289 mosml, 151 mg per dose). This was the dose used by Hughes *et al* in their adult study of 52 patients where they demonstrated a significant effect in lung function improvement at 90 minutes post treatment (Hughes 2003).

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 (Turner 2011) 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 3). This illustrates how difficult it is to make any comparison and firm conclusion when comparing the literature (Powell 2012). This is also a similar research consideration in the adult data.

- **Aggarwal 2006** (ages 13 - 60 years, n=110); 1ml MgSO4 (500mg) three doses 20 minutes apart with beta agonist. Total Mg used: **1500mg** (3 times 500mg)

- **Ashtekar 2008** and this study, **MAGNETIC** (ages 2- 16 years, n=508) 2.5mls of 250 mmol/L, tonicity 289 mosmol, 151 mg per dose. Total Mg used: **453 mg** (3 times 151 mg)

- **Drobina 2006** (ages 12 - 60 years, n=110); 125mg MgSO4 0.25 mls of 50% solution (three doses 20 minutes apart with beta agonist. Total Mg used: **375 mg** (3 times 125mg)

- **Khashabi 2008** (ages mean age 3.55 years) two doses of isotonic magnesium sulphate not stated.

- **Mangat 1998** (ages 12 - 60 years, n=33); 3 mls (95mg) MgSO4 (4 doses, 20 minutes apart) compared to beta two agonist. Total Mg used: **380 mg** (4 times 95mg)

- **Mahajan 2004** (ages 5-17 years, n=62); 2.5ml isotonic MgSO4 solution (6.3%) with single dose of beta agonist (dose)

- **Meral 1996** (ages <16 years, n=40); 2 ml MgSO4 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.

5.3.2 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 (Coates AL 2011). The Pari LC Star had an appropriate particle size distribution but a very slow aerosol output rate. The Omron MicroAir 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 was 16.0 +/- 0.4 mg/min in older children and approximately a 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 underway in the USA.

5.3.3 Un-blinding of randomised treatments during the study and protocol deviations and missing values

5.3.3.1 Un - blinding of randomised treatments during the study

The treatment allocation was un-blinded during the course of the trial for only two children, one in each group (Table 3.12) and the children were withdrawn from the study due to SAEs which 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.

5.3.3.2 Protocol deviations

Table 3.4 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 pre treatment 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.

5.3.3.3 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 (Appendix 5 Table C-2). The reasons for the missing components of the ASS in these 36 cases are illustrated in Appendix 5 Table C-3. 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 (missing completely at random) assumption.

Three sensitivity analyses were performed (Appendix 5; C2.1, C2.2, C2.3) to explore this assumption:

1) reason for missingness (Table C-4); adjusted difference in mean (-0.32 (95%CI; -0.56 to -0.08) $p < 0.01$),
2) multiple imputations (Table C-5); adjusted difference in mean -0.28 (95%CI; -0.51 to -0.05),
3) joint modelling of the longitudinal first 60 minute data (Table C-6).

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. Figures C-2, C-3 and Table C-7 illustrate that the dropout in the magnesium group was due to those subjects getting better (Figure C-3) and not getting worse. This does not affect the final conclusion that the effect of magnesium on 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.

5.4 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 (Di Greggorio 1999) 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 to 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 (Table 3.12). 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, that the administration of nebulised magnesium at these does and frequency is safe. This is supported by the data from all published 16 studies using nebulised magnesium sulphate (Appendix 1, Table 3, Powell 2012).

5.5 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 (Mohammed 2007) was that '*insufficient data exist to draw reliable conclusions regarding the role of nebulised magnesium sulphate in children*'.

Only two paediatric studies were included in this review and the conclusion was based on the lack of significant effect upon 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 were of insufficient power and methodological rigor to make 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 magnesium sulphate 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 adult and children who gain benefit the most benefit (Blitz 2005, Mohammed 2007, Powell 2012). 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 in section 5.2.4.2 we generated the hypothesis that there may be a more marked response to 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 are 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 only have had 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 all 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 asthma; 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 (Coates 1993). Slow onset cases fatality have shown to be more eosinophilic inflammatory mediated response and the more sudden onset a more neutrophil mediated with acute bronchospasm (Sur 1993). More recent data 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 (Wang 2011). Indeed this group has suggested that there are a number of phenotypes eosinophilic, neutrophilic, mixed granulocytic and paucigranulocytic asthma (Simpson 2006). 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 the introduction 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 effect (Cairns 1996). Indeed in a guinea pig model of asthma developed by part of this current research group has also demonstrated this phenomenon (Turner 2011). 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. The study by Aggarwal (2006) showed no effect in a RCT of reasonable power of 100 adults with acute asthma but both study groups had on average a 72 hour history preceding their recruitment to the study. So there may have been more of the later inflammatory response in those subjects and thus the lack of clinical response (Aggawal 2006). A recent study by Gallegos- Solorzano *et al* (Gallegos- Solorzano M 2010), showed 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 study by Kokturk et al (Kokturk 2005) with 26 patients, no difference was seen in PEFR and clinical scores with the addition of nebulised magnesium to a standardised regimen. The duration of attack was not reported and thus the duration of attack and response relationship cannot be commented upon. There were also no data on the duration of attack in the Hughes study (Hughes 2003).

In the study by Mahajan with 62 children where they had shown a minimal short term response of lung function to nebulised magnesium, these children had average duration of

attack of 42 hours in both groups; shorter than those subjects in Aggawal's study, but still longer than those children in our study which has shown 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.

5.6 Health economics data

The economic evaluation undertaken alongside the MAGNETIC trial compared the addition of magnesium sulphate to standard treatment versus 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 magnesium sulphate in children with asthma. The economic evaluation was conducted according to nationally agreed design and reporting standards (NICE 2008, Drummond 2005). The economic evaluation has three key strengths. Firstly, 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. Secondly, 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. Thirdly, 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: (i) a CEA that used the child's ASS score as the health outcome of interest, and (ii) 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 to 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 one 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 were 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 wa

s 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% to 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. Firstly, 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 to the control, rather than affirming 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.

Secondly, 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. Due 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 one 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 due 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^{TM} 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^{TM} data but without EQ-5D data). It was also necessary to map data from completed PedsQL^{TM} Asthma Modules to the EQ-5D scoring system for those children under 5 years whose parents/carers completed the EQ-5D questionnaire unaware that they were not required to do so. Finally, the choice of EQ-5D scores employed 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 that 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.

5.7 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 un-blinding. 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 magnesium sulphate 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 healthcare

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. 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.

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:

a) exploration of the relationship between ASS and the BTS definition of acute severe asthma

b) assessment of the value of the area under the curve analysis of ASS

c) 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. There is currently another large study in adults, the 3MG study, coming to a conclusion (Goodacre 2007) and there is another paediatric

study in the USA currently underway (Coates 2011). There are limited trial data in children with only four published studies [including the pilot study MAGNETIC (Ashtekar 2008)]. This is the largest study if nebulised magnesium sulphate 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 2007-006227-12

MREC 07/H1010/101

Protocol

The MAGNETIC Trial Protocol is available from http://www.hta.ac.uk/project/1615.asp (accessed October 2011)

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Contributions of Authors

Dr Colin Powell, Chief Investigator

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

Dr Angela Boland was a member of the Trial Management Group, 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 Trial Management Group, and prepared the report for publication.

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

Professor Kerenza Hood (Director, South East Wales Trials Unit) was a member of the Trial Management Group, contributed to the design and conduct of the study, and reviewed a draft of the report.

Professor Paula Williamson (Director, MCRN Clinical Trials Unit) was a member of the Trial Management Group, led the statistical team, contributed to the design and conduct of the study and reviewed a draft of the report.

The MAGNETIC Study Group

Dr Colin Powell Ann Russell Anwen Howells	Principal Investigator Research Nurse	University Hospital of Wales, Cardiff
Dr David Levy Sonia Keane Claire Fish	Principal Investigator Research Nurse Research Nurse	Tameside General Hospital
Dr Faisal Al-Zidgali Sue Langworth Anne Cook Zoe Thomas	Principal Investigator Ward manager Research Nurse Research Nurse	Wythenshawe Hospital
Dr Kate Goldberg Jacqueline Woods Jacqueline Bradley	Principal Investigator Research Nurse Research Nurse	Blackpool Victoria Hospital
Dr Anil Shenoy Helena Prady Jane Howell Jamie Dolan	Principal Investigator Research Nurse Research Nurse Research Nurse	Royal Albert Edward Infirmary Wigan
Dr Dhia Mahmood Jacqueline Woods	Principal Investigator Research Nurse	Royal Preston Hospital
Dr Huw Thomas Victoria Payne Tracey Bingham Phoebe Moulsdale	Principal Investigator Research Nurse Research Nurse Research Nurse	Bristol Royal Childrens Hospital
Dr Adrian Harris Su Wilkins Michelle Curtis Layla Price Sue Ward	Principal Investigator Research Nurse Research Nurse Research Nurse Research Nurse	Royal Devon and Exeter Hospital
Dr Ravi Jayaram Caroline Burchett	Principal Investigator Research Nurse	Countess of Chester Hospital
Dr Ang Ho Joanne Shippey	Principal Investigator Research Nurse	Macclesfield District General Hospital
Dr Sharryn Gardner Dr Matouk Zbaeda Zena Haslam Moira Morrison	Principal Investigator Principal Investigator Research Nurse Research Nurse	Ormskirk and District General Hospital
Dr Patrick Ukwade Kirsti Soanes	Principal Investigator Advanced Nurse	Birmingham Heartlands Hospital

Indy Birak Mark Smith	Practitioner Research Nurse Research Nurse	
Dr Kathleen Berry Mark Smith Indy Birak	Principal Investigator Research Nurse Research Nurse	Birmingham Children's Hospital
Dr Tina Newton Hilary Shepley Katharine Beamond	Principal Investigator Research Nurse Research Nurse	University Hospital of North Staffordshire
Dr Mansoor Ahmed Jane Maiden Stephanie Rawlins	Principal Investigator Research Nurse Research Nurse	Queens Hospital, Burton
Dr Richard Brooker Lindsay Cameron	Principal Investigator Research Nurse	Aberdeen Childrens Hospital
Dr James Paton Vincent Choudury Christine Kerr Emma Scobie	Principal Investigator Lead A&E Consultant PA to Principal Investigator Research Nurse	Royal Hospital for Sick Children, Glasgow
Dr Hitesh Pandya Melanie McFeeters Samantha Hunt	Principal Investigator Consultant Nurse Research Nurse	Leicester Royal Infirmary
Dr Will Carroll Coral Smith Vanessa Unsworth Samantha Jones Nicola Watson	Principal Investigator Research Nurse Research Nurse Research Nurse Research Nurse	Derbyshire Children's Hospital
Dr Chris Fitzsimmons Dr Mark Everard Katy Treherne Alyson Barber	Principal Investigator Principal Investigator Research Nurse Research Nurse	Sheffield Children's Hospital
Dr Clare Dieppe Prof Harish Vyas Helen Smith Yvonne Hooton	Principal Investigator Principal Investigator Research Nurse Research Nurse	Queens Medical Centre Nottingham
Dr John Criddle Lorraine Hodsdon Victoria Timms	Principal Investigator Research Nurse Research Nurse	St Thomas' Hospital
Dr Ami Parikh Frances Ling Gemma Barry	Principal Investigator Research Nurse Research Nurse	Royal London Hospital

Pauleen Waithe	Research Nurse	
Dr Jane Bayreuther Eniola Nsirim	Principal Investigator Research Nurse	University Hospital Lewisham
Dr Michael Smith Sara Gilpin	Principal Investigator Research Nurse	Craigavon Area Hospital
Dr Damien Armstrong Julie Brown	Principal Investigator Research Nurse	Altnagelvin Area Hospital
Dr Katherine Potier Anne Cook Helena Prady	Principal Investigator Research Nurse Research Nurse	Manchester Children's Hospital
Dr Hazel Evans Cilla Long Michelle Casey	Principal Investigator Research Nurse Research Nurse	Southampton General Hospital
Dr Anil Tuladhar Dr Venkata Paturi Catherine Tarn Nozedar	Principal Investigator Sub Investigator Research Nurse	University Hospital North Tees
Dr Anne Prendiville Jo Webber Hannah Solomon	Principal Investigator Research Nurse Research Nurse	Royal Cornwall Hospital

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APPENDICES

APPENDIX 1: Summary of the features of the 16 published RCTs on nebulised magnesium up to 2012
APPENDIX 2: Summary of methods of resource use valuation
APPENDIX 3: Statistical analysis plan
APPENDIX 4: Details of protocol amendments
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APPENDIX 6: Sensitivity analyses for centre effect
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APPENDIX 1: Summary of the features of the 16 published RCTs on nebulised magnesium up to 2012

Table 1: Summary of severity, definitions used and age of population examined

Study	Severity	Based on	Adult/mixed/paediatric
Abreu-Gonzalez 2002	Moderate	FEV1 and PEFR at baseline	Adults (?)
Aggarwal 2006	Severe and life threatening	BTS definition clinical features and PEFR	Mixed (13-60)
Ashtekar 2008	Severe	BTS definition clinical features	Paediatric (2-16)
Bessmertny 2002	Moderate to severe	PEFR between 40%-80%	Adults (18-65)
Dadhich 2005	Severe	PEFR < 50%	Adults (?)
Drobina 2006	Unclear	Used PEFR and clinical signs	Adults (?)
Gallegos-Solórzano 2010	Moderate to severe	FEV1<60%	Adults >18
Gaur 2008	Severe	FEV1 < 30%	Adults (18-60)
Hughes 2003	Severe	FEV1 <50%	Adults (16-65)
Khashabi 2008	Unclear	Clinically defined as respiratory distress	Paediatric (mean age 3.55 years)
Kokturk 2005	Moderate to severe	Clinical scores and PEFR	Adults (18-60)
Mahajan 2004	Moderate to severe	FEV1 between 45% and 75%	Paediatric (5-17)
Mangat 1998	Moderate to severe	PEFR < 300L/Min	Mixed (12-60)
Meral 1996	Moderate to severe	PEFR <75%	Paediatric (? age)
Nannini Jr 2000	Severe	PEFR <50%	Adult (> 18)
Neki 2006	Severe	FEV1 < 40% or PEFR < 300l/Min	Adult (15-60)

? = age limits not recorded

Table 2: 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	Not clear	Tenerife Spain	FEV1 and PEFR	None documented (24)	None documented	None documented
Aggarwal 2006	Emergency department	New Delhi India	PEFR	Palpitations (Sal/Mg; 13 and Sal/placebo; 11) and tremors (7 and 7). Nothing else noted (100)	None documented	Clinicians free to administer steroids, more salbutamol if needed –iv hydrocortisone
Ashtekar 2008	Children's Assessment Unit after GP referral	Cardiff, Wales	ASS (Yung 1996)	One given Mg had tingling in fingers and another one transient self limiting hypotension (TSLH) with facial flushing (17)	None documented	2mg/kg prednisolone
Bessmertny 2002	Emergency department	Brooklyn, USA	FEV1 (% predicted)	No serous adverse events noted (74)	No theophylline or anticholinergics 2 hours prior to presentation	2mg/kg hydrocortisone 6 hourly
Dadhich 2005	Emergency department	Ajmer India	PEFR	'*Side effects were self limiting'* (71)	Not stated	Not stated
Drobina 2006	Emergency department	USA	PEFR and admissions	No comment (110)	Not stated	50 mg oral prednisolone
Gallegos-Solórzano	Emergency	Mexico City, Mexico	% change FEV1, O2 post treatment and	dry and bitter mouth in Mg group (1) and	Use of steroids prior to	1 mg/kg/day for 10 days

Study	Presentation to which department?	Origin	Primary outcome (s)	Side effects (patients in study)	Pharmaceutical Exclusions	Other Interventions
2010	department		admission rates	dizziness (one in each) (60)	presentation	prednisolone,
Gaur 2008	Emergency Department	Delhi, India	FEV1	None documented (60)	None stated	IV hydrocortisone
Hughes 2003	Emergency departments	Wellington New Zealand	FEV1	None reported (52)	None	100 mg hydrocortisone
Khashabi 2008	Unclear	Urmia, Iran	Mean duration of O2 therapy and Respiratory Distress Score (? which one)	There were no side effects (40)	Not stated	Not stated
Kokturk 2005	Emergency department	Gazi, Turkey	PEFR difference	TSLH in Mg 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, anticholinergics and salbutamol given at clinicians discretion
Mahajan 2004	Emergency department	Detroit, USA	% change in FEV1	No side effects occurred (62)	Having received steroids, ipratropium or theophylline in the last three days.	2 mg/kg prednisolone

Study	Presentation to which department?	Origin	Primary outcome (s)	Side effects (patients in study)	Pharmaceutical Exclusions	Other Interventions
Mangat 1998	Emergency department	St John's College, India	PEFR, Fischl index score and admissions	TSLH,(1) palpitation (1) tremors(2) all in control group and only one TSLH n in Mg group (33)	Oral parenteral bronchodilators (6 hours) steroids (last 12 hours)	100mg hydrocortisone IV
Meral 1996	Not clear	Izmir, Turkey	% change in PEFR ASS (Davies Leffert, Dabbous score!) (Davis 1977)	No side effects noted (BP and HR monitored) (40)	No medication taken in the previous 12 hours (beta two agonists and theophylline)	No other medication given
Nannini Jr 2000	Emergency Department	Four hospitals in Argentina	PEFR and admissions	None observed (35)	Oral or parenteral steroids in the last 7 days	None stated
Neki 2006	Not clear	Amritsar Punjab	PEFR, RR and Fischl index (Fischl 1981)	Not commented upon (40)	Oral, inhaled or parenteral bronchodilators in past 6 hours and steroids in last 12 hours	All given 100mg hydrocortisone IV.

Table 3: Summary of Interventions and controls

Study	Magnesium dose	Mixed with	Control comparison	Mixed with
Abreu-Gonzalez 2002 24 patients	2 mls Mg sulphate (isotonic) 13 patients	400mcg Salbutamol (? once)	2 mls of a physiological serum of an inhaled form 11 patients	400 mcg Salbutamol
Aggarwal 2006 100 patients	1 ml of 500mg/ml Mg sulphate AS – 29 ALT - 21	1 ml salbutamol (? dose) 8 mls distilled water (295 mosml/kg) times three in an hour (ultrasonic nebuliser)	7.5 mls normal saline AS - 30 ALT - 20	1 ml salbutamol (? dose) 1.5 mls distilled water (287 mosml/kg) three times on one hour
Ashtekar 2008 17 patients	2.5 mls isotonic Mg sulphate ((151 mg /dose) 7 patients	500 mcg Ipratropium bromide 2.5 mg salbutamol or 5 mg salbutamol (2-5 and >5 years) three times in one hour	2.5 mls of isotonic saline) 10 patients	500 mcg Ipratropium bromide 2.5 mg salbutamol or 5 mg salbutamol (2-5 and >5 years) three times in one hour
Bessmertny 2002 74 patients	Mg sulphate (384 mg) 34 patients (3 withdrawn)	Followed by (ie not mixed) Albuterol 2.5 mg/mls Three times I one hour	Normal saline (no volume documented) 34 patients (3 withdrawn)	Followed by (i.e. not mixed) Albuterol 2.5 mg/mls three times in one hour
Dadhich 2005 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 110 patients	150mg Mg Sulphate (0.3mL of 50% magnesium sulphate heptahydrate) 60 patients (from Goodacre)	Albuterol sulphate (0.5%) 5mg/ml) and 0.5mg ipratropium bromide (0.02% inhalation solution) Unclear how frequent	No placebo so volume will be less – i.e. blinding my be an issue 50 patients (from Goodacre)	Albuterol sulphate (0.5%) 5mg/ml) and 0.5mg ipratropium bromide (0.02% inhalation solution)
Gallegos-Solórzano 2010 112 patients (60 completed)	3 mls (333mg) of 10% isotonic Mg sulphate (1g/10ml). 60 randomised 30 completed	2.5 mg albuterol and 500 mcg ipratropium three doses in an hour	3 mls of isotonic saline 52 randomised 30 completed	2.5 mg albuterol and 500 mcg ipratropium three doses in an hour
Gaur 2008 60 patients	3 ml (3.2gms%) 30 patients isotonic Mg sulphate 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 52 patients	2.5ml isotonic Mg sulphate (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

Study	Magnesium dose	Mixed with	Control comparison	Mixed with
Khashabi 2008 40 patients	Isotonic Mg sulphate (? dose) Unclear how many	Salbutamol (? dose) Possible 2 doses	2.5 ml normal saline Unclear how many	Salbutamol (?dose) Possibly 2 doses
Kokturk 2005 26 patients	Isotonic Mg Sulphate (2.5ml) 14 patients	Salbutamol (? dose) Three doses in an hour then hourly for the rest of the four hours)	2.5 ml normal saline 12 patients	Salbutamol (? dose) Three doses in an hour then hourly for the rest of the four hours)
Mahajan 2004 62 patients	2.5 ml Isotonic (6.3%) Mg sulphate solution 31 patients	Albuterol 2.5mg One dose only	2.5 ml normal saline 31 patients	Albuterol 2.5 mg one dose only
Mangat 1998 33 patients	3.2% solution Mg sulphate = 95mg) 16 patients	Four does every 20 minutes	3 ml (2.5mg) salbutamol 17 patients	Four doses every 20 minutes
Meral 1996 40 patients	2 ml Mg Sulphate (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 35 patients	3 ml isotonic Mg Sulphate (286 mOsml, 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 40 patients	20 patients 3.2G% Mg Sulphate 20 patients	Four dose twenty minutes apart	3 ml of ? 25mg salbutamol 20 patients	Four dose 20 minutes apart
Total 896 randomized but 33 interventions and 25 controls withdrawn after randomization so TOTAL completed studies 838	452 + the Drobina presumed 20 = 472 minus the 33 withdrawals = 439 completed intervention studies		404 + the Drobina presumed 20 = 424 minus the 25 controls withdrawn = 399 completed the control studies	

? = 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: BNF60 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.
Accident and Emergency visit	All children incurred the cost of an Accident and Emergency 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 • Visit leading to admitted (£131) • Visit NOT leading to admitted (£97) In the sensitivity analysis, NHS Reference Costs 2009-2010 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 high dependency unit (HDU)/paediatric intensive care unit (PICU). The per diem general medical ward cost (£368) was taken from the NHS Reference Costs 2009-10 (DZF15F-Asthma without complications without intubation). This closely matched a general ward per diem estimate provided by the Finance/Accounts Department of Alder Hey Hospital, Liverpool of £348. 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 (Critical Care Paediatric Beddays) 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 less than 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, 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 less than 12 hours were not costed in the analysis.
Adverse events	The cost of concomitant medications used to treat adverse events were estimated using Prescription Costs Analysis data (2010). The costs of additional days in hospital as a result of an adverse event were included in the hospital stay costs up until 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. 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. 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 (DZF15F-Asthma without complications without intubation). This closely matched a general ward per diem estimate provided by the Finance/Accounts Department of Alder Hey Hospital, Liverpool of £348.
Outpatient attendance	All costs were taken from PSSRU Unit Costs of Health Care 2010. Outpatient attendance costs were divided into three separate cost categories: Accident and Emergency 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) 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 calls 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 Out of hours walk-in appointment (£38)[VB11Z, No investigation with no significant treatment). In the sensitivity analysis, the NHS Reference Cost (2009-10) out of hours walk-in appointment cost of £45 was used (VB09Z, Category one investigation with 1-2 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, childcare 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.
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, childcare costs and "other" expenses. Expenses also included a specific "other" cost category: e.g. 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.

APPENDIX 3: Statistical analysis plan

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

Parent outcomes at follow-up (1 month)

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

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:

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

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

Exclusion Criteria

j. Coexisting respiratory disease such as cystic fibrosis or chronic lung disease of prematurity
k. Severe renal disease
l. Severe liver disease
m. Known to be pregnant
n. Known to have had a reaction to magnesium previously
o. Parents who are unable to give informed consent
p. Previously randomised into MAGNETIC trial
q. Patients who present with life threatening symptoms
r. 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

Recruiting Centre	Minimum Target Accrual per centre
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 randomization 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 randomized.

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.

Randomization 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^{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)

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: k. Oxygen saturations less than 92% while breathing room air l. Too breathless to talk m. Heart rate greater than 120 bpm n. Respiratory rate greater than 30 breaths/min o. 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 k. Oxygen saturations less than 92% while breathing room air l. Too breathless to talk m. Heart rate greater than 130 bpm n. Respiratory rate greater than 50 breaths/min **o.** 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	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

Protocol specification	Potential deviation(s)	Impact	Justification (in terms of whether bias is likely in the assessment of 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+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	Deviation in the method of assessment	Major	Introduce bias in the assessment of response
Number and frequency of additional salbutamol administration			
Requirement for intravenous bronchodilator treatment			
Intubation and/or admission to a paediatric intensive care unit (PICU)			
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 confident 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.

A1. Changes to SAP

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 SaO2, due to reasons explained in Section 3.9 of 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+15mins) 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 or less. Therefore if this timing was greater than 55 minutes, this was defined as a deviation outside the acceptable window.

APPENDIX 4: Details of protocol amendments

Final Protocol Version: 6.1, 18/01/2010

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

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

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

Pg 21 7.2 Formulation, Packaging, Labelling, Storage and Stability: This section has been amended to update the procedure for storing the trial medication once dispensed from site pharmacies

Pg 21 7.2.1 Preparation, dosage and administration of study treatment/s: This section has been updated to clarify the procedure for disposal of residual nebuliser volume

Pg 22 7.4 Accountability procedures for study treatment/s: This section has been amended to update the procedure for storage of the trial medication

Pg 30 11.3 Informed consent process: The section has been updated to indicate that approvals for placement/distribution of study information in primary care settings may be sought.

Pg 36 10.9 Responsibilities- MCRN CTU: This section has been updated to confirm that all SAEs will also be reported to the trial IDSMC

Pg 43 13.4 Data Monitoring at MCRN CTU: The process for data querying as been clarified

Pg 57 Appendix C: Change of Investigator- Fairfield General Hospital

Pg 60 Appendix C: Addition of participating site- City General Hospital, UHNS

Pg 61 Appendix C: Change of Investigator- Royal London Hospital

Pg 63 Appendix C: Addition of participating site- University Hospital Lewisham

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

Pg 21 7.2 Formulation, Packaging, Labelling, Storage and Stability: The details of the manufacturing and QP release units have been amended to St Mary's Pharmaceutical Unit, Cardiff and Vale NHS Trust.

Pg 20 6.2 Randomisation: This section has been amended to remove details of stratification of the randomisation in to two age groups.

Pg29 9.2 Method of Randomisation: This section has been amended to remove details of stratification by age. The randomisation will be stratified by centre only.

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

Pg 11 The flow chart has been updated to clarify that follow up will continue if patients are admitted to hospital following the initial 4 hour phase.

Pg 24-25 8.1 Schedule for follow up: This section has been amended to clarify that data will be collected in the event patients are admitted to hospital. Table 2 has been updated to clarify that adverse events and concomitant medication monitoring will continue in the event of admission.

Pg 58 Change in Principal Investigator at Leighton Hospital: The principal Investigator at Leighton Hospital has been changed to Dr Julie Ellison, Consultant Paediatrician.

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

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

Pg 20 6. 1 Screening: Blood pressure, oxygen saturations and respiratory rate will be recording at screening.
6.2 Randomisation: Blood pressure, oxygen saturations and respiratory rate will be recorded prior to randomisation.

Pg 24 8.1 Schedule for follow-up: Blood pressure, oxygen saturations and respiratory rate will be recorded at 20, 40, 60, 120, 180 and 240 minutes following randomisation

Pg 25 Table 2: Blood pressure, oxygen saturations and respiratory rate will be recorded at screening, prior to randomisation, and at 20, 40, 60, 120, 180 and 240 minutes following randomisation

Pg 26 8.3 Procedures for assessing safety: Clarification that blood pressure will also be measured at 20, 40, 60, 120, 180 and 240 minutes following randomisation

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

Pg 21 The role of Stockport Pharmaceuticals and QCNW in IMP manufacture and QP release has been clarified.

Pg 22 The role of the site pharmacies at trial close (return, accountability and destruction) has been clarified.

Pg 38 Age ranges for simplified patient information have been redefined

Pg 39 Reference to the distribution of the flyer/poster has been added

Pg 56 Change of Principal Investigator at Wythenshawe Hospital, South Manchester University Hospitals NHS Foundation Trust.

Pg 60 Change of Principal Investigator at Queens Medical Centre, Nottingham University Hospitals NHS Trust

APPENDIX 5: Description of missing primary outcome data and sensitivity analyses

Table C-1: Key baseline characteristics for those with observed baseline and T60 ASS

Baseline Characteristic	Magnesium (n=228)	Placebo (n=244)
Age (in 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 24hrs	149 (66)	150 (62)
For the last 6hrs or less	30 (13)	38 (16)
SaO2, Mean(SD), range	(n=227) 93.7 (3.5), 84-100	(n=241) 93.4 (3.4), 81-100
Respiratory rate, Mean(SD), range	(n=225) 43.5 (10.5), 20-72	(n=238) 42.4 (10.8), 20-70
Oxygen therapy, n(%)	(n=222)	(n=235)
Yes	88 (40)	94 (40)
No	134 (60)	141 (60)

Table C-2: 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 (in 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 1700-2200 2200-0900	 325 (69) 101 (21) 46 (10)	 24 (67) 7 (19) 5 (14)
ASS at baseline Mean (SD), range	(n=470) 5.8 (1.3), 2-9	(n=32) 5.0 (1.3), 2-7
Duration of the most recent asthma attack, n(%) For the last few days For the last 24hrs For the last 6hrs or less	(n=469) 102 (22) 299 (64) 68 (14)	 6 (17) 25 (69) 5 (14)
SaO2, Mean(SD), range	(n=468) 93.5 (3.4), 81-100	(n=35) 94.4 (3.5), 84-100
Respiratory rate, Mean(SD), range	(n=463) 43.0 (10.6), 20-72	(n=34) 41.6 (11.5), 25-70
Oxygen therapy, n(%) Yes No	(n=457) 182 (40) 275 (60)	(n=31) 10 (32) 21 (68)

C.1 Reasons for exclusion of children from primary outcome analysis

There were 25 children on magnesium group who did not contribute data for the adjusted analysis of the primary outcome of ASS at T60. There were 13 children on placebo group who did not contribute data for the adjusted analysis of the primary outcome. Four children (3 from the magnesium group, 1 from the placebo group) could not contribute ASS data at either baseline or T60.

Table C-3: Reasons for missing primary outcome data

Reason for missing data	Magnesium		Placebo	
	T0	T60	T0	T60
	Number of children	Number of children	Number of children	Number 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*
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[†]	24	2[‡]	12

[†]3 of these also had missing T60 data, [‡]1 of these also had missing T60 data
* One of these is related to poor status

C.2 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 3.6, 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.

C.2.1 Sensitivity analysis (1)

Firstly, if the reason for missingness of ASS at T60 was related to good status, the missing value was replaced by 0 (for 3 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 C-4.

Table C-4: Sensitivity analyses: single imputation based on reason for missingness

	Magnesium n_m=231	Placebo n_p=245	Estimate (95% CI), p-value	
	T60 mean (sd), range	T60 mean (sd), range	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

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% confidence interval.

C.2.2 Sensitivity analysis (2)

Secondly, a model-based imputation of MICE (see Appendix 3, SAP Section 7.4.2) 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 5 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 C-5.

Table C-5: Sensitivity analysis (2): Multiple imputation

	Magnesium n_m=252	Placebo n_p=256	Estimate (95% CI), p-value	
	T60 mean (sd), range	T60 mean (sd), range	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

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

C.2.3 Sensitivity analysis (3)

Thirdly, the problem of non-ignorable missing ASS data was addressed through joint modeling of the longitudinal data and the time to dropout from the study. In this analysis, children who withdrew from the 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 dropout from the study before T60 were censored at T60. In the joint analysis, dropout was modeled 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 3.3 (Section 3.8.1) shows the mean longitudinal profiles over T0 to T60. As shown in Figure 3.3, the mean profiles are almost identical for both Magnesium and placebo groups. However, this pattern could be an artefact of selective drop out, and it would be a biased comparison between the groups unless it is adjusted with joint modelling.

ASS data at T0 were not available for 6 children and their records were excluded from this analysis. Note that these 6 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 C-1 which tends to show that dropout in Magnesium group occurred is because patients get better (most children were clinically well and ready to discharge, as shown in Table 3.13) whilst dropout in placebo occurred is because patients get worse. The results from the joint model are presented in Table C-6.

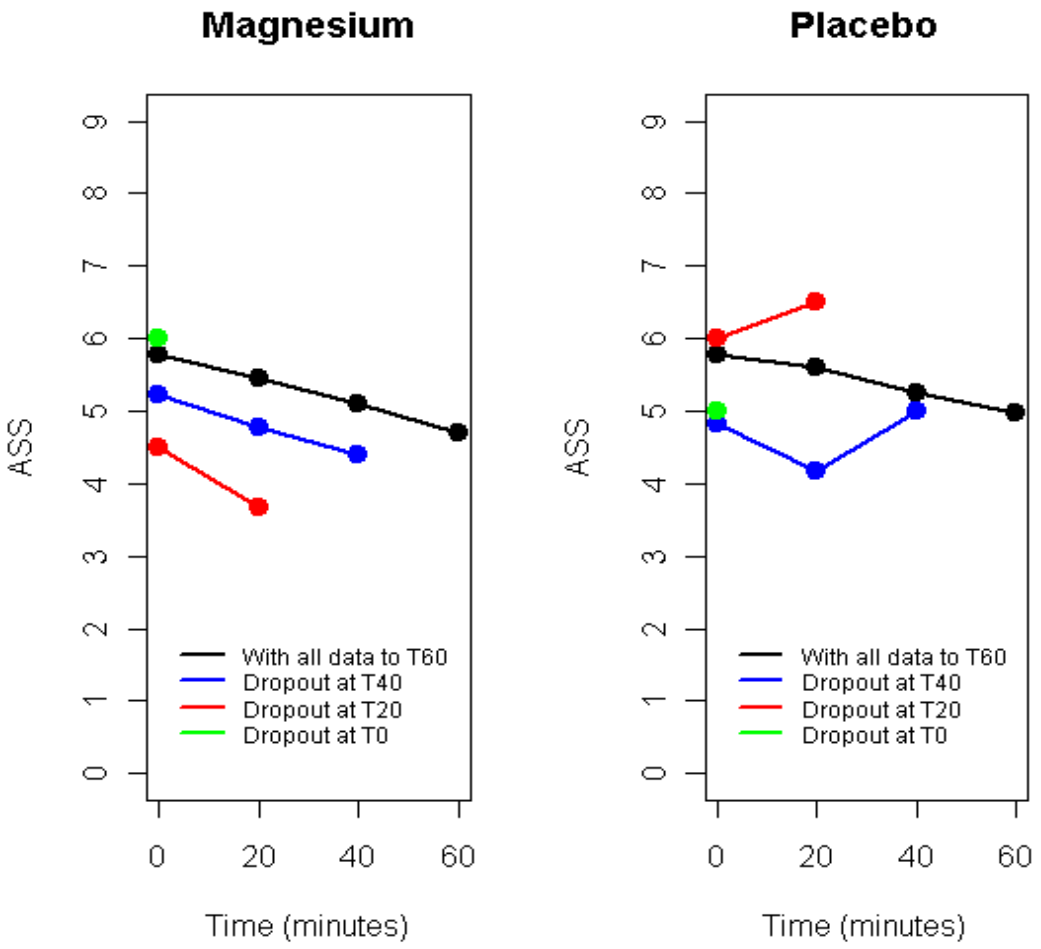


Figure C-1: Mean profiles prior to dropout

Table C-6: Sensitivity analysis (3.1): Joint modelling for T60 data

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

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 modeling. 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 C-2 and the longitudinal mean profiles prior to dropout are shown in Figure C-3. Pattern in Figure C-2 remains the same as that in Figure 3.3 over entire follow-up, however comparison of between groups in this setting may be biased as explained above. Figure C-3 shows similar pattern to Figure C-1 that dropout in Magnesium group is due to children get better and ready to discharge. The results from the joint model are presented in Table C-7. The analysis still shows a statistically significant association between ASS and dropout (95% CI for the parameter γ does not include zero).

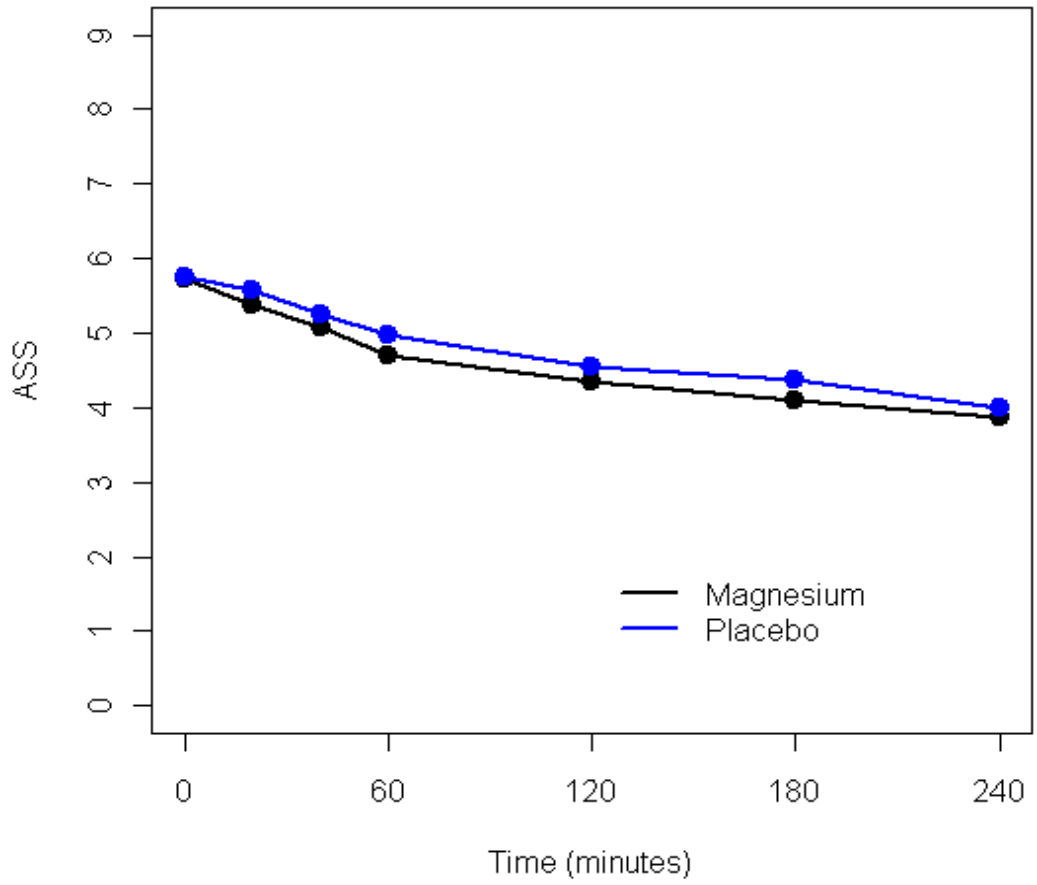


Figure C-2: Mean profiles over entire follow-up

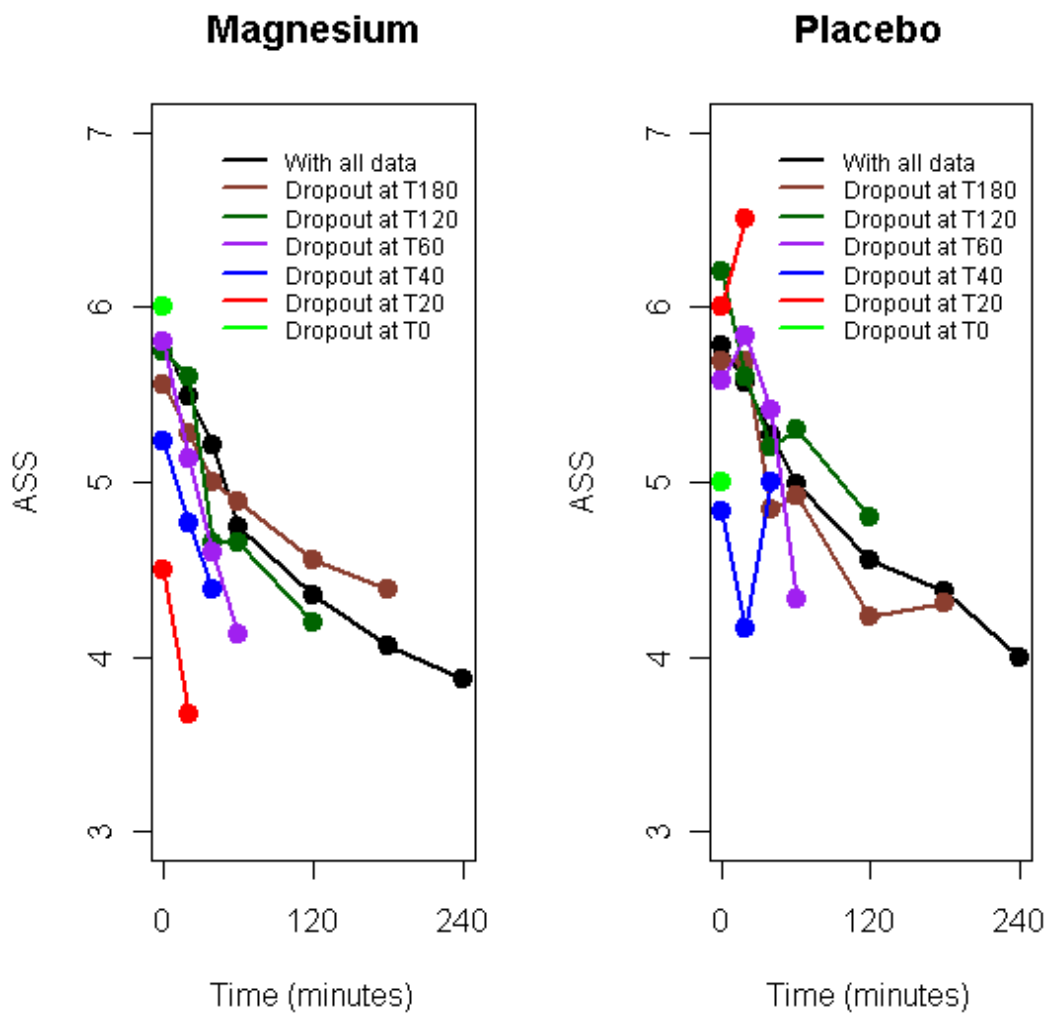


Figure C-3: Mean profiles prior to dropout over entire follow-up

Table C-7: Sensitivity analysis (3.2): Joint modelling for follow-up up to T240

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

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 2nd 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. Both models were also adjusted for baseline ASS. The results are presented in Table D-1.

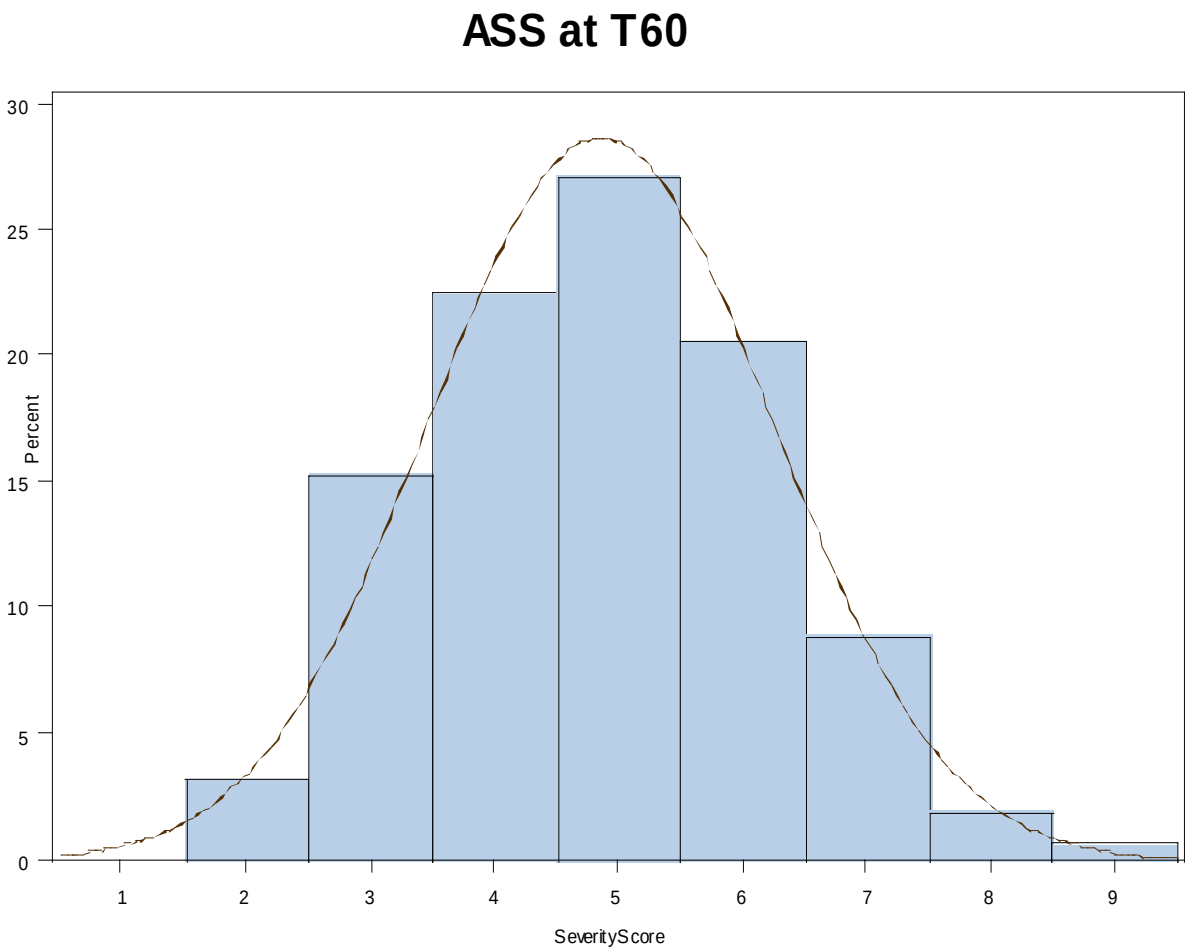
Both random effects analysis of variance and the fixed effect model indicated significant main effect of centre but there is no evidence that the treatment effect varies by centre.

Table D-1: Treatment-centre interaction

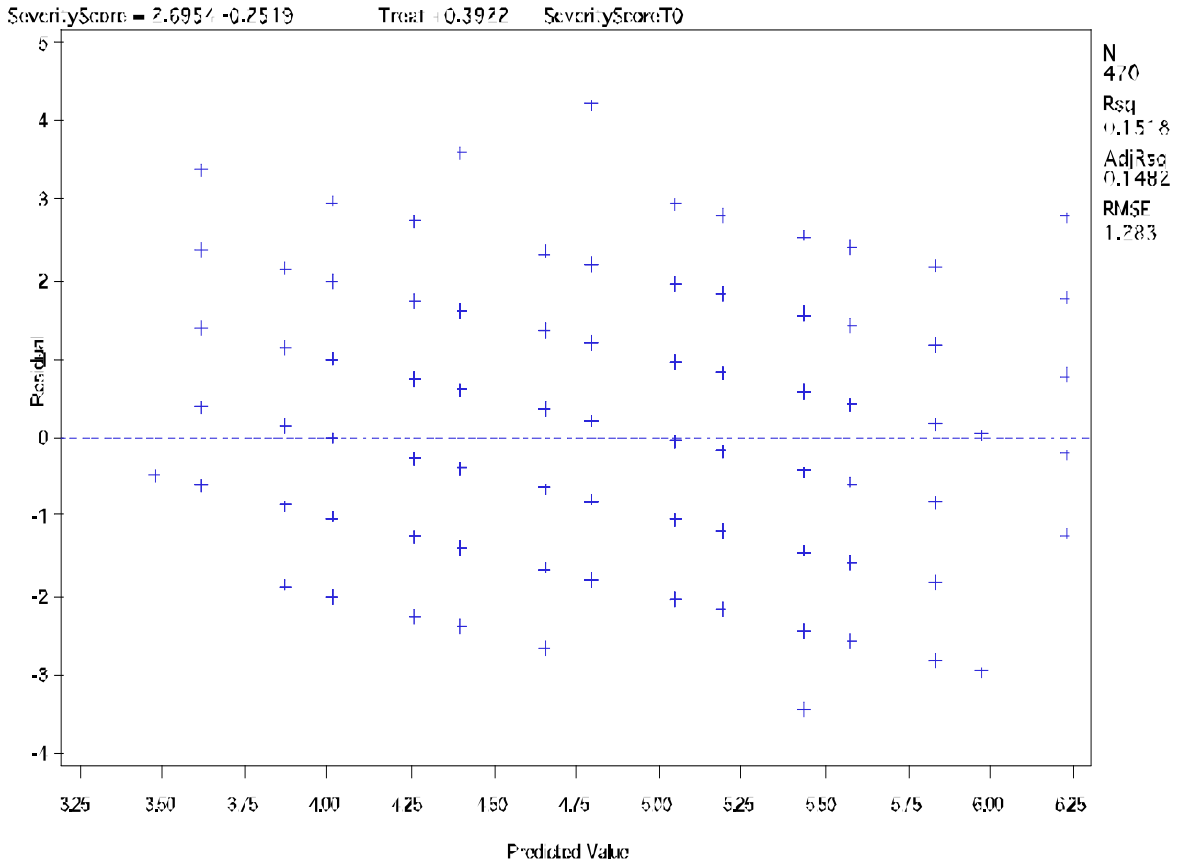
	Model 1: Fixed effects		Model 2: Random effects
	F-value, Type II SS, p-value	F-value, Type III SS, p-value	F-value, Type III SS, p-value
Treatment	5.53, 8.47, p=0.0191	1.83, 2.81, p=0.1766	2.38, 2.81, p=0.1265
Centre	2.56, 113.87, p<0.0001	2.31, 102.81, p=0.0002	3.61, 102.81, p=0.0005
ASS at T0	66.72, 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

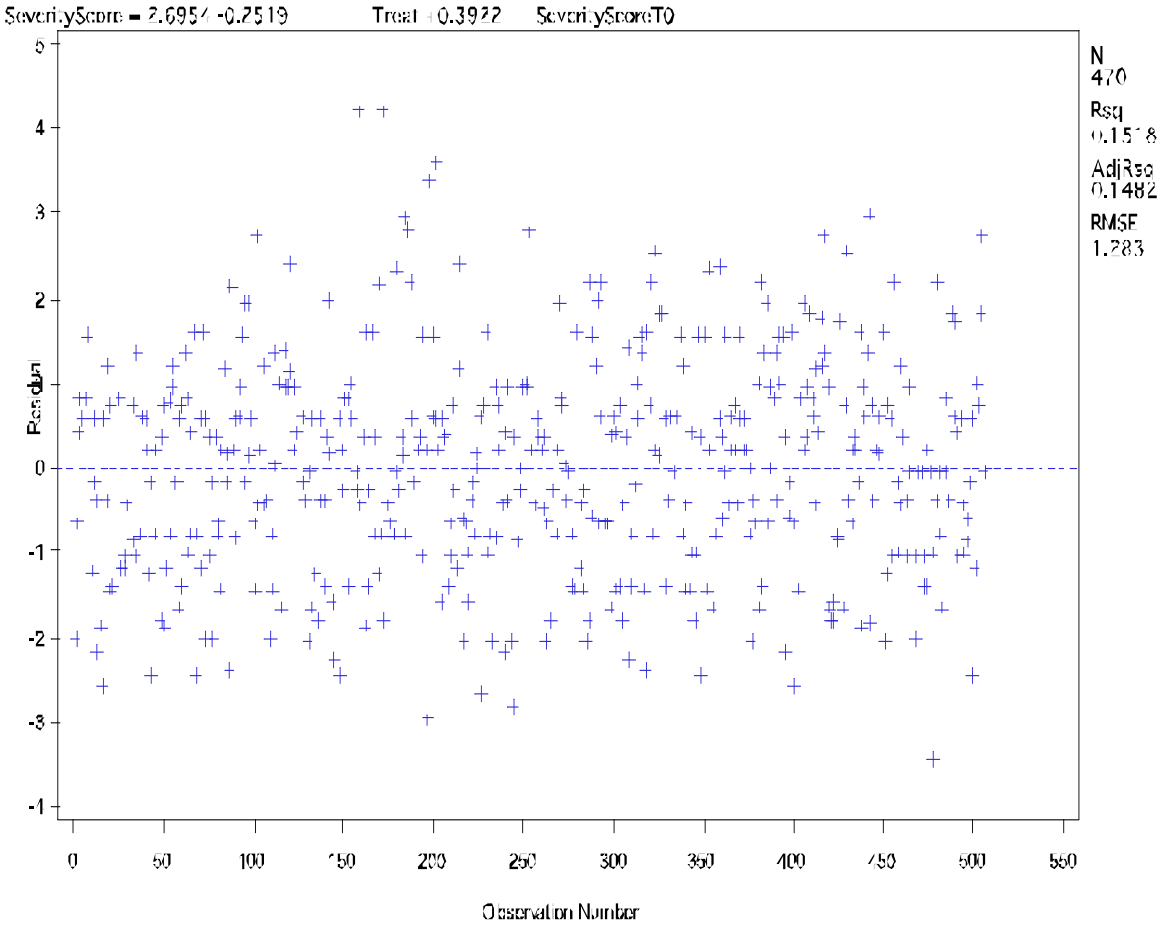
Histogram of ASS at T60 to check normality assumption



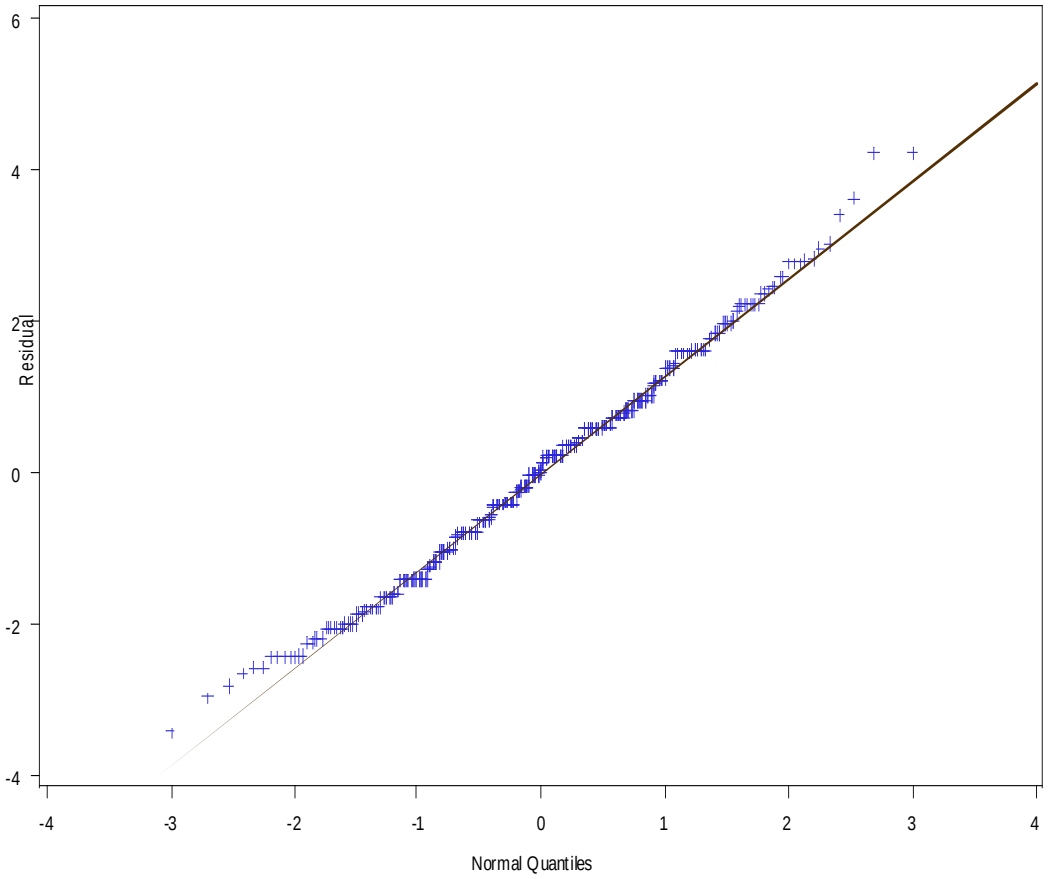
Plot of residuals vs fitted values to check for heteroscedasticity



Index plot to check for correlation between observations

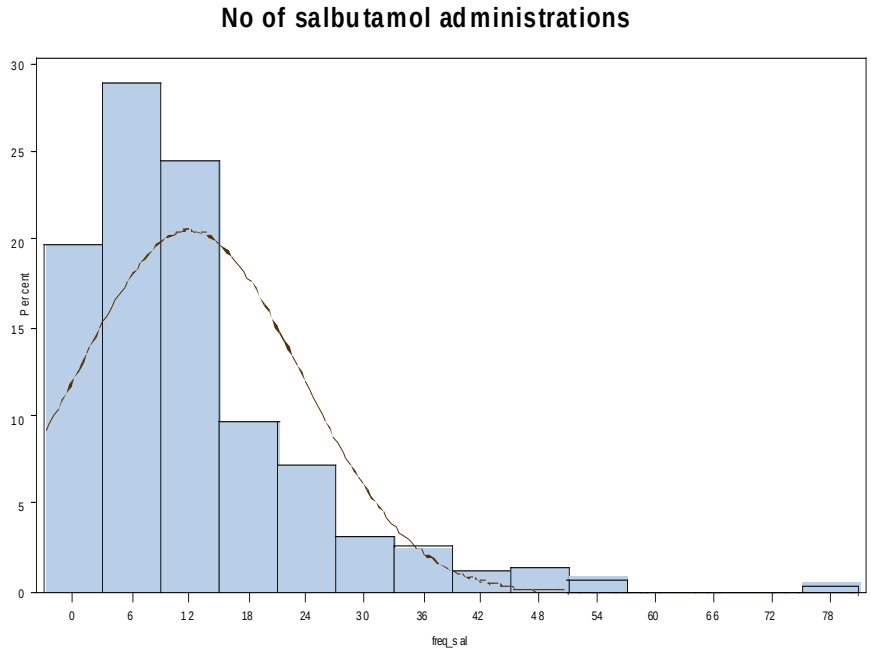


qq-plot to check normality of residuals

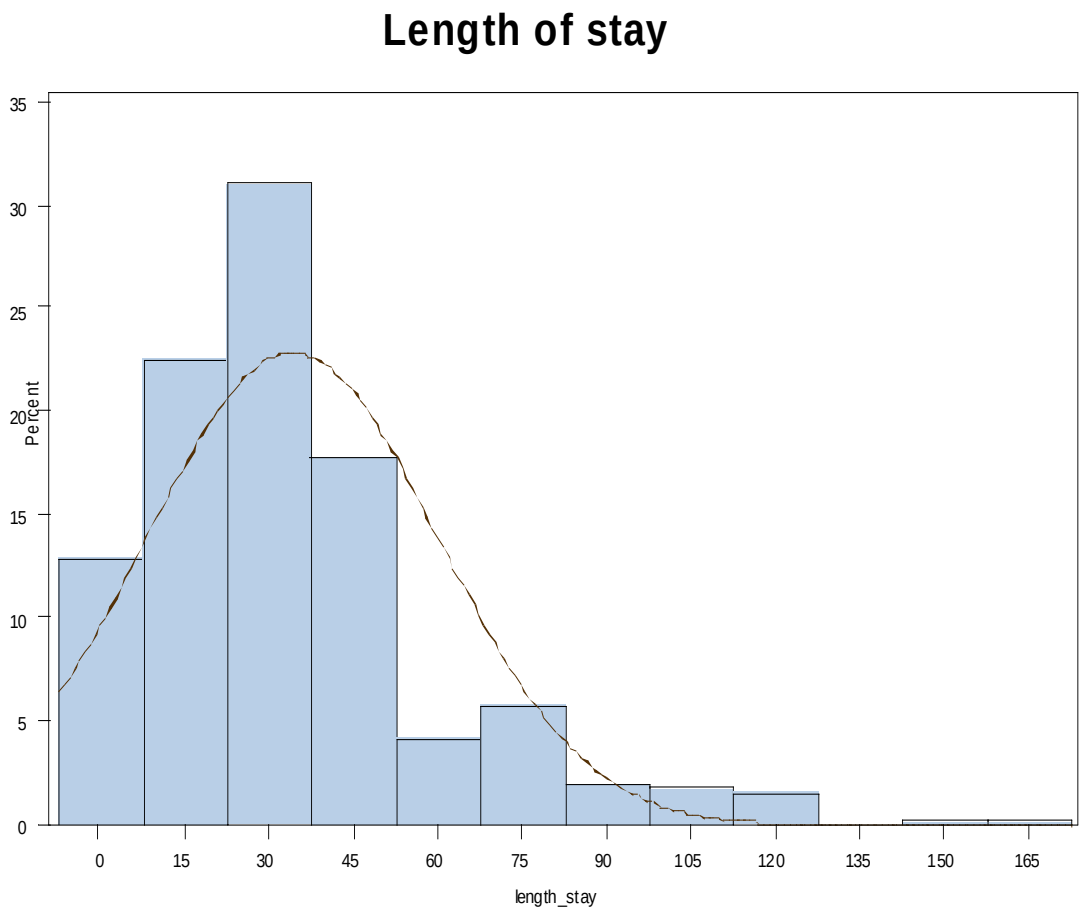


Histograms of continuous secondary outcomes

Number of salbutamol administrations



Length of stay in hours



APPENDIX 8: Patient information sheets

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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

Error! Reference source not found.

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

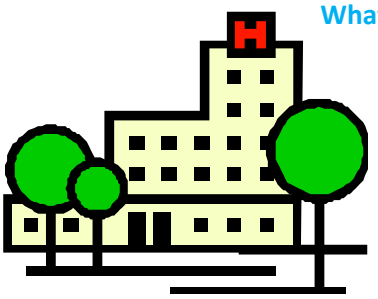
MAGnesium NEbuliser Trial In Children (MAGNETIC) - A randomised, placebo controlled study of nebulised magnesium in acute severe asthma in children.

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.

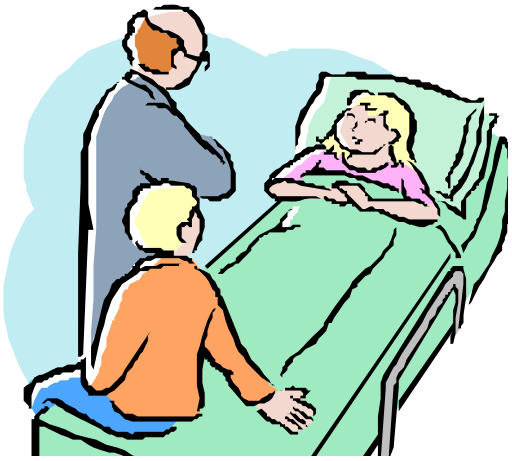
What is happening to me?



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?

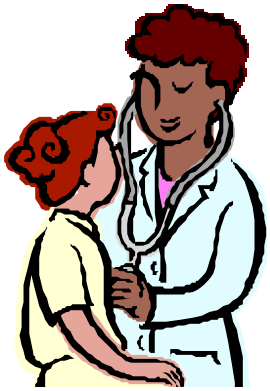
We hope that the medicine might help you to get better more quickly. Other people have had the medicine and were OK.

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.

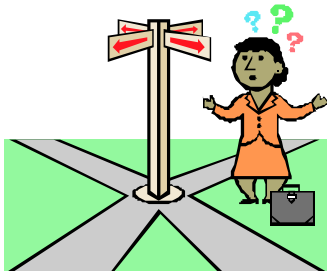
What else will happen in the study?

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.

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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.

Error! Reference source not found.

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?

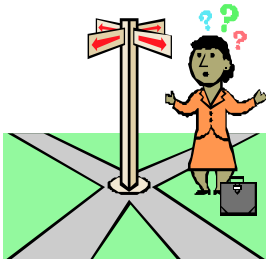
You have been asked because you are having a bad asthma attack.

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?

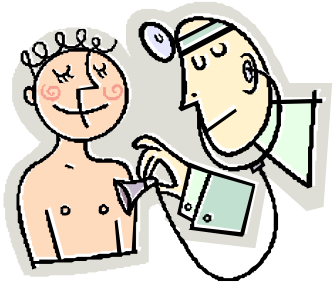


No- not at all, it's up to you. Just say if you don't want to take part; nobody will mind. If you do take part, you will need to write your name on an 'assent form'. This form is to say that you understand the study and what will happen if you take part. You will be given your own copy of the form to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

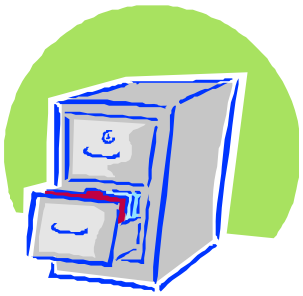
We cannot promise that, but if the medicine helps you get better more quickly we will be able to tell people who will be able to help other children.

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

Error! Reference source not found.

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.

Error! Reference source not found.

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.

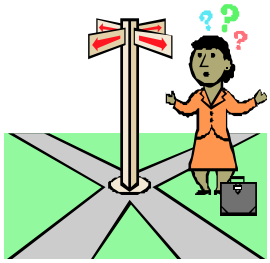
The magnesium sulphate used in this project has been especially made. Half the children will be given the magnesium and half will be given the placebo medicine. You will not be able to choose which medicine you take and will not know which medicine you are taking. Your doctor and nurse will not know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

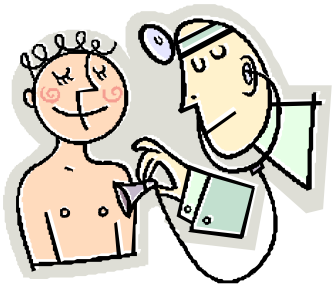


No- not at all. We only want people to take part if they would like to. If you decide not to, don't worry, it won't change how you are looked after. If you decide to take part and then change your mind, that's OK as well- you can stop at any time and don't have to say why if you don't want to.

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

Error! Reference source not found.

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.