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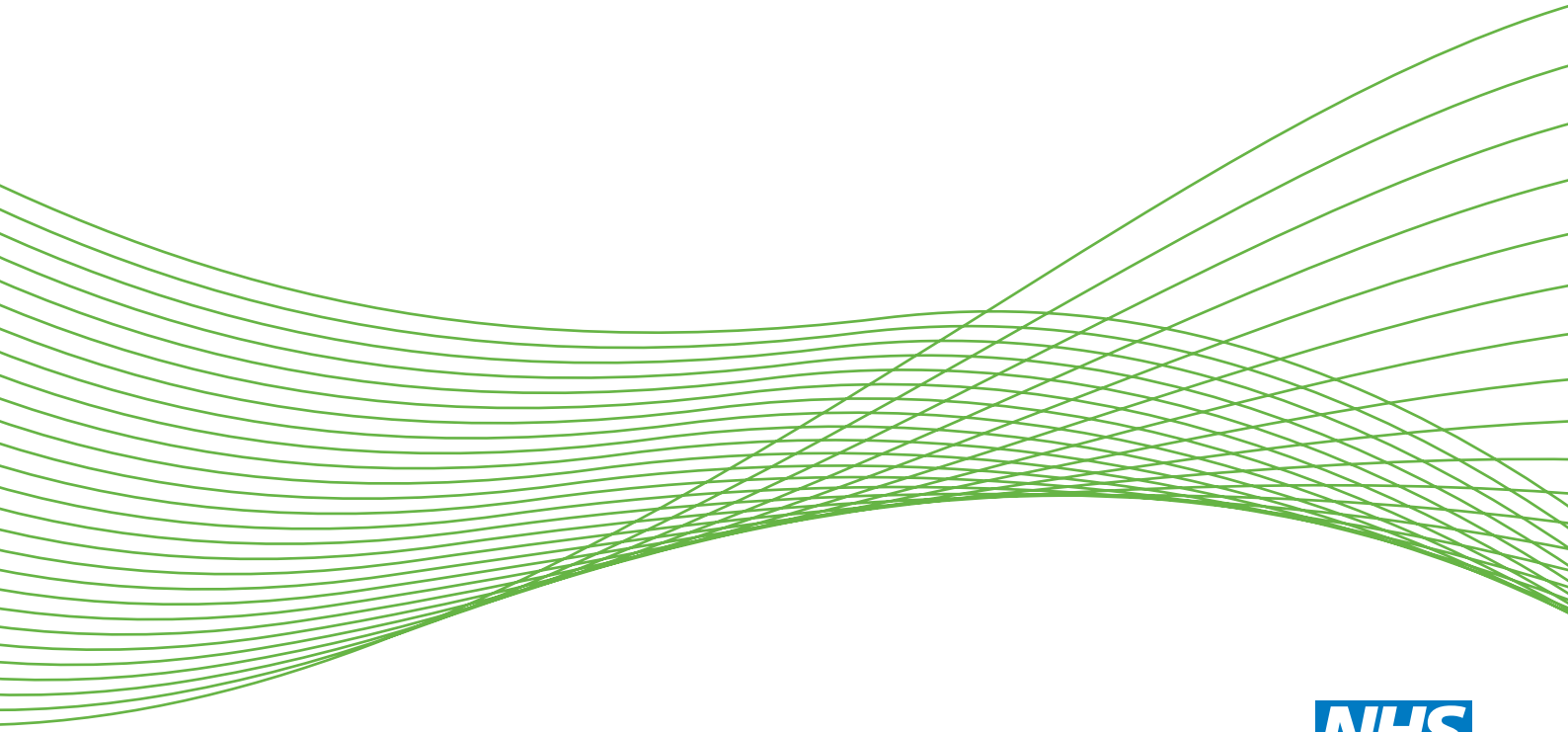

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Abstract

The 3Mg trial: a randomised controlled trial of intravenous or nebulised magnesium sulphate versus placebo in adults with acute severe asthma

Steve Goodacre,[1]* Judith Cohen,[1] Mike Bradburn,[1] John Stevens,[1] Alasdair Gray,[2] Jonathan Benger[3] and Tim Coats[4] on behalf of the 3Mg Research Team

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Background: Magnesium sulphate, administered by the intravenous (i.v.) or inhaled (nebulised) route, has been proposed as a treatment for adults with acute severe asthma. Existing trials show mixed results and uncertain evidence of benefit.

Objectives: We aimed to determine whether i.v. or nebulised magnesium sulphate improves symptoms of breathlessness and reduces the need for hospital admission in adults with acute severe asthma.

Design: Multicentre, double-blind, placebo-controlled, three-arm, randomised trial.

Setting: The emergency departments of 34 acute hospitals in the UK.

Participants: We recruited 1109 adults (age > 16 years) with acute severe asthma [peak expiratory flow rate (PEFR) < 50% of best/predicted, respiratory rate > 25 breaths per minute, heart rate > 110 beats per minute or inability to complete sentences in one breath]. Patients with life-threatening features or a contraindication to either nebulised or intravenous magnesium sulphate were excluded.

Interventions: Participants were randomly allocated to i.v. magnesium sulphate (2 g over 20 minutes) or nebulised magnesium sulphate (3 × 500 mg over 1 hour) or standard therapy alone.

Main outcome measures: The primary outcome was the proportion of patients admitted to hospital (either after emergency department treatment or at any time over the subsequent 7 days) and breathlessness measured on a 100-mm visual analogue scale (VAS) over 2 hours after initiation of treatment.

Results: We randomised 406 patients to i.v. magnesium sulphate, 339 to nebulised magnesium sulphate and 364 to placebo. Hospital admission was recorded for 394, 332 and 358 patients, respectively, and VAS breathlessness for 357, 296 and 323 patients respectively. Mean age was 36.1 years and 763 out of 1084 (70%) patients were female. Intravenous magnesium sulphate was associated with an odds ratio (OR) of 0.73 [95% confidence interval (CI) 0.51 to 1.04; $p = 0.083$] for hospital admission, an improvement in VAS breathlessness that was 2.6 mm (95% CI –1.6 to 6.8 mm; $p = 0.231$) greater than that associated with placebo and an improvement in PEFR that was 2.4 l/minute (95% CI –8.8 to 13.6 l/minute; $p = 0.680$) greater than that associated with placebo. Nebulised magnesium sulphate was associated with an OR of

0.96 (95% CI 0.65 to 1.40; $p = 0.819$) for hospital admission, an improvement in VAS breathlessness that was 2.6 mm (95% CI –1.8 mm to 7.0 mm; $p = 0.253$) less than that associated with placebo and an improvement in PEFR that was 2.6 l/minute (95% CI –9.2 to 14.5 l/minute; $p = 0.644$) less than that associated with placebo. There were no significant differences between i.v. or nebulised magnesium sulphate and placebo for any other outcomes. The number (%) of patients reporting any side effect was 61 (15.5%) in the i.v. group, 52 (15.7%) in the nebuliser group and 36 (10.1%) in the placebo group. The ORs for suffering any side effect were 1.68 (95% CI 1.07 to 2.63; $p = 0.025$) for i.v. compared with placebo and 1.67 (95% CI 1.05 to 2.66; $p = 0.031$) for nebuliser compared with placebo.

Conclusions: We were unable to demonstrate a clinically worthwhile benefit from magnesium sulphate in acute severe asthma. There was some weak evidence of an effect of i.v. magnesium sulphate on hospital admission, but no evidence of an effect on VAS breathlessness or PEFR compared with placebo. We found no evidence that nebulised magnesium sulphate was more effective than placebo.

Trial registration: Current Controlled Trials ISRCTN04417063.

Source of funding: This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 18, No. 22. See the NIHR Journals Library programme website for further project information.

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List of abbreviations

AUROC	area under the receiver operating characteristic
BNF	*British National Formulary*
BTS	British Thoracic Society
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
ED	emergency department
EQ-5D	European Quality of Life-5 Dimensions
FEV_1	forced expiratory volume in 1 second
GCP	good clinical practice
GP	general practitioner
HDU	high-dependency unit
IB	investigator's brochure
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IMP	investigational medicinal product
IMPD	investigational medicinal product dossier
i.v.	intravenous
MHRA	Medicines and Healthcare products Regulatory Agency
MIA	manufacturer's/importer's licence
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OR	odds ratio
PEFR	peak expiratory flow rate
PI	principal investigator
PMG	Project Management Group
QALY	quality-adjusted life-year
QP	qualified person
REC	Research Ethics Committee
RHH	Royal Hallamshire Hospital
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SMD	standardised mean difference
SOP	standard operating procedure
STH	Sheffield Teaching Hospitals
TSC	Trial Steering Committee
VAS	visual analogue scale

Scientific summary

Background

Magnesium sulphate, administered by the intravenous (i.v.) or inhaled (nebulised) route, has been proposed as a treatment for acute severe asthma. Meta-analysis of 11 trials (1018 patients) of i.v. magnesium sulphate in adults with acute asthma showed evidence of an effect on respiratory function [standardised mean difference (SMD) 0.35, 95% confidence interval (CI) 0.06 to 0.64; $p = 0.02$] but not hospital admission [relative risk (RR) 0.85, 95% CI 0.68 to 1.06; $p = 0.14$]. Meta-analysis of seven trials (430 patients) of nebulised magnesium sulphate in adults with acute asthma showed weak evidence of improved respiratory function (SMD 0.17, 95% CI –0.02 to 0.36; $p = 0.09$) but not hospital admission (RR 0.87, 95% CI 0.70 to 1.08; $p = 0.22$). No previous trials have directly compared i.v. with nebulised magnesium sulphate. It is not clear whether changes in measures of respiratory function are associated with important changes in patient management or a clinically meaningful improvement in symptoms.

Objectives

We aimed to measure the effectiveness and cost-effectiveness of i.v. and nebulised magnesium sulphate in acute severe asthma. Our specific objectives were to determine whether (1) i.v. or nebulised magnesium sulphate reduces the proportion of patients who require admission at initial presentation or during the following week and (2) i.v. or nebulised magnesium sulphate improves patients' assessment of their breathlessness over 2 hours after initiation of treatment. We also measured the effect of i.v. or nebulised magnesium sulphate on length of hospital stay; use of the intensive care unit (ICU) or high-dependency unit (HDU); mortality; adverse events and use of respiratory support; change in peak expiratory flow rate (PEFR) and physiological variables after initial treatment; health utility; patient satisfaction with care; use of health and social services over the following month; time taken off work; and health and social care costs.

Methods

We undertook a multicentre, double-blind, placebo-controlled, three-arm, randomised trial in 34 emergency departments (EDs) in the UK. Adults (age > 16 years) attending the ED with acute severe asthma were eligible for recruitment (i.e. acute asthma with either PEFR < 50% of best or predicted, respiratory rate > 25 breaths per minute, heart rate > 110 beats per minute or inability to complete sentences in one breath). We excluded patients who had life-threatening features, a contraindication to either nebulised or i.v. magnesium sulphate (pregnancy, hepatic or renal failure, heart block or known hypermagnesaemia), those unable to provide written or oral consent and previous participants in the 3Mg trial. We amended the protocol during the trial to also exclude those patients who had received magnesium sulphate in the 24 hours prior to recruitment. Written or verbal consent was sought from all participants.

Consented participants were randomised to either (1) i.v. magnesium sulphate, 8 mmol (2 g) in 100 ml normal saline given over 20 minutes and three 7.5-ml vials of 0.9% saline nebulised at 20-minutes intervals; or (2) i.v. normal saline, 100 ml given over 20 minutes and three 7.5-ml vials of 2 mmol (500 mg) magnesium sulphate nebulised at 20-minute intervals; or (3) i.v. normal saline, 100 ml given over 20 minutes and three 7.5-ml vials of 0.9% saline nebulised at 20-minute intervals.

Standard therapy was provided in accordance with guidelines from the British Thoracic Society and Scottish Intercollegiate Guidelines Network (SIGN) and consisted of oxygen, nebulised salbutamol, nebulised ipratropium bromide and oral prednisolone administered during recruitment, followed by up to 5 mg of salbutamol added to each trial nebuliser. Other treatments were given at the discretion of the clinician.

Two primary outcomes were specified: (1) admission to hospital, either after ED treatment or at any time over the subsequent week, and (2) visual analogue scale (VAS) for breathlessness over 2 hours after initiation of treatment. Secondary outcomes included mortality; adverse events; use of ventilation or respiratory support; length of hospital stay; use of ICU or HDU; change in PEFR and physiological variables (oxygen saturation, heart rate, respiratory rate, blood pressure) over 2 hours; quality of life at baseline and at 1 month; number of unscheduled health-care contacts over the subsequent month; and satisfaction with care.

We planned to recruit 1200 participants divided equally between the three trial arms (400 participants per arm) to provide the following statistical power: (1) assuming that 80% of patients with acute severe asthma were admitted to hospital, the study would have 90% power to detect a 10% absolute reduction in the proportion admitted (i.e. to 70%) for any pair of treatment groups compared (two-sided $\alpha = 0.05$); and (2) assuming that 80% of participants have their VAS measured, then the study would have 90% power to detect a 0.8-cm difference in a 10-cm VAS at 2 hours after treatment initiation (two-sided $\alpha = 0.05$). Based on the pre-existing evidence, we selected two primary comparisons for analysis: (1) active treatment (i.v. and nebulised combined) compared with placebo and (2) i.v. compared with nebulised treatment. Secondary comparisons were undertaken between i.v. treatment and placebo, and between nebulised treatment and placebo.

Economic evaluation took an approach consistent with the National Institute for Health and Care Excellence (NICE) reference case analysis and the perspective of the NHS and personal social services. Health benefits were measured in two ways using trial data: (1) quality-adjusted life-years (QALYs) using the European Quality of Life-5 Dimensions (EQ-5D) over a 30-day time horizon and (2) breathlessness on 100-mm VAS at 1 and 2 hours after the initiation of study treatment. Resource use data relating to hospital care, community health and social services, and medications were collected using either the hospital records or a patient questionnaire. Productivity loss as a consequence of the number of days patients took off work during the study was determined using the patient questionnaire and separate analyses were conducted excluding and including productivity loss. The primary economic analysis was a cost-effectiveness analysis using the QALYs associated with treatment, focusing on the probability that the intervention arms would be cost-effective at funding thresholds of £20,000 and £30,000 per QALY. Additionally, the change from baseline in breathlessness 2 hours after the initiation of study treatment was used as a secondary cost-effectiveness analysis.

We also planned to undertake an additional analysis of trial data to identify factors that predict unsuccessful treatment for acute severe asthma. We examined the ability of PEFR, physiological variables, age, sex, ethnicity, smoking status, and previous hospital high-dependency and intensive care admissions to predict unsuccessful treatment, defined at two levels: (1) need for critical care (HDU or ICU admission, ventilator support, respiratory arrest, cardiac arrhythmia or death) and (2) need for emergency medical treatment, either by return to the ED or unscheduled medical review as an inpatient. Univariate analysis was undertaken to identify factors that are associated with either outcome ($p < 0.15$), which were then entered into multivariate models for each outcome to identify independent predictors of unsuccessful treatment.

Results

Patients were recruited across 34 hospitals between 30 July 2008 and 30 June 2012. Of the 1109 patients recruited, 25 either withdrew or were recruited in error (protocol violations) and, therefore, 1084 were

included in the analysis. The mean age of patients was 36.1 years; 763 (70%) were female, 974 (90%) were white and 363 (33%) were current smokers. Salbutamol was given to 1074 out of 1084 participants (99%) in the ambulance or ED prior to randomisation or up to 4 hours after, with a mean total dose of 8.3 mg [standard deviation (SD) 3.4 mg]. Overall, 1032 out of 1084 (95%) of the trial population received corticosteroid therapy at some point from 24 hours prior to hospital attendance to 4 hours after randomisation. Adherence to the trial protocol was high, with 89% receiving the full 100-ml i.v. infusion and 99% receiving three trial nebulisers.

The proportion of participants admitted to hospital was 285 out of 394 (72%) in the i.v. magnesium sulphate group, 261 out of 332 (79%) in the nebulised group and 281 out of 358 (78%) in the placebo group. The odds ratios (ORs) for admission to hospital were 0.84 (95% CI 0.61 to 1.15; $p = 0.276$) for active treatment compared with placebo, 0.76 (95% CI 0.53 to 1.10; $p = 0.146$) for i.v. compared with nebuliser, 0.73 (95% CI 0.51 to 1.04; $p = 0.083$) for i.v. compared with placebo and 0.96 (95% CI 0.65 to 1.40; $p = 0.819$) for nebuliser compared with placebo.

The change in VAS at 2 hours was recorded in 976 out of 1084 (90%) of the cohort. The mean (SD) change from baseline to 2 hours was 34.3 mm (SD 27.7 mm) in the i.v. group, 28.2 mm (SD 27.4 mm) in the nebulised group and 31.3 mm (SD 29.4 mm) in the placebo group. The mean differences in improvement in VAS were 0.0 mm (95% CI –3.7 to 3.7 mm; $p = 0.999$) for active treatment compared with placebo, 5.1 mm (95% CI 0.8 to 9.4 mm; $p = 0.019$) for i.v. compared with nebuliser, 2.6 mm (95% CI –1.6 to 6.8 mm; $p = 0.231$) for i.v. compared with placebo and –2.6 mm (95% CI –7.0 to 1.8, $p = 0.253$) for nebuliser compared with placebo.

Mean (SD) length of hospital stay was 57.0 hours (SD 75.1 hours) in the i.v. group, 63.2 hours (SD 79.7 hours) in the nebuliser group and 63.3 hours (SD 84.3 hours) in the placebo group (overall log-rank test, $p = 0.48$). The number of participants (%) in each group admitted to ICU was 11 (3%) in the i.v. group, nine (3%) in the nebulised group and five (1%) in the placebo group ($p = 0.161$ active vs. placebo; $p = 0.947$ i.v. vs. nebuliser). The number of participants (%) admitted to HDU was 23 (6%) in the i.v. group, 22 (7%) in the nebuliser group and 20 (6%) in the placebo group ($p = 0.690$ active vs. placebo, $p = 0.661$ i.v. vs. nebuliser). The number of participants (%) requiring ventilator support was six (2%) in the i.v. group, three (1%) in the nebuliser group and four (1%) in the placebo group ($p = 0.936$ active vs. placebo; $p = 0.458$ i.v. vs. nebuliser).

The mean (SD) change from baseline to 2 hours in PEFR was 61.0 l/minute (SD 73.6 l/minute) in the i.v. group, 58.3 l/minute (SD 77.3 l/minute) in the nebulised group and 62.5 l/minute (69.4 l/minute) in the placebo group. The mean differences in improvement in PEFR were –2.5 (95% CI –12.5 to 7.5; $p = 0.625$) for active treatment compared with placebo, 0.3 (95% CI –11.2 to 11.7; $p = 0.964$) for i.v. compared with nebuliser, –2.4 (95% CI –13.6 to 8.8; $p = 0.680$) for i.v. compared with placebo and –2.6 (95% CI –14.5 to 9.2; $p = 0.664$) for nebuliser compared with placebo. There were no significant differences in the primary comparisons for other physiological secondary outcomes (heart rate, respiratory rate, blood pressure and oxygen saturation).

Rates of adverse events were low, with most of the events recorded being hospital admission due to underlying asthma or other unrelated conditions. There were two deaths, one cardiac arrest, two cases of arrhythmia, seven intubations and seven cases requiring non-invasive ventilation (17 patients). The number (%) of patients reporting any side effect was 61 (15.5%) in the i.v. group, 52 (15.7%) in the nebuliser group and 36 (10.1%) in the placebo group. The ORs for suffering any side effect were 1.68 (95% CI 1.11 to 2.52; $p = 0.014$) for active treatment compared with placebo, 1.00 (95% CI 0.66 to 1.52; $p = 0.988$) for i.v. compared with nebuliser, 1.68 (95% CI 1.07 to 2.63; $p = 0.025$) for i.v. compared with placebo and 1.67 (95% CI 1.05 to 2.66; $p = 0.031$) for nebuliser compared with placebo.

Satisfaction with care was generally high across all three treatment groups and across most dimensions of care. The dimensions of care relating to personal interest in the patient and their medical problems, the

amount of time given by hospital staff, and especially advice given about ways to avoid illness and stay healthy were generally rated lower. There were no significant differences in any of the primary comparisons between the treatment groups.

The mean EQ-5D scores at baseline were 0.726 (SD 0.354) in the i.v. group, 0.734 (SD 0.327) in the nebulised group and 0.746 (SD 0.323) in the placebo group. Corresponding scores at 1 month were 0.731 (SD 0.329), 0.721 (SD 0.326) and 0.810 (SD 0.250). There were no significant differences in any of the comparisons between treatment groups.

The primary economic analysis (without productivity costs) showed mean QALYs per patient of 0.060 (SD 0.0033), 0.060 (SD 0.0028) and 0.063 (SD 0.0030), and mean costs per patient of £1870 (SD £110.80), £1974 (SD £115.30) and £1610 (SD £89.70) for the i.v., nebulised and placebo groups respectively. Mean costs per patient increased to £2219 (SD £120.40), £2401 (SD £120.80) and £2007 (SD £107.20), respectively, when productivity costs were included. There was a 93% and 92% chance that the placebo had the highest net benefit at thresholds of £20,000 and £30,000 respectively.

The baseline PEFR ($p = 0.017$), baseline heart rate ($p < 0.001$), change in PEFR after treatment ($p = 0.015$), change in heart rate after treatment ($p < 0.001$) and the presence of another serious illness ($p = 0.019$) predicted the need for critical care. The baseline PEFR ($p = 0.010$), baseline heart rate ($p < 0.001$), baseline respiratory rate ($p = 0.017$), change in PEFR after treatment ($p = 0.003$), change in heart rate after treatment ($p = 0.001$) and the presence of another serious illness ($p = 0.023$) predicted the need for emergency medical treatment within 7 days.

Conclusions

We were unable to demonstrate a clinically worthwhile benefit from magnesium sulphate in acute severe asthma. Intravenous magnesium sulphate was associated with a lower rate of hospital admission than placebo, but the difference was not significant and there was no evidence of an effect on VAS breathlessness compared with placebo. There was also no evidence of any clinically worthwhile effect from i.v. magnesium sulphate on secondary outcome measures, including PEFR. We found no evidence that nebulised magnesium sulphate was more effective than placebo. In fact, any non-significant trends in the outcomes involving nebulised magnesium sulphate tended to favour the placebo.

Adherence to the trial protocol was high and most patients received appropriate cotreatments. Patients generally responded well to treatment with improvements in breathlessness and PEFR and a low rate of requirement for ventilator support, HDU or ICU care. This suggests that optimal treatment with salbutamol, ipratropium bromide and corticosteroids may leave little scope for further improvement with magnesium sulphate.

Trial registration

This trial is registered as ISRCTN04417063.

Funding

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Chapter 1 Introduction

Asthma is a chronic inflammatory disease of the airways characterised by reversible airflow obstruction and bronchospasm. An acute asthma exacerbation (commonly referred to as an asthma attack) is characterised by shortness of breath, wheezing and chest tightness. Acute asthma was responsible for 55,259 emergency admissions and 153,877 bed-days in England in 2011–12,[1] and many more emergency department (ED) attendances.

Management of acute asthma

The management of acute asthma in the UK NHS is subject to guidance issued by the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN).[2] The severity of an acute asthma attack is categorised on the basis of presenting clinical characteristics into near-fatal, life-threatening, severe, moderate and brittle asthma. Patients with any features of life-threatening or severe asthma are referred to hospital for emergency treatment.

Prehospital and ED treatment of acute asthma in adults includes supplemental oxygen therapy, oral or parenteral steroids (prednisolone or hydrocortisone), nebulised β_2-agonist bronchodilators (salbutamol or terbutaline) and nebulised ipratropium bromide. Patients are admitted to hospital if they have any feature of a life-threatening or near-fatal attack or any feature of a severe attack persisting after initial treatment. Patients whose peak flow is greater than 75% best or predicted 1 hour after initial treatment may be discharged from the ED unless they meet any of the following criteria, when admission may be appropriate: persistent significant symptoms; concerns about compliance; living alone/socially isolated; psychological problems; physical disability or learning difficulties; previous near-fatal or brittle asthma; exacerbation despite adequate dose steroid tablets prepresentation; presentation at night; or pregnancy.

Magnesium sulphate in acute asthma

Magnesium is an essential mineral nutrient that is present in every cell of every organism. Magnesium-dependent enzymes appear in virtually every metabolic pathway but notably, magnesium ions block calcium channels and, thus, affect nerve and muscle activity. Magnesium sulphate has an established therapeutic role in pre-eclampsia,[3] torsade de pointes[4] and hypomagnesaemia.[5] Its use has also been explored in ventricular arrhythmias other than torsade de pointes,[6] cardiac arrest,[7] myocardial infarction,[8] atrial fibrillation[9,10] and acute asthma.[11]

The use of magnesium sulphate in acute asthma is based on possible smooth muscle relaxation and anti-inflammatory action. It can be given via the intravenous (i.v.) or nebulised route and may have a role augmenting treatment in a therapeutic 'gap' between the immediate action of nebulised bronchodilators and the delayed action of steroids. Doses of 1.2–2 g have been evaluated in acute severe asthma,[11] although doses of 4–6 g can be used in other conditions.[3] The dose of nebulised magnesium sulphate is limited by the need to avoid administering a hypertonic nebulised solution and concurrent therapeutic need for nebulised β_2-agonist. The maximum dose is therefore 500 mg per nebuliser.

Evidence for intravenous magnesium sulphate in acute asthma

Intravenous magnesium sulphate has been compared with placebo in five meta-analyses,[11–15] two of which analysed adults separately from children.[11,14] The meta-analyses included a total of 15 randomised trials,[16–30] nine of which were undertaken in adults.[16–24] The trials of adults used a bolus dose of either 1.2 g or 2.0 g of magnesium sulphate, given over 20–30 minutes. Only one trial followed the bolus dose with an infusion.[18]

The most recent meta-analysis[11] included all nine adult trials.[16–24] A variety of methods were used to measure pulmonary function, therefore these outcomes were pooled by calculating a standardised mean difference (SMD). The pooled relative risk (RR) for hospital admission after treatment with i.v. magnesium sulphate was 0.91 [95% confidence Interval (CI) 0.78 to 1.07; $p = 0.27$] and the pooled SMD in pulmonary function was 0.15 (95% CI 0.01 to 0.29; $p = 0.035$). The authors concluded that treatment with i.v. magnesium sulphate was associated with a modest improvement in pulmonary function, but the clinical significance of this effect was uncertain. Although there was no significant effect on hospital admission, the summary estimate included a potentially important reduction in admissions of up to 22%. Existing evidence was therefore insufficient to either recommend i.v. magnesium sulphate as standard treatment for acute severe asthma or rule out a potentially valuable role.

One further trial ($n = 63$) of i.v. magnesium sulphate has been published since the most recent meta-analysis was undertaken.[31] The trial reported a significant effect on predicted forced expiratory volume in 1 second (FEV_1) at 120 minutes (62.84% vs. 56.7%; mean difference = 6.07; 95% CI 1.87 to 10.62; $p < 0.01$) and fewer patients admitted to hospital in the intervention group (2/30 vs. 9/30). Addition of these data to the most recent meta-analysis resulted in a pooled SMD of 0.35 (95% CI 0.06 to 0.64; $p = 0.02$) and a pooled RR for hospital admission of 0.85 (95% CI 0.68 to 1.06; $p = 0.14$).

Evidence for nebulised magnesium sulphate in acute asthma

Nebulised magnesium sulphate has been compared with placebo in three meta-analyses[11,32,33] and eight randomised trials,[34–41] of which five were undertaken in adults,[34–38] two in children[39–40] and one in a mixed population.[41] The most recent meta-analysis[11] was the only one to report trials of adults and children separately. The trial with a mixed population was analysed with the trials of adults. The dose of magnesium sulphate used ranged from 95 to 500 mg, given up to four times, with doses every 20 to 30 minutes. The pooled RR for hospital admission after treatment with nebulised magnesium sulphate was 0.66 (95% CI 0.44 to 1.00; $p = 0.048$) and the pooled SMD in pulmonary function was 0.20 (95% CI –0.02 to 0.42; $p = 0.076$). Although the effect of nebulised magnesium sulphate on hospital admissions just reached significance, most of the admissions in this analysis were in one trial,[36] and the effect was not consistent across the other trials. The authors concluded that the existing evidence was inadequate to either support nebulised magnesium sulphate as standard treatment for acute severe asthma or rule out a potentially valuable role.

Comparison between intravenous and nebulised magnesium sulphate

No previous trials have compared i.v. with nebulised magnesium sulphate.

Limitations of the existing evidence for intravenous or nebulised magnesium sulphate

The existing evidence for both i.v. and nebulised magnesium sulphate suggests a potentially worthwhile effect on pulmonary function and hospital admissions, but estimates of effect are imprecise and include the possibility of either no clinically worthwhile effect or a substantial effect. Furthermore, the existing evidence is subject to the following limitations:

1. Most previous trials were relatively small and powered to detect changes in pulmonary function rather than hospital admission.
2. Even if meta-analysis suggests a statistically significant difference in pulmonary function it is not clear whether such changes are important to patients or affect their clinical outcome.
3. Factors such as publication bias may influence selection of studies into meta-analysis, leading to overestimates of effectiveness. It has been noted that 35% of subsequent large trials conflict with the results of a previous meta-analysis.[42]
4. The clinically important change in admission rate in patients with severe asthma identified in the meta-analysis by Rowe *et al.*[12] was based on post-hoc subgroup analysis.
5. No previous trials have included a head-to-head comparison of nebulised with i.v. magnesium sulphate.

Current use of intravenous and nebulised magnesium sulphate in the National Health Service

Current BTS/SIGN guidelines for the management of acute asthma[2] state that there is limited evidence that, in adults, magnesium sulphate has bronchodilator effects and, although experience suggests that magnesium sulphate is safe when given by the i.v. or nebulised route, trials comparing these routes of administration are awaited. The guidelines suggest considering giving a single dose of i.v. magnesium sulphate to patients with acute severe asthma who have not had a good initial response to inhaled bronchodilator therapy or who have life-threatening or near-fatal asthma. Similar advice is provided by guidelines used in the USA.[43]

A postal survey of the use of magnesium sulphate in the treatment of acute asthma in the ED was undertaken in the UK in 2009.[44] The lead clinician of each ED was mailed a survey asking about the use of magnesium sulphate in his or her department and 180 out of 251 responded (72%). Magnesium sulphate was reportedly used in 93% of the EDs, mostly because it was expected to relieve breathlessness (70%) or reduce critical care admissions (51%). Most departments used magnesium sulphate for patients with acute severe asthma (84%) and life-threatening exacerbations (87%), with 68% stating they would give the drug if there was no response to repeated nebulisers. In comparison, nebulised magnesium sulphate was used in only two EDs (1%). The main reason given for not administering via a nebuliser was insufficient evidence (51%). The authors commented that the reported use of i.v. magnesium sulphate was more extensive than current guidelines or available evidence appeared to support.

Research objectives

We aimed to measure the clinical effectiveness and cost-effectiveness of i.v. and nebulised magnesium sulphate in acute severe asthma and, thus, determine whether or not either should be standard first-line treatment for patients presenting to the ED with acute severe asthma.

We planned to test the following specific hypotheses:

1. intravenous or nebulised magnesium sulphate will reduce the proportion of patients who require admission at initial presentation or during the following week
2. intravenous or nebulised magnesium sulphate will improve patient assessment of their breathlessness over 2 hours after initiation of treatment.

We also planned to measure the effect of i.v. or nebulised magnesium sulphate on:

1. length of hospital stay and use of high-dependency unit (HDU) or intensive care unit (ICU)
2. mortality, adverse events and use of respiratory support
3. change in peak expiratory flow rate (PEFR) and physiological variables after initial treatment
4. patient-reported health utility
5. patient satisfaction with care
6. use of health and social services over the following month
7. time taken by patients off work
8. health and social care costs and productivity losses.

Chapter 2 Methods

The 3Mg trial was a multicentre, double-blind, placebo-controlled, three-arm, randomised trial and economic analysis of i.v. or nebulised magnesium sulphate in acute severe asthma. The trial took place in 34 EDs in England and Scotland.

Recruitment and allocation of participants

Adults (age over 16 years) attending the ED with acute severe asthma were recruited to the trial. Acute severe asthma was defined as acute asthma with one or more of the following: PEFR < 50% of best or predicted; respiratory rate > 25 breaths per minute; heart rate > 110 beats per minute; or inability to complete sentences in one breath. The percentage of best or predicted PEFR was calculated using the patient's recent best PEFR (within 2 years) if it was known. If the recent best PEFR was not known, the predicted PEFR from age and height charts was used. This approach is recommended in BTS/SIGN guidance[2] and was used to calculate all estimates of the percentage of best or predicted PEFR used in the trial. For convenience we use the term '% predicted PEFR' to encompass all such estimates.

The following individuals were excluded:

1. patients with life-threatening features, defined as one or more of the following: oxygen saturation < 92% despite supplemental oxygen; silent chest; cyanosis; poor respiratory effort; bradycardia; arrhythmia; hypotension; exhaustion; coma; or confusion
2. patients with a contraindication to either nebulised or i.v. magnesium sulphate: pregnancy; hepatic or renal failure; heart block; or known hypermagnesaemia
3. patients who were unable to provide written or verbal consent
4. previous participants in the 3Mg trial
5. patients who had received i.v. or nebulised magnesium sulphate in the 24 hours prior to attendance at the ED.

The final exclusion criterion was added as a protocol amendment during the trial.

Anonymised basic details (age, sex, time and date of ED attendance) were collected from all potentially eligible patients to allow completion of a CONsolidated Standards Of Reporting Trials (CONSORT) flow chart. Patients were identified by ED medical staff, who completed a patient recruitment form (see *Appendix 1*) to verify that the patient met the eligibility criteria and to record that consent was taken prior to randomisation. Eligible patients were initially given a brief information sheet with details of the study design, trial treatments and potential side effects (see *Appendix 2*). When their condition permitted, they were given a full information sheet with further details on trial processes and requirements (see *Appendix 3*). All patients were required to give consent before being recruited to the trial. If the patient's condition permitted, full written consent was taken before recruitment using the Research Ethics Committee (REC)-approved consent form (see *Appendix 4*). If not, verbal consent was obtained from the patient, recorded on the consent form and written consent requested as soon as the patient's condition improved. No provisions were made for personal or professional legal representation or for recruitment before consent. Therefore, any patient unable to provide written or verbal consent was excluded from the trial. Both oral and written consent were taken in the presence of a witness who also signed the consent form, in addition to the person taking consent.

Once eligibility had been confirmed and consent acquired, the participants were randomly allocated to a treatment group. The recruiting clinician accessed a web-based randomisation system or automated telephone hotline provided by the Sheffield Clinical Trials Research Unit (CTRU) in partnership with epiGenesys (a University of Sheffield subsidiary software development company) and participants were

allocated to a numbered treatment pack kept in the ED. The randomisation system only revealed the allocated pack number after patient details had been recorded and the patient irreversibly entered into the trial. A simple randomisation sequence was used in the first 20 hospitals open to recruitment, as planned in the protocol.[45] However, recruitment rates were lower than anticipated and, therefore, additional hospitals were opened to recruitment. To reduce the risk of random imbalances in the number allocated to each arm of the trial, blocked randomisation (block sizes of four or six), stratified by hospital, was used for subsequent centres. To avoid the risk of subversion of the randomisation process in these hospitals, decisions regarding the randomisation sequence were made independently by the CTRU and were not communicated to the investigators.

Each treatment pack contained an i.v. infusion and nebuliser solutions, either of which could be active treatment or placebo. Participants, hospital staff and research staff were all blind to allocated treatment, unless the formal unblinding procedure was undertaken. An emergency unblinding (code-break) procedure was in place to enable hospital staff to reveal the allocation of treatment when it was essential to know for their on-going clinical care whether or not the patient had received magnesium sulphate. A 24-hour unblinding service was available via the randomisation system (online or telephone), which immediately provided treatment allocation to the site and automatically alerted the study team and local principal investigator (PI) by e-mail that a participant had been unblinded. In case the online and telephone systems were unavailable, emergency unblinding envelopes were also prepared by the pharmacy production unit according to the randomisation schedule and stored with the investigational medicinal products (IMPs) at site. Tamper stickers were checked regularly to ensure that envelopes had not been opened and were returned, still sealed, to the central study team to ensure full accountability. If an envelope was opened it was reported to the study team and recorded as a participant unblinding.

Interventions

Patients were randomised to one of three treatment arms. Each patient received one i.v. and one nebulised treatment (consisting of three nebuliser vials given consecutively). The i.v. infusions and nebuliser vials were prepared as apparently identical solutions, with identical primary packaging and labelling to ensure blinding. Blinded treatment packs were assembled and labelled with a participant number in accordance with a randomisation schedule supplied by the CTRU. The three treatment arms are shown in *Table 1*.

All three groups received standard therapy at the discretion of the treating physician, but guided by BTS/SIGN guidelines[2] and the 3Mg Clinical Protocol (see *Appendix 5*). Recommended standard therapy included supplemental oxygen, nebulised salbutamol, nebulised ipratropium bromide and oral prednisolone, administered during recruitment, followed by up to 5 mg of salbutamol added to each trial nebuliser. The BTS/SIGN guidelines[2] do not recommend magnesium sulphate, but suggest that i.v. use should be considered in patients with life-threatening features or those with severe asthma who do not

TABLE 1 Treatment arms

Treatment arm	Intravenous infusion	Nebulisers
1	i.v. magnesium sulphate, 8 mmol (2 g) in 100 ml of water for injections, adjusted to isotonicity with sodium chloride, given over 20 minutes	7.5-ml vial of 0.9% saline, given three times 20 minutes apart
2	i.v. 0.9% saline, 100 ml given over 20 minutes	7.5-ml vial of 2 mmol (500 mg) magnesium sulphate, given three times 20 minutes apart
3	i.v. 0.9% saline, 100 ml given over 20 minutes	7.5-ml vial of 0.9% saline, given three times 20 minutes apart

respond to treatment. We, therefore, did not prohibit the use of magnesium sulphate outside the trial or recommend its use in patients unresponsive to treatment. During the trial we identified the occasional use of magnesium sulphate at an early stage of treatment of patients without life-threatening features. We therefore added an additional exclusion criteria that patients must not have received magnesium sulphate in the previous 24 hours before entry into the study.

Patients were managed in the ED and data collected until 2 hours after randomisation. At this point, if not already undertaken, a final disposition decision (hospital admission or discharge) was made.

Outcome measures

Two primary outcomes were specified in the trial protocol:

1. The health service primary outcome – the proportion of patients admitted to hospital, either after ED treatment or at any time over the subsequent week.
2. The patient-centred primary outcome – the patient's visual analogue scale (VAS) for breathlessness over 2 hours after initiation of treatment.

Secondary outcomes included mortality; adverse events; the use of ventilation or respiratory support; length of hospital stay; use of HDU or ICU; change in PEFR and physiological variables (oxygen saturation, heart rate, respiratory rate, blood pressure) over 2 hours; quality of life at baseline and at 1 month [measured by European Quality of Life 5-Dimensions (EQ-5D)]; number of unscheduled health-care contacts (ED, walk-in centre or general practitioner attendances) over the subsequent month; and satisfaction with care.

The two primary outcome measures were selected to identify important changes in patient management and symptoms of asthma. The primary outcome of hospital admission included any admission over the following week, because this time period would encompass the expected duration of an asthma exacerbation and a typical course of associated treatment. Admission during this time therefore represented an overall failure of treatment, whereas admission later than 1 week was considered a separate episode.

The VAS and the Borg scale have both been used to measure breathlessness during exercise,[46] but have only recently been tested in acute asthma. Kendrick *et al.*[47] showed that the Borg scale correlated with measures of respiratory function in a cohort of patients with asthma or chronic obstructive pulmonary disease, whereas Karras *et al.*[48] and Gupta *et al.*[49] showed correlation between the VAS and measures of respiratory function in cohorts with acute asthma. The study by Karras[48] also showed that the mean VAS change among patients who reported their asthma to be 'a little better' after treatment was 22 mm on a 100-mm VAS and concluded that this represented a minimum clinically significant change. On the basis of these studies we concluded that the VAS was the best validated measure, offering a simple and reliable means of measuring symptomatic breathlessness in people with acute asthma, with an estimate of the minimum clinically significant change in VAS.

Outcomes were measured in two phases: (1) over 2 hours after randomisation and (2) at 1 month after attendance. During the first phase we measured variables that reflect patient response to emergency treatment, such as VAS, PEFR and physiological variables. During the second phase we measured variables that reflect the overall patient experience of an asthma attack and its subsequent treatment, such as adverse events, use of health services, satisfaction with care and quality of life.

Data collection and management

A recruitment form was completed for all patients attending the ED with acute severe asthma at participating sites. These data were used to complete the CONSORT flow chart and generate reports on non-recruited patients for discussion at management group meetings.

Clinical staff recorded baseline data, details of co-interventions and outcome data up to 2 hours after randomisation on the paper case report form (CRF) (see *Appendix 6*). Further data were collected up to 1 month after recruitment by research nurses using routine data sources and by patient self-completion questionnaire. A postal survey consisting of the EQ-5D, a health-care resource use questionnaire, and a patient satisfaction questionnaire was mailed to all participants who were alive and had not withdrawn from the trial 1 month after recruitment (see *Appendices 7* and *8*). A repeat mailing was undertaken for all non-responders at 2 weeks, with telephone completion of the EQ-5D attempted 2 weeks later for non-responders to either mailings. Patients who had not responded to mail or telephone contact by 8 weeks after study entry were recorded as lost to follow-up for questionnaire data.

Trial data were entered via web-based interface to a database developed in-house by the CTRU. The system, and its underlying database, resided on a server in Corporate Information and Computing Services at the University of Sheffield. Automated backups were made nightly. Prospect was accessed remotely via a secure web browser and all data transmissions were encrypted. Access was restricted by username and password (issued by the CTRU) and an automated audit trail recorded when (and by which user) records were created, updated or deleted. The profile of each user was set to allow only the appropriate information to be viewed and edited, e.g. site data inputters could only enter and view data about patients from their own sites. Quality control procedures were applied to validate the trial data. Error reports were generated where data clarification was required and data queries resolved by research nurses at sites. All activities were performed in accordance with Sheffield CTRU standard operating procedures (SOPs).

Proposed sample size

We planned to recruit 1200 participants, divided equally between the three trial arms (400 participants per arm). We anticipated that the hospital admission would be recorded for all participants, but that a proportion of cases would not have VAS measured. The sample size would therefore provide the following statistical power:

1. Proportion of patients admitted – assuming that 80% of patients with severe asthma are admitted after ED management, the study would have 90% power to detect a 10% absolute reduction in the proportion admitted (i.e. to 70%) for any pair of treatment groups compared ($\alpha = 0.05$).
2. VAS breathlessness – assuming that the standard deviation on a 100-mm VAS is 3 cm, that 2.2 cm represents a minimum clinically significant difference[48] and that 20% of participants will not have their VAS measured, the study would have 90% power to detect a 8-mm difference in a 100-mm VAS at 2 hours after treatment initiation ($\alpha = 0.05$).

Statistical analysis

Analysis of coprimary outcomes

For the health service primary outcome, patients were considered to have been admitted if either (i) they had not been discharged within 4 hours and/or (ii) if they were recorded as having been readmitted at any point within 7 days following randomisation. The proportion admitted was analysed using logistic regression. We anticipated that data would be missing from only a very small proportion of the trial

population (those withdrawing within a few hours of recruitment) and, therefore, planned only a complete case analysis.

For the patient-centred primary outcome, breathlessness was defined as the change in VAS from baseline to 2 hours and was analysed using linear regression. As both missing data and measurements outside the allotted time window were anticipated, the analysis plan proposed three analyses:

1. 'As is' – complete case analysis, no adjustment is made for timing.
2. 'Imputed'– measurements more than ± 15 minutes from their scheduled time were adjusted by linear interpolation or extrapolation.
3. Multiple imputation by chained estimation. Missing 2-hour VAS scores ($n = 108$; 10%) were imputed based on age, sex, smoking status, previous admission for asthma, previous admission to ICU or HDU for asthma, time since last admission for asthma, baseline and 1-hour VAS, PEFR and heart rate over 2 hours' observations, and status at 4 hours (i.e. discharged or admitted/awaiting decision).

Analysis was undertaken on an intention-to-treat basis. Patients were removed from analysis post randomisation only if recruitment was an unequivocal protocol violation (i.e. no consent had been recorded or if they had previously been recruited) or if the patient withdrew from the trial prior to any treatments having been administered. In all other cases, participants were analysed in accordance with the groups they were allocated to regardless of whether or not they actually completed their allocated treatment. A secondary, per-protocol analysis excluded participants who did not receive treatment, defined as a minimum nebulised dosage of 7.5 ml (the equivalent of one nebuliser) or 50 ml of i.v. volume (50% of the i.v. dose).

The primary and most of the secondary analyses included two covariates: treatment group and centre (hospital). For the purposes of the analysis, hospitals recruiting fewer than 10 patients in total were combined into one group for analyses in which centre was used as a covariate. The robustness of the findings to potential differences in baseline characteristics was assessed, in particular the initial breathlessness (VAS) and age.

We used Simes' method,[50] which is a modification of the Bonferroni method but has better power to adjust for multiplicity arising from having two primary outcomes. However, we did not adjust the CIs associated with the estimate of the treatment effect with each outcome. We tested the two hypotheses simultaneously through the analysis of variance. With three groups (A = nebuliser, B = i.v. and C = control) we had two degrees of freedom for analysis, which we split into two orthogonal contrasts (–2, +1, +1) to contrast both active treatments compared with control and (0, –1, +1) to contrast the active treatments.

Secondary outcomes

The length of hospital stay was analysed using a log-normal distribution, which allowed for interval censoring of non-admitted patients and right censoring of hospital duration among those still in hospital 30 days after randomisation. PEFR and physiological measures were analysed in the same manner as breathlessness. All secondary analyses were undertaken as complete case, intention-to-treat analyses.

Subgroup analyses

We prospectively defined three subgroup analyses, within which patients were stratified on the basis of:

1. Asthma severity, according to whether baseline PEFR (pretreatment PEFR as a percentage of predicted value) was above or below median baseline PEFR. A previous meta-analysis[12] suggested that i.v. magnesium sulphate is more effective in patients with severe asthma.
2. Age, above or below 50 years. Older patients with a diagnosis of asthma are more likely to have chronic respiratory disease that may be less responsive to treatment with magnesium sulphate.
3. Treatment before arrival. We recruited patients on arrival at hospital, thus testing magnesium sulphate as a first-line treatment. However, some patients received prehospital treatment with nebulisers, thus

making magnesium sulphate, in effect, a second-line treatment. Patients with severe asthma after receiving prehospital treatment are likely to have more severe asthma than those presenting without prehospital treatment.

Economic evaluation

The economic evaluation took an approach consistent with the National Institute for Health and Care Excellence (NICE) reference case analysis.[51] The perspective taken was that of the NHS and personal social services. Health benefits were measured in quality-adjusted life-years (QALYs) using the EQ-5D and the time horizon over which health benefits were derived was 30 days. Health benefit was also measured by assessing breathlessness on a 100-mm VAS at 1 and 2 hours after the initiation of study treatment. The data collected 2 hours after the initiation of treatment were used in the cost-effectiveness analysis.

The following resources were identified as being important and collected using either the CRF or patient-completed questionnaire:

- trial medication
- ICU – asthma related (days)
- HDU – asthma related (days)
- ward – asthma related (days)
- ICU – non-asthma related (days)
- HDU – non-asthma related (days)
- ward – non-asthma related (days)
- telephone health advice [e.g. general practitioner (GP), NHS Direct] (number of times used)
- GP surgery consultations (number of times used)
- GP home visits (number of times used)
- nurse home visits (number of times used)
- social worker visits (number of times used)
- ED attendances (number of times used)
- attendance at hospital as an outpatient (number of times used)
- asthma-related concomitant medications: salbutamol, prednisolone, ipratropium bromide, salmeterol xinafoate/fluticasone propionate (Seretide®, GlaxoSmithKline), budesonide (Pulmicort®, AstraZeneca), montelukast, beclometasone dipropionate (Clenil® Modulite®, Chiesi Ltd), aminophylline, theophylline, hydrocortisone, tiotropium (Spiriva®, Boehringer Ingelheim Ltd), magnesium sulphate, salmeterol, ipratropium bromide/salbutamol (Combivent®, Boehringer Ingelheim) and terbutaline (Bricanyl®, AstraZeneca UK Ltd).

Inpatient stays and medications were collected via CRFs, with the remainder collected by patient questionnaire. Productivity loss as a consequence of the number of days patients took off work during the study was collected using the patient questionnaire and separate analyses were conducted excluding and including productivity loss.

Unit costs for medication were taken from the *British National Formulary* (BNF),[5] with the implied dose being that of the most common recorded within the trial (*Table 2*). Other unit costs were derived primarily from NHS reference costs[52] and the Personal Social Service Research Unit annual unit costs publication.[53] NHS reference costs were inflated to 2011/12 prices using the gross domestic product deflator (as the relevant Hospital and Community Health Services Index figure is not yet available). The costs of NHS Direct advice were estimated from an evaluation of this service[54] and the costs of production losses were estimated using data from the Office for National Statistics.[55] These unit costs are shown in *Table 3*.

TABLE 2 Unit costs of medications

Item of resource (medications[a])	Route	Dose	Cost per dose[b] (£)
Treatment arm 1 (2 mg of i.v. magnesium sulphate)	–	–	7.39
Treatment arm 2 (2 mg of nebulised magnesium sulphate)	–	–	7.39[c]
Treatment arm 3 (saline)	–	–	0
Aminophylline	Oral	1 × 225 mg	0.04
Aminophylline	i.v.	2 × 10-ml ampoule	1.56
Beclometasone dipropionate	Inhaled	2 × 100 µg	0.07
Combivent	Nebulised	1 × 2.5 ml	0.40
Hydrocortisone	Oral	1 × 20 mg	1.53
Hydrocortisone	i.v.	2 × 100 mg	2.16
Ipratropium bromide	Nebulised	1 × 500 µg	0.37
Ipratropium bromide	Inhaled	2 × 20 µg	0.05
Magnesium sulphate	i.v.	1 × 2 g	7.39
Methylprednisolone	Oral	2 × 16 mg	1.14
Montelukast	Oral	1 × 10 mg	0.96
Prednisolone	Oral	8 × 5 mg	0.35
Pulmicort	Nebulised	1 × 1 mg	30.30
Pulmicort	Inhaled	1 × 200 µg	0.12
Salbutamol	i.v.	1 × 5 mg	0.19
Salbutamol	Nebulised	1 × 5 mg	0.19
Salbutamol	Inhaled	2 × 100 mg	0.02
Salmeterol (Serevent®, GlaxoSmithKline)	Inhaled	2 × 25 µg	0.46
Seretide	Inhaled	2 × 250 µg	0.60
Terbutaline	Inhaled	1 × 500 µg	0.07
Theophylline	Oral	1 × 200 mg	0.05
Tiotropium	Inhaled	1 × 18 µg	1.06

a Dose represents most common for drug/route.
b Any associated devices and consumables not included.
c Nebulised magnesium sulphate not available in BNF. Same price as 2-g prefilled syringe assumed.

TABLE 3 Non-medication unit costs

Item of resource	Cost per unit (£)	Year	Citation
Telephone advice from NHS Direct	25	2011/12	54
GP surgery consultations	37	2011/12	53
GP home visits	124	2011/12	53
Nurse home visits	37	2011/12	53
Social worker visits	108	2011/12	53
ED attendance	96	2011/12	52
Outpatient visits – asthma related	133	2011/12	52
Inpatient days – asthma related	358	2011/12	52
Inpatient days – asthma and other related	261	2011/12	52
ICU days	868	2011/12	52
HDU days	623	2011/12	52
Days off work	101	2011/12	55

Quality-adjusted life-years were calculated for each patient over the duration of the study using the EuroQoL tariff[56] and by applying the trapezoidal rule based on data at baseline and at 30 days. The change from baseline in breathlessness 2 hours after the initiation of study treatment, as measured using a 100-mm VAS, was calculated for each patient. Reduction from baseline is defined as minus one times the change from baseline to reflect the fact that a reduction in breathlessness is a positive outcome.

The primary analysis was a cost-effectiveness analysis using the QALYs associated with treatment. Additionally, the change from baseline in breathlessness 2 hours after the initiation of study treatment, as measured using a 100-mm VAS, was used as a secondary cost-effectiveness analysis. The focus of the analysis is on the probability that the intervention arms are cost-effective at funding thresholds of £20,000 and £30,000 per QALY. In addition, cost-effectiveness acceptability frontiers are presented over the range £0–100,000 per QALY. As with all cost-effectiveness analyses, it is necessary for the measure of effectiveness to be linear in the sense that the value of an incremental increase of E units of effectiveness is EK, where K is the value to the decision-maker of increasing effectiveness by one unit. Unlike QALYs, it is not clear how much value a decision-maker may give to a unit reduction in breathlessness on the VAS scale, but is likely to be much less than that for a QALY. Cost-effectiveness acceptability frontiers are presented over the range £0–1000 per unit reduction in breathlessness. Sensitivity analyses were performed incorporating production losses (i.e. time taken from paid employment).

Missing data were imputed using a single-value imputation approach. A multiple imputation algorithm was attempted but it failed to converge, possibly as a consequence of the large number of missing data associated with some outcome measures and the assumptions being made about their underlying probability distributions in the multiple imputation algorithm.

The analysis was initially planned to use bootstrapping, but this was replaced by an analysis using a Bayesian approach using a bivariate normal likelihood function for the effectiveness and total cost.[57] The bivariate normal likelihood function is justified by appealing to the central limit theorem, which says that for data from any underlying probability distribution with finite mean and variance, the distribution of the sample means will tend to be a normal distribution with sufficiently large sample sizes. This change was undertaken in advance of the analysis commencing.

The analysis was conducted using the freely available software WinBUGS 1.4.3 (Imperial College and Medical Research Council, UK).[58] Weak prior information was included in the analysis. The model converged very quickly but for accuracy and precision purposes the results are based on 100,000 Markov chain Monte Carlo iterations after a burn-in of 25,000 iterations.

With sample sizes as large as those in this study, the results are expected to be similar to what would have been generated using bootstrap or a more exact approach that specifically models the underlying distribution of the derived effectiveness and total cost data. Nevertheless, a benefit of this approach is that it allows a more direct interpretation about the probability associated with the parameters of interest (i.e. population mean incremental cost and effectiveness) and the probability of positive net benefit.

Predictors of unsuccessful treatment

To maximise the value of this project, we planned to undertake an additional analysis of trial data to identify factors that predicted unsuccessful treatment for acute severe asthma. Predicting unsuccessful treatment would be helpful for deciding which patients need asthma nurse review after discharge,[59] which need hospital admission and which need HDU or ICU support. Currently these decisions are made largely on PEFR recordings,[2] although it is not clear how useful these are as predictors of relapse.

Data collection for the trial included variables that may be potentially useful predictors of unsuccessful treatment, such as baseline and post-treatment PEFR, physiological variables, age, sex, smoking status, and previous hospital, HDU and ICU admissions. We examined the ability of these factors to predict unsuccessful treatment, defined at two levels: (1) need for critical care, i.e. HDU or ICU care, airway management, respiratory support or cardiopulmonary resuscitation or respiratory arrest, cardiac arrhythmia or death within 7 days of initial attendance; and (2) need for emergency medical treatment (including critical care) within 7 days of presentation, either by attendance at the ED or unscheduled inpatient review.

Models were fitted separately for the two definitions. For each, an initial screening phase assessed potential covariates, with those achieving a minimum significance level of $p < 0.15$ retained for the multivariable modelling. Outcomes were modelled using logistic regression. Continuous covariates (physiological variables, PEFR and age) were modelled using fractional polynomials,[60] but the resultant model compared with two alternative functional forms (linear and quadratic) to assess whether or not a simpler model could achieve an adequate fit. Predictive ability was assessed by calculating the area under the receiver operator characteristic (AUROC) curve of the model. Internal validation was performed by two methods: (1) bootstrap validation, assessing the robustness of model covariates and (2) cross-validation. The model was fitted separately to the following subgroups defined by (i) seasonality (October–March vs. April–September), (ii) time period (2008–10 vs. 2011–12) and (iii) type of hospital (teaching vs. non-teaching). In each case the resultant models were assessed for consistency between the subgroups.

For each definition, three models were incrementally compared:

1. a model based solely on %PEFR at admission
2. a model using the best-fitting combination of baseline (pretreatment) physiological covariates
3. a model incorporating change in physiological measures over 2 hours, in addition to those used in model 2.

Ethical issues

The trial was undertaken in accordance with the Medicine for Human Use (Clinical Trials) Regulations 2004[61] and subsequent amendments, and was approved by the Scotland A REC. The main ethical issue

was that patients with acute severe asthma may lack capacity to provide informed consent or the ability to complete a written consent form, yet the very nature of the trial required that recruitment should take place quickly in an emergency and include acutely ill patients.[62,63] We initially planned to use personal or professional legal representatives to provide proxy consent for patients lacking capacity. However, on the advice of the ethics committee this provision was dropped and only patients able to provide some form of consent were recruited to the trial. In addition to the person taking consent, a witness also had to sign the consent form to verify that the patient had capacity to give informed consent. It was felt that patients who were too ill to consent were likely to have life-threatening asthma and that excluding patients lacking capacity would not compromise validity.

Participants were therefore only recruited into the trial if they could provide written or verbal-informed consent. We used the following process for seeking consent, based on the Medicine for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, and taking into account the ethics committee review:

1. All patients were given emergency treatment with supplemental oxygen, salbutamol nebuliser and ipratropium bromide nebuliser while consent was being sought. Initial investigations, such as arterial blood gas sampling and chest radiography, continued simultaneously.
2. Potential participants were given a brief initial information sheet (see *Appendix 2*) and asked if they wished to consider participation in the trial.
3. Those patients that would consider participation were given further verbal information.
4. Potential participants who were able to express their consent and were able to complete the consent form (see *Appendix 4*) were asked to provide written consent.
5. Potential participants who were able to express their consent but unable to complete the consent form as a result of their acute illness were recorded on the consent form as having provided verbal consent.
6. If the potential participant was not competent to give written or verbal consent, then he or she was not recruited into the trial.
7. Every recruited participant was reviewed at regular intervals during their treatment. As soon as their condition improved, they were provided with the full information sheet (see *Appendix 3*). Those participants who had completed a written consent form were asked if they were happy to remain in the trial. Those participants who had not completed a written consent form were asked to do so.

The risks to participants in this trial were considered to be low. Magnesium sulphate has been used by i.v. and nebulised routes in a number of trials and, although unlicensed, has frequently been used in the treatment of acute severe asthma. It is also included as a possible treatment for acute asthma in BTS/SIGN guidelines.[2] Although minor side effects such as nausea or flushing are common, serious side effects (arrhythmias and coma) are uncommon. Potential participants were advised of these risks when they were invited to participate.

Research governance

The trial was conducted in accordance with Medical Research Council (MRC) Guidelines for Good Clinical Practice (GCP)[64] and the Medicines for Human Use (Clinical Trials) Regulations 2004. Sheffield Teaching Hospitals (STH) NHS Foundation Trust was the trial sponsor. The trial was an IMP trial covered by clinical trial regulations from the Medicines and Healthcare products Regulatory Agency (MHRA). A clinical trial authorisation was applied for and received from the MHRA. A site agreement between the sponsor, participating site, CTRU and University of Sheffield outlined responsibilities of all parties and was signed prior to commencement of recruitment at sites.

All clinicians responsible for recruiting patients to the trial were required to complete training in GCP. This presented substantial logistical barriers as, at the time the trial commenced, there was no requirement for GCP training as part of emergency medicine specialist training and there was a rapid turnover of doctors in

emergency medicine. To address this we established GCP training on the emergency medicine specialist training curriculum, developed a GCP training package and made it available through the College of Emergency Medicine website, and promoted GCP training in the *Emergency Medicine Journal*.[65]

Blinded treatment packs were manufactured in conjunction with the CTRU, initially by STH NHS Foundation Trust Pharmacy Production Unit at the Royal Hallamshire Hospital (RHH) and subsequently by Tayside Pharmaceuticals. All products were checked by a qualified person (QP) prior to release. The change to Tayside Pharmaceuticals was necessary as RHH did not maintain its manufacturer's authorisation for IMPs, the manufacturer's/importer's licence (MIA), after the production of the first batch of IMPs. However, RHH continued to label the kits with a randomisation code in accordance with a randomisation schedule supplied by the CTRU and distribute kits to sites. This assembly service is permitted under the exemption for hospitals (regulation 37, UK SI 2004/1031). The pharmacy production units maintained an investigational medical products dossier (IMPD) (see *Appendix 9*) and relevant documentation.

Blinded treatment kits were manufactured, assembled and labelled as per European Commission Good Manufacturing Practice annex 13 requirements[66] to enable the treatment to be identified and the batch source of the materials traced. Treatment kits consisted of a box containing an infusion bag and three nebuliser solution vials. Boxes carried an outer label identifying the trial and kit number. An unblinded kit number list and randomisation schedule (accessed via the online randomisation system using a pharmacy production unique username) allowed the RHH production unit to identify which arm of the trial each kit belonged to, and label the kits with a randomisation code. IMPs were supplied on a demand basis to the participating sites with minimal waste of materials. Treatment kit accountability logs were maintained by all parties (production units, CTRU, sites, hospital pharmacies), to allow full reconciliation of IMPs including assignment to patients.

Three committees were established to govern the conduct of the trial: the Trial Steering Committee (TSC), the independent Data Monitoring and Ethics Committee (DMEC) and the Project Management Group (PMG). These committees functioned in accordance with Sheffield CTRU SOPs.

The TSC consisted of four independent members [Professor of Respiratory Medicine (as chairperson), statistician, consultant in emergency medicine, patient representative] and three members of the trial team (chief investigator, emergency medicine co-applicant on the grant and the project manager). The TSC supervised the trial and in particular, the progress of the trial, adherence to protocol, patient safety and consideration of new information. The TSC made the decisions on how to proceed with the trial following recommendations from the DMEC.

The DMEC consisted of an independent statistician, a respiratory consultant and an emergency medicine consultant. The principal duty of the DMEC was patient safety. The DMEC agreed a charter stating the intended interim analyses and stopping rules for the study, and made recommendations to the TSC and PMG. The DMEC could make recommendations to:

(a) continue recruiting
(b) stop the trial
(c) continue, with modification to the protocol.

The PMG consisted of the chief investigator, co-applicants, project manager and co-ordinators, statistician, research nurses and sponsor representative. The role of this group was to oversee the day-to-day management of the trial.

Reporting of serious adverse events

Serious adverse events (SAEs) were reported in accordance with the 3Mg trial SAE reporting protocol and the sponsor's (STH) SOP[67] for reporting, managing and recording adverse events for STH studies. All SAEs occurring within 30 days of recruitment to the trial were reported immediately to the sponsor on learning of their occurrence. Site trial staff and delegated ED staff were responsible for recording all adverse events that were reported by the participant and making them known to the PI. An investigators' brochure (IB) was maintained by the trial team as the reference safety information for reporting SAEs (see *Appendix 10*).

Magnesium sulphate is a naturally occurring compound that is a normal constituent of the human body and, since the trial involved administering magnesium sulphate over a single 1-hour period, it was expected that any effect on other medications would be limited to the first few hours after administration. Thus, the SAE reporting procedure for the 3Mg trial only recorded those concomitant medications given in the 48-hour period after the trial drug was administered.

Reporting of protocol violations and deviations

Protocol violations and deviations were reported in accordance with the 3Mg and STH protocol violation and deviation SOPs. The site research nurse was responsible for reviewing the participant CRF and ED notes after entry into the trial to determine if treatment was given in accordance with the protocol, consent was obtained correctly and by a suitably trained and delegated doctor, and that the patient met the eligibility criteria. Any suspected protocol violation or deviation was reported to the local PI and to the central 3Mg team. The chief investigator/CTRU reviewed and confirmed if the incident was a violation/deviation and reported to the sponsor. Participants continued to participate in the trial except if the patient had given no informed consent or if they have requested to be withdrawn from the study. Fully consented patients enrolled on the trial were followed up and analysed as per intention-to-treat analysis outlined in the 3Mg protocol (see *Appendix 11*).

Trial monitoring

Throughout the trial there was ongoing management and monitoring to ensure that the integrity of the data and the rights and well-being of participants were protected. Monitoring was completed both at site and at a central level, and regular reports were submitted to relevant parties.

Reporting

The trial team were required to submit annual reports on trial progress, data completion rates, and safety and protocol compliance to the MHRA and MREC; and 6-monthly reports to the funding body [National Institute for Health Research (NIHR) Health Technology Assessment programme]. Reports were also prepared for all-trial oversight committees.

Site monitoring

On-site monitoring was performed before (prior to recruitment commencing at site), during (after third patient recruited and then annually) and after recruitment ended at a trial site. Monitors checked the following during site visits:

- source data verification – data recorded on the CRFs against available source documents
- SAEs/suspected unexpected serious adverse reactions – reported to the sponsor and followed up to resolution
- resolution of data queries
- investigator site file maintenance
- training records for site staff (3Mg trial specific and GCP) and appropriate delegation of duties

- IMP accountability and storage of IMPs in both ED and pharmacy
- patient consent procedures
- reporting of protocol deviations/violations.

Central data validation

Validation checks were built into the database which enabled validation reports to be generated monthly. Any missing values, values out of range or inconsistent with the data set were flagged. Queries were sent to sites and followed up to resolution prior to data lock. Data entry validation was completed on 5% of CRFs and questionnaires, queries resolved, and database entry error rates reviewed to assess if they were within acceptable limits.

Production of investigational medicinal product

Monitors independent of the study team checked QP-release certificates for all batches of product and verified that labelling with randomisation number had been done correctly according to the randomisation number and unblinded kit list.

During the trial we had to change the supplier of the IMPs. Initially the IMPs were supplied by the pharmacy production unit at RHH. However, this unit did not maintain a MIA licence and subsequently stopped fully supporting IMP trials during the trial, so we moved production to Tayside Pharmaceuticals. Labelling and distribution services remained the responsibility of the RHH pharmacy production unit.

Changes to the trial protocol

All changes to the trial protocol and study conduct were reviewed by the sponsor and submitted to the REC and MHRA for approval as appropriate. In summary, the following amendments were made:

- prior to first participant recruitment:
  - change of sponsor from the University of Sheffield to STH NHS Foundation Trust
  - option for consent from a legal representative removed, written or oral informed consent must be obtained, as required by the REC
  - changes to statistical analysis plan to clarify that the primary analysis incorporated an adjustment for hospital; clarification that covariate adjusted analysis would be performed; subgroup analysis for asthma severity to be based on PEFR instead of VAS score (prior to recruitment commencing).
- during trial recruitment:
  - changes to the number of recruiting sites and list of participating sites/PIs
  - minor changes to study documents for clarity or administrative purposes
  - changes to the storage requirements for the IMP, to allow storage at temperatures up to 30 °C
  - research alert page introduced as a study document to use at sites
  - IMPD and IB updates
  - option to telephone patients to collect EQ-5D data if no response from initial and reminder postal questionnaire
  - pharmacy production unit changed to Tayside Pharmaceuticals
  - addition of extra exclusion criteria – patients who have received i.v. or nebulised magnesium sulphate in the previous 24 hours prior to attendance at the ED
  - clarification that concomitant medications in SAE reports to be reported only for the period up to 48 hours post IMP administration
  - extension of recruitment period to 30 June 2012
  - change from ‘doctors will consent the patient’ to include the option for other health-care professionals to take consent.

Archiving

The site files and all study documentation were sent to the CTRU and archived according to the sponsor SOP for a period of 15 years. A log of all documents archived and a list of named individuals who can access the archive is kept by the CTRU.

Chapter 3 Results

Trial progress

The project started on 1 September 2007. Original recruitment predictions were based on the assumption of 12 hospitals recruiting one patient per centre per week for 2 years, with recruitment complete by the end of February 2010. The process of setting up the trial took much longer than anticipated and, after the start of recruitment at the first site, it took a further year until the original target of 12 recruiting sites was achieved. The main reasons for the delays were (a) slow progress in drawing up contracts between the sponsor and participating sites; (b) slow progress in securing NHS research governance approval at the participating sites; and (c) the time taken to provide GCP training for recruiting clinicians. Ethical approval, by contrast, was secured quickly and efficiently. The need to provide GCP training for emergency physicians was a specific problem for this trial. Owing to the acuity of the condition, patients could present to the ED at any time and we aimed to train as many emergency physicians as possible. There appeared to be no existing NHS infrastructure for supporting trials in emergency medicine, so we developed a GCP training package that was proportionate to the limited trial activities that the recruiting doctors were involved with and promoted it through the College of Emergency Medicine.

Patient recruitment

The trial opened to recruitment on 30 July 2008 and closed on 30 June 2012. A total of 1109 participants were recruited to the trial, 92% of the intended sample size of 1200. *Figure 1* shows the number of patients recruited and the number of recruiting centres open per month, alongside the cumulative recruitment to the trial. *Figure 2* shows the actual recruitment compared with the initial planned recruitment and subsequent revised recruitment plan.

Recruitment at the participating centres was slower than expected as a result of a combination of a lower than anticipated availability of eligible patients and difficulties in ensuring that GCP-trained staff were available to recruit. To address the shortfall in recruitment, we increased the number of sites and promotional activities. Later in the trial we replaced existing sites that were experiencing recruitment fatigue or had small numbers of eligible patients with new sites that we identified via the NIHR Injuries and Emergencies National Priority Group. We were granted a funded extension to the trial to continue recruitment until 30 June 2012.

Using data available at the time of the funded extension request (after 276 patients were recruited), we revised the recruitment predictions assuming that we would recruit, on average, 0.4 patients per site per week and adjusted this for the predicted number of sites that would be recruiting each month. At this stage, we predicted that we would reach the target number by March 2012. Mid-trial we had to change the IMP manufacturer, and recruitment to the trial had to be suspended between May and June 2010 as the new IMPs were not delivered as a result of a problem with the sterile production process. The seasonality of asthma usually meant that recruitment increased in the winter months, but the final winter season saw generally lower numbers of presenting patients. We kept a large proportion of the sites open to recruitment for an additional 3 months compared with the revised recruitment plan, staggering the close of sites to assist with scheduling close-out monitoring.

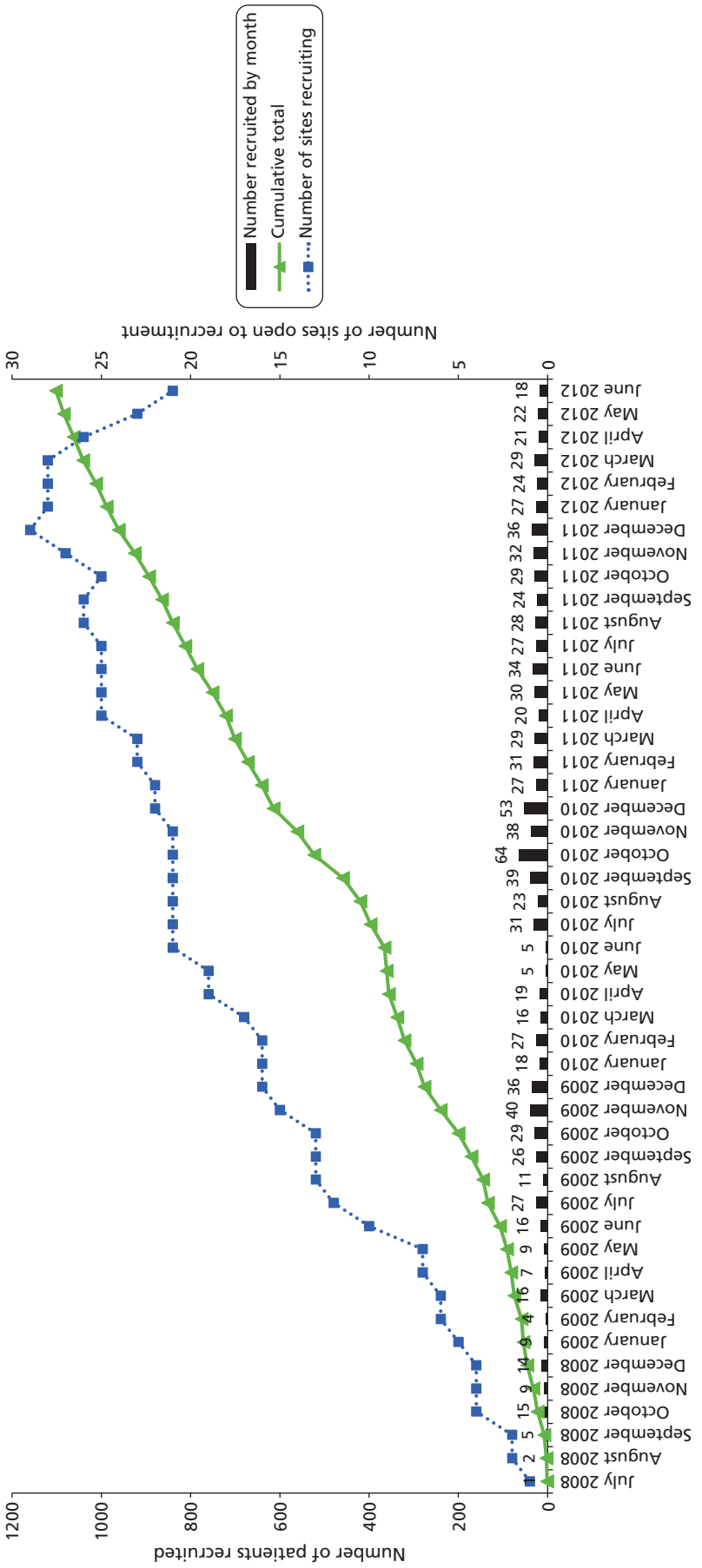

FIGURE 1 Number of recruiting centres and actual recruitment rates (30 July 2008–30 June 2012).

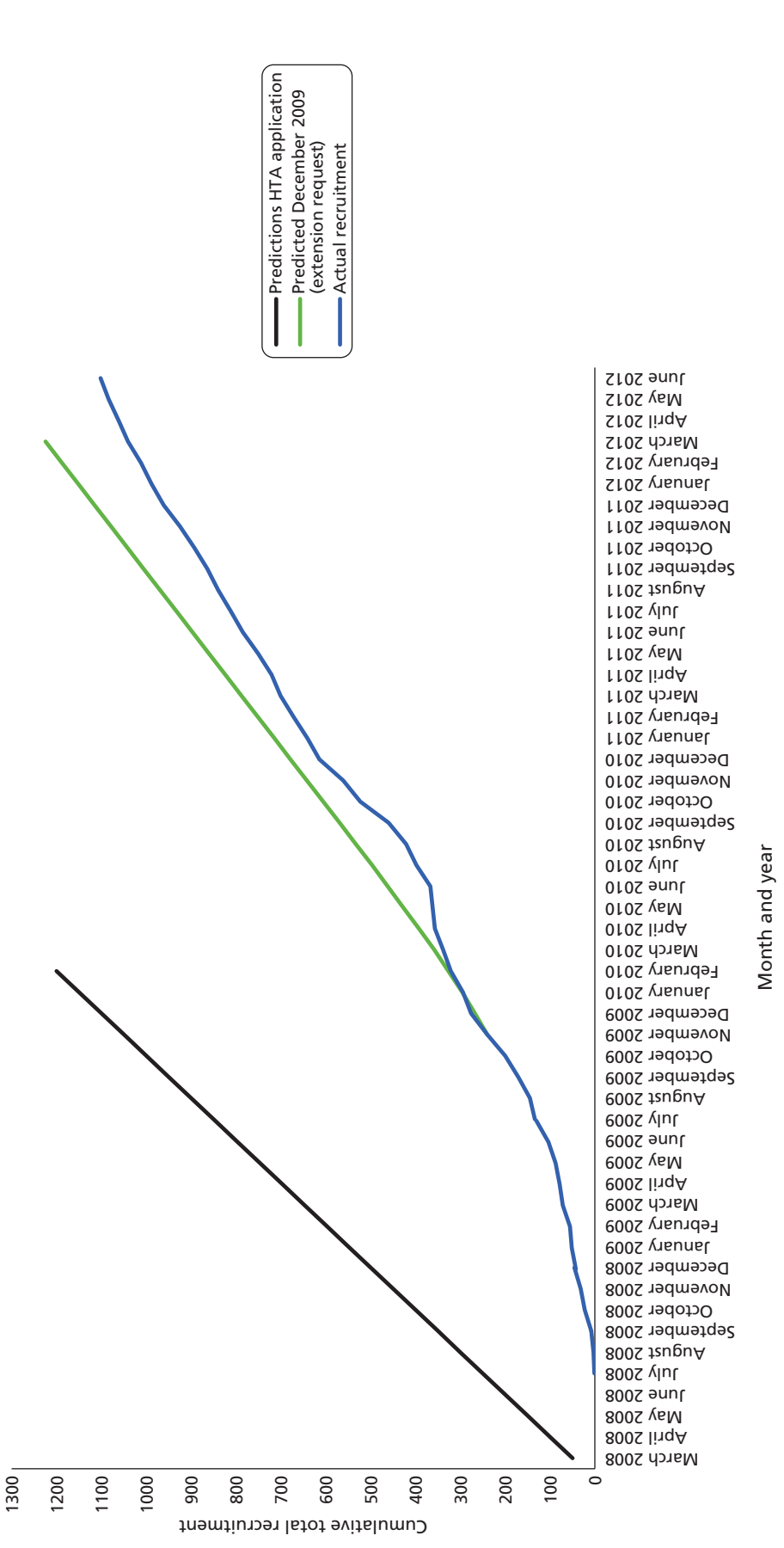

FIGURE 2 Predicted vs. actual recruitment of participants.

Non-recruited patients

During the trial we asked participating centres to record basic anonymised details of patients attending ED aged 16 years or over with acute severe asthma who were not recruited. These data were captured by a mixture of prospective screening by recruiting doctors and retrospective case note review by research nurses. Unfortunately, limited research nurse availability and service pressure in the ED prevented reliable collection of these data at some centres. Nevertheless, data were collected from a total of 3948 non-recruited patients attending at recruiting centres during the trial. Of these, 1165 patients were not identified by recruiting doctors because of a variety of administrative reasons (the ED was too busy, no GCP-trained doctors were available or no treatment packs were available) but were retrospectively identified by research nurses on the basis of information in the ED record. The remaining 2783 patients were identified prospectively, but excluded on the basis of ineligibility ($n = 847$), declining to participate ($n = 200$), inability to give consent ($n = 21$), administrative reasons as outlined above ($n = 306$) and other reasons ($n = 201$), while no reason was recorded for 89 patients. The patient characteristics recorded (age and sex) were not obviously different between those who did not take part and those who did (*Table 4*), with the possible exception of the subset who were eligible but unable to give consent.

The trial population

The CONSORT flow chart (*Figure 3*) shows the flow of participants through the trial. Of the 1109 participants randomised, 25 were excluded from the analysis. Eleven patients received no medication and no data were collected after randomisation. These patients either withdrew consent prior to any medication being delivered or recruiting doctors had randomised them before taking consent and patients subsequently refused consent. Two patients self-discharged without being treated. There were nine occasions where the numbered medication pack was not available in the ED and no treatment was subsequently given. The remaining three patients received treatment but there were protocol violations and these patients should not have been recruited: two were subsequently found to be previous participants and one was a prisoner. All remaining 1084 patients were included in analyses according to intention-to-treat principles, regardless of whether or not they received any medication.

Protocol deviations which did not result in the participants being removed from analysis were also reported and reviewed at PMG meetings. A total of 203 protocol deviations were reported, which can be broadly categorised as follows: 42 deviations from the trial treatment protocol (randomised but trial treatment not commenced, treatment started but not completed or incorrect treatment), 143 consent not fully documented (no witness signature, verbal but not written consent, consent taken by a doctor without GCP training and/or not on delegation, log or tick boxes not completed), 15 administrative errors

TABLE 4 Non-recruited patients

Patient classification	Age (years), mean (SD)	Sex, *n* (%) male
Recruited ($N = 1109$)	36 (14)	321 (30)
Not identified ($N = 1165$)	36 (16)	359 (31)
Ineligible ($N = 847$)	37 (15)	217 (26)
Declined to participate ($N = 200$)	37 (16)	62 (31)
Unable to give consent ($N = 31$)	44 (19)	11 (36)
Administrative reasons ($N = 306$)	37 (15)	94 (31)
Other ($N = 201$)	38 (17)	50 (25)
Not recorded ($N = 89$)	35 (18)	30 (33)

SD, standard deviation.

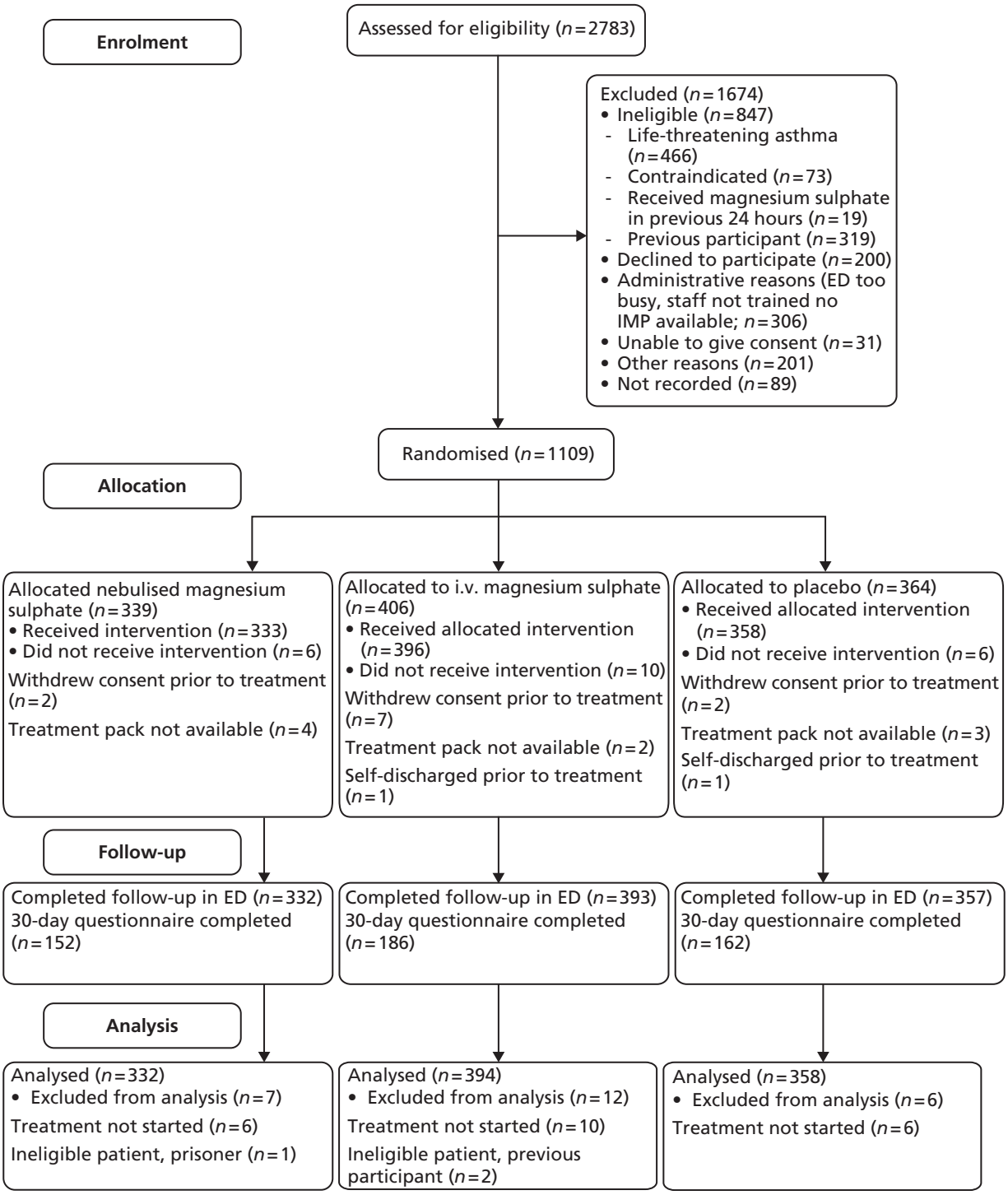

FIGURE 3 The CONSORT flow chart.

(prescription incorrectly completed, patient details recorded incorrectly, randomisation after treatment commenced or pack opened in error), and three screening assessment queries. The apparently high number of deviations can be attributed to the complexities of recruiting in an emergency setting and our requirement for sites to report any deviation from the protocol, however minor. Deviations from the consent procedure were reviewed to ensure that there was sufficient evidence that consent had been obtained before deciding if the participant should remain in the trial.

Table 5 summarises the recruitment and allocation of patients across the centres. Overall, 34 centres recruited to the study, of which 24 recruited 10 or more patients. The remaining centres were combined into one group for the purposes of all analyses. *Table 6* shows the demographics and characteristics of the

TABLE 5 Recruitment and allocation across trial centres

Centre	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Total (*n* = 1084)
Royal Infirmary of Edinburgh	56 (17%)	67 (17%)	56 (16%)	179 (17%)
Sheffield – Northern General Hospital	30 (9%)	41 (10%)	35 (10%)	106 (10%)
Royal United Hospital Bath	25 (8%)	29 (7%)	23 (6%)	77 (7%)
Aberdeen Royal Infirmary	17 (5%)	23 (6%)	17 (5%)	57 (5%)
University Hospital of N. Staffordshire	20 (6%)	17 (4%)	20 (6%)	57 (5%)
Crosshouse Hospital	18 (5%)	15 (4%)	19 (5%)	52 (5%)
Bristol Frenchay Hospital	13 (4%)	17 (4%)	18 (5%)	48 (4%)
Barnsley Hospital	14 (4%)	14 (4%)	18 (5%)	46 (4%)
Plymouth – Derriford Hospital	12 (4%)	14 (4%)	12 (3%)	38 (4%)
York Hospital	10 (3%)	15 (4%)	13 (4%)	38 (4%)
Ayr Hospital	9 (3%)	12 (3%)	10 (3%)	31 (3%)
Royal Devon and Exeter Hospital	12 (4%)	8 (2%)	11 (3%)	31 (3%)
Bristol Royal Infirmary	10 (3%)	11 (3%)	9 (3%)	30 (3%)
Leicester Royal Infirmary	9 (3%)	7 (2%)	14 (4%)	30 (3%)
Kettering General Hospital	9 (3%)	10 (3%)	10 (3%)	29 (3%)
Lancaster Royal Infirmary	8 (2%)	16 (4%)	5 (1%)	29 (3%)
Derbyshire Royal Infirmary	6 (2%)	11 (3%)	11 (3%)	28 (3%)
Fife – Queen Margaret Hospital	5 (2%)	11 (3%)	10 (3%)	26 (2%)
Hull Royal Infirmary	10 (3%)	9 (2%)	4 (1%)	23 (2%)
Royal Alexandra Hospital – Paisley	7 (2%)	8 (2%)	6 (2%)	21 (2%)
University Hospital Coventry	5 (2%)	7 (2%)	7 (2%)	19 (2%)

TABLE 5 Recruitment and allocation across trial centres (*continued*)

Centre	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Total (*n* = 1084)
Fife – Victoria Hospital	5 (2%)	5 (1%)	5 (1%)	15 (1%)
Addenbrookes Hospital, Cambridge	3 (1%)	6 (2%)	4 (1%)	13 (1%)
The Royal London Hospital	3 (1%)	4 (1%)	4 (1%)	11 (1%)
Southend University Hospital	4 (1%)	2 (1%)	3 (1%)	9 (1%)
James Cook University Hospital – Middlesbrough	3 (1%)	3 (1%)	1 (< 1%)	7 (1%)
Hairmyres Hospital	2 (1%)	3 (1%)	2 (1%)	7 (1%)
Leeds Teaching Hospitals	1 (< 1%)	1 (< 1%)	3 (1%)	5 (< 1%)
Northampton General Hospital	1 (< 1%)	1 (< 1%)	3 (1%)	5 (< 1%)
Rotherham General Hospital	2 (1%)	3 (1%)	0	5 (< 1%)
Doncaster Royal Infirmary	0	3 (1%)	1 (< 1%)	4 (< 1%)
Bradford Royal Infirmary	1 (< 1%)	0	2 (1%)	3 (< 1%)
Queens Medical Centre, Nottingham	1 (< 1%)	1 (< 1%)	1 (< 1%)	3 (< 1%)
Pinderfields Hospital	1 (< 1%)	0	1 (< 1%)	2 (< 1%)

Values in brackets denote per cent of total.

TABLE 6 Patient demographics and characteristics

Patient characteristic	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Total (*n* = 1084)
Age (years)				
Mean (SD)	36.5 (14.8)	35.6 (13.1)	36.4 (14.1)	36.1 (14.0)
Median (IQR)	35.0 (23–47)	34.0 (25–44)	34.5 (24–47)	34.0 (24–46)
Min., max.	16, 85	16, 84	16, 88	16, 88
Sex[a]				
Male	100 (30%)	115 (29%)	106 (30%)	321 (30%)
Female	232 (70%)	279 (71%)	252 (70%)	763 (70%)
Ethnicity[a]				
White	286 (86%)	369 (94%)	319 (89%)	974 (90%)
Mixed	2 (1%)	1 (< 1%)	5 (1%)	8 (1%)
Asian or Asian British	14 (4%)	8 (2%)	16 (4%)	38 (4%)
Black or black British	2 (1%)	5 (1%)	4 (1%)	11 (1%)
Other	2 (1%)	0	0	2 (< 1%)
Not stated	22 (7%)	8 (2%)	11 (3%)	41 (4%)
Missing	4 (1%)	3 (1%)	3 (1%)	10 (1%)

continued

TABLE 6 Patient demographics and characteristics (*continued*)

Patient characteristic	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Total (*n* = 1084)
Smoking status[a]				
Never	151 (45%)	156 (40%)	143 (40%)	450 (42%)
Current	98 (30%)	138 (35%)	127 (35%)	363 (33%)
Previous	72 (22%)	95 (24%)	81 (23%)	248 (23%)
Missing	11 (3%)	5 (1%)	7 (2%)	23 (2%)
Predicted PEFR				
n	324	389	346	1059
Mean (SD)	430.0 (118.8)	431.8 (116.9)	435.0 (110.8)	432.3 (115.4)
Median (IQR)	425.0 (350–500)	435.0 (350–500)	425.0 (350–500)	425.0 (350–500)
Min., max.	100, 700	140, 800	150, 790	100, 800
Previous admissions with asthma				
At least one previous ITU admission[a]	56 (17%)	61 (15%)	39 (11%)	156 (14%)
At least one previous admission[a]	226 (68%)	260 (66%)	213 (59%)	699 (64%)
If yes, time since last admission with asthma (months)				
n	221	256	208	688
Mean (SD)	42.0 (72.2)	38.5 (69.5)	40.8 (61.9)	40.1 (68.0)
Median (IQR)	12.0 (4–47)	12.0 (4–37)	17.0 (6–48)	12.5 (4–47)
Min., max.	3 days, 32 years	1 day, 50 years	1 day, 40 years	1 day, 50 years
Entry criterion for acute severe asthma[a,b]				
PEFR < 50% of best or predicted	179 (54%)	205 (52%)	192 (53%)	576 (53%)
Heart rate > 110 beats per minute	213 (64%)	251 (64%)	218 (61%)	682 (63%)
Respiratory rate > 25 breaths per minute	178 (54%)	227 (58%)	204 (57%)	609 (67%)
Unable to complete sentences in one breath	138 (42%)	159 (40%)	139 (39%)	436 (40%)
Baseline PEFR[a]				
< 33% predicted	53 (16%)	50 (13%)	56 (16%)	156 (15%)
33–50% predicted	112 (34%)	116 (29%)	116 (32%)	344 (32%)
50–75% predicted	107 (32%)	148 (38%)	118 (33%)	373 (34%)
≥ 75% predicted	36 (11%)	61 (15%)	37 (10%)	134 (12%)
Not recorded	24 (7%)	19 (5%)	31 (9%)	74 (7%)

IQR, interquartile range; max., maximum; min., minimum; SD, standard deviation.
a Value in brackets denotes per cent of total.
b More than one may apply.

trial population. PEFR values reported in this table are predicted values. The actual baseline values are reported alongside the 1- and 2-hour values in *Table 25*. Patients were generally female (70%), white (90%) and relatively young (82% were below the age of 50 years). Overall, 64% of patients had previously been admitted to hospital for asthma, with the percentage being higher in the active two arms (68% nebulised, 66% i.v. and 59% placebo) and 14% of patients had previously been admitted to ITU. Where previous admissions had been recorded, around half had been admitted in the past year.

Trial and other treatments given

Table 7 shows the concurrent medications given in the 24 hours prior to hospital attendance, in the ambulance and ED immediately prior to randomisation, and alongside trial treatments in the 4 hours immediately after randomisation. Most patients (88%) had used salbutamol in the 24 hours prior to attendance and one-third had taken prednisolone. Use of salbutamol (95%) and ipratropium bromide (72%) was typical in the ambulance or ED prior to randomisation, whereas 41% were given prednisolone and 21% hydrocortisone. Salbutamol, ipratropium bromide, prednisolone and hydrocortisone were also commonly given alongside trial treatments.

Table 8 shows the proportion of patients receiving prednisolone or hydrocortisone at any point from 24 hours before attendance to 4 hours after randomisation. Around one-third of patients had taken corticosteroids in the 24 hours before attendance, 61% were given corticosteroids before randomisation and 21% after. Some patients were given additional corticosteroids in the ambulance or ED despite having taken corticosteroids in the previous 24 hours and, therefore, overall 95% of the trial population received corticosteroid therapy at some point from 24 hours prior to hospital attendance to 4 hours after randomisation. *Table 9* shows the total dose of salbutamol given in the ambulance or ED prior to randomisation or up to 4 hours after randomisation. All but 10 patients (1%) received salbutamol at some point and 95% received salbutamol prior to randomisation, with a mean dose of 4.9 mg. Overall, it appears that there was adherence to BTS/SIGN guidance and substantial use of standard treatments that are known to be effective.[2]

Three patients (all in the placebo group) were given i.v. magnesium sulphate in the ED or ambulance prior to randomisation. After these cases were identified, the protocol was amended to exclude patients who had received magnesium sulphate in the 24 hours prior to randomisation. A further 58 patients (5%) received i.v. magnesium sulphate after randomisation as a result of the treating physician deciding that the patient's response to initial treatment suggested that they were no longer in equipoise. These cases were evenly distributed across the three groups.

Table 10 shows the trial medications received by the three groups. Most patients (89%) received the full i.v. infusion and only 2% received less than half. Similarly, most patients (99%) received all three nebulisers and a substantial proportion of the nebuliser solution.

TABLE 7 Medication usage prior to attendance, during and after treatment

Medication Usage	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Total (*n* = 1084)
Used medication 24 hours prior to attendance	304 (92%)	370 (94%)	320 (89%)	994 (92%)
Salbutamol	293 (88%)	350 (89%)	309 (86%)	952 (88%)
Prednisolone	115 (35%)	140 (36%)	106 (30%)	361 (33%)
Seretide	58 (17%)	54 (14%)	62 (17%)	174 (16%)
Ipratropium bromide	42 (13%)	58 (15%)	47 (13%)	147 (14%)
Pulmicort	32 (10%)	33 (8%)	24 (7%)	89 (8%)
Beclometasone (Clenil)	25 (8%)	23 (6%)	22 (6%)	70 (6%)
Montelukast	15 (5%)	12 (3%)	14 (4%)	41 (4%)
Amoxicillin	9 (3%)	13 (3%)	12 (3%)	34 (3%)
Salmeterol (Serevent)	12 (4%)	10 (3%)	7 (2%)	29 (3%)
Terbutaline (Bricanyl)	8 (2%)	9 (2%)	8 (2%)	25 (2%)
Theophylline	8 (2%)	7 (2%)	7 (2%)	22 (2%)
Tiotropium (Spiriva)	7 (2%)	5 (1%)	7 (2%)	19 (2%)
Hydrocortisone	6 (2%)	5 (1%)	4 (1%)	15 (1%)
Aminophylline	7 (2%)	4 (1%)	3 (1%)	14 (1%)
Formoterol (Oxis®, AstraZeneca UK Ltd)	5 (2%)	1 (< 1%)	0	6 (1%)
Clarithromycin	2 (1%)	1 (< 1%)	0	3 (< 1%)
Combivent	0	2 (1%)	1 (< 1%)	3 (< 1%)
Zarfirlukast	2 (1%)	0	1 (< 1%)	3 (< 1%)
Other	5 (2%)	4 (1%)	6 (2%)	15 (1%)
Given medication in ambulance or ED prerandomisation	325 (98%)	375 (95%)	344 (96%)	1044 (96%)
Salbutamol	320 (96%)	367 (93%)	338 (94%)	1025 (95%)
Ipratropium bromide	241 (73%)	279 (71%)	259 (72%)	779 (72%)
Prednisolone	126 (38%)	154 (39%)	168 (47%)	448 (41%)
Hydrocortisone	71 (21%)	86 (22%)	69 (19%)	226 (21%)
Combivent	9 (3%)	19 (5%)	10 (3%)	38 (4%)
Amoxicillin	7 (2%)	3 (1%)	3 (1%)	13 (1%)
Amoxicillin trihydrate/ potassium clavulanate (Augmentin®, GlaxoSmithKline UK)	2 (1%)	5 (1%)	2 (1%)	9 (1%)

TABLE 7 Medication usage prior to attendance, during and after treatment (*continued*)

Medication Usage	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Total (*n* = 1084)
Clarithromycin	1 (<1%)	2 (1%)	4 (1%)	7 (1%)
Aminophylline	2 (1%)	1 (< 1%)	0	3 (< 1%)
Magnesium sulphate	0	0	3 (1%)	3 (< 1%)
Theophylline	0	1 (< 1%)	1 (< 1%)	2 (< 1%)
Montelukast	0	1 (< 1%)	0	1 (< 1%)
Pulmicort	0	0	1 (< 1%)	1 (< 1%)
Other	2 (1%)	0	0	2 (< 1%)
Given medication 0–4 hours post randomisation	180 (54%)	195 (49%)	182 (51%)	557 (51%)
Salbutamol	107 (32%)	101 (26%)	93 (26%)	301 (28%)
Prednisolone	64 (19%)	62 (16%)	54 (15%)	180 (17%)
Ipratropium bromide	59 (18%)	50 (13%)	53 (15%)	162 (15%)
Hydrocortisone	16 (5%)	25 (6%)	19 (5%)	60 (6%)
Magnesium sulphate	21 (6%)	16 (4%)	21 (6%)	58 (5%)
Amoxicillin	9 (3%)	16 (4%)	15 (4%)	40 (4%)
Augmentin	11 (3%)	12 (3%)	7 (2%)	30 (3%)
Combivent	7 (2%)	13 (3%)	7 (2%)	27 (2%)
Clarithromycin	7 (2%)	9 (2%)	9 (3%)	25 (2%)
Aminophylline	8 (2%)	7 (2%)	9 (3%)	24 (2%)
Pulmicort	2 (1%)	3 (1%)	1 (< 1%)	6 (1%)
Seretide	0	1 (< 1%)	1 (< 1%)	2 (< 1%)
Theophylline	1 (< 1%)	1 (< 1%)	0	2 (< 1%)
Other	9 (3%)	3 (1%)	3 (1%)	15 (1%)

Values in brackets denote per cent of total.

TABLE 8 Hydrocortisone or prednisolone usage

Usage	Nebulised magnesium (*n* = 332)	Intravenous magnesium (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
Any usage in or before ED	316 (95%)	372 (94%)	344 (96%)	1032 (95%)
Last 24 hours before attendance	119 (36%)	143 (36%)	110 (31%)	372 (34%)
Ambulance/ED pre randomisation	191 (58%)	236 (60%)	231 (65%)	658 (61%)
After randomisation 0–4 hours	77 (23%)	83 (21%)	69 (19%)	229 (21%)

Values in brackets denote per cent of total.

TABLE 9 Salbutamol dosage

Usage	Nebulised magnesium (*n* = 332)	Intravenous magnesium (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
Usage in ambulance or ED				
Any usage[a]	329 (99%)	391 (99%)	354 (99%)	1074 (99%)
Mean (SD) dose given (mg)	8.7 (3.4)	8.0 (3.4)	8.2 (3.4)	8.3 (3.4)
Prerandomisation usage (ambulance or ED)				
Any usage[a]	320 (96%)	367 (93%)	338 (94%)	1025 (95%)
Mean (SD) dose given (mg)	5.0 (1.3)	4.8 (1.5)	4.9 (1.4)	4.9 (1.4)
Post-randomisation usage in ED				
Any usage[a]	232 (70%)	243 (62%)	232 (65%)	707 (65%)
Mean (SD) dose given (mg)	3.8 (3.4)	3.3 (3.3)	3.4 (3.2)	3.4 (3.3)

SD, standard deviation.
a Values in brackets denote per cent of total.

TABLE 10 Trial medications received

Medication received	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Total (*n* = 1084)
Total volume of i.v. infusion (ml)				
Mean (SD)	97.2 (14.8)	96.5 (16.1)	97.9 (12.7)	97.1 (14.6)
100[a]	299 (90%)	349 (89%)	320 (89%)	968 (89%)
90–99.9[a]	11 (3%)	18 (5%)	16 (4%)	45 (4%)
70–89.9[a]	8 (2%)	8 (2%)	4 (1%)	20 (2%)
50–69.9[a]	0	2 (1%)	1 (< 1%)	3 (< 1%)
0–49.9[a]	7 (2%)	11 (3%)	6 (2%)	24 (2%)
Missing[a]	7 (2%)	6 (2%)	11 (3%)	24 (2%)
Number of nebulisers given				
0	0	0	0	0
1[a]	2 (1%)	4 (1%)	0	6 (1%)
2[a]	5 (2%)	1 (< 1%)	2 (1%)	8 (1%)
3[a]	323 (98%)	387 (99%)	355 (99%)	1065 (99%)
Missing[a]	2	2	1	5
Total volume of nebuliser excluding salbutamol (ml)				
Mean (SD)	21.0 (4.1)	21.5 (3.9)	21.5 (3.6)	21.3 (3.9)
22.5[a]	261 (79%)	349 (89%)	307 (86%)	917 (85%)
20–22.4[a]	11 (3%)	7 (2%)	8 (2%)	26 (2%)
15–19.9[a]	21 (6%)	12 (3%)	18 (5%)	51 (5%)
7.5–14.9[a]	18 (5%)	9 (2%)	9 (3%)	36 (3%)
0–7.4[a]	5 (2%)	9 (2%)	6 (2%)	20 (2%)
Missing[a]	16 (5%)	8 (2%)	10 (3%)	34 (3%)

SD, standard deviation.
a Values in brackets denote per cent of total.

Primary outcome analysis

Table 11 shows the primary, service-orientated outcome, namely admission to hospital at presentation or within 1 week of presentation. Overall, 827 out of 1084 (76%) of patients were admitted to hospital within 1 week: 811 were admitted at initial attendance, 14 were initially discharged but were admitted within the next week, and the status of two patients was unknown and, therefore, the patients were analysed as having been admitted. The percentage admitted was lowest in the i.v. magnesium sulphate group (72%) but similar in the placebo (78%) and nebulised magnesium sulphate (79%) groups. None of the contrasts or pairwise comparisons was statistically significant at the 5% level. These findings were also borne out in the per-protocol subset, which showed very similar results (*Table 12*).

TABLE 11 Admission to hospital at presentation or within 1 week

Classification	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Total (*n* = 1084)
Status at 4 hours				
Admitted[a]	254 (77%)	279 (71%)	278 (78%)	811 (75%)
Discharged[a]	77 (23%)	114 (29%)	80 (22%)	271 (25%)
Dead	0	0	0	0
Unknown[a]	1 (< 1%)	1 (< 1%)	0	2 (< 1%)
Subsequent hospital admission within 7 days[a]	15 (5%)	10 (3%)	7 (2%)	32 (3%)
Subsequent hospital admission following discharge at initial attendance[a]	6 (2%)	5 (1%)	3 (1%)	14 (1%)
Admitted to hospital at any time within 7 days[a]	261 (79%)	285 (72%)	281 (78%)	827 (76%)
Comparisons	**Odds ratio (95% CI)**			***p*-value**
Active vs. placebo	0.84 (0.61 to 1.15)			0.276
i.v. vs. nebuliser	0.76 (0.53 to 1.10)			0.146
i.v. vs. placebo	0.73 (0.51 to 1.04)			0.083
Nebuliser vs. placebo	0.96 (0.65 to 1.40)			0.819

a Values in brackets denote per cent of total.

TABLE 12 Admission to hospital at presentation or within 1 week, per protocol

Classification	Nebulised magnesium sulphate (*n* = 305)	Intravenous magnesium sulphate (*n* = 368)	Placebo (*n* = 333)	Total (*n* = 1006)
Status at 4 hours				
Admitted[a]	236 (77%)	263 (71%)	258 (77%)	757 (75%)
Discharged[a]	69 (23%)	105 (29%)	75 (23%)	249 (25%)
Dead	0	0	0	0
Unknown	0	0	0	0
Subsequent hospital admission within 7 days[a]	14 (5%)	8 (2%)	7 (2%)	29 (3%)
Subsequent hospital admission following discharge at initial attendance[a]	6 (2%)	4 (1%)	3 (1%)	13 (1%)
Admitted to hospital at any time within 7 days[a]	242 (79%)	267 (73%)	261 (78%)	770 (77%)
Comparisons	**Odds ratio (95% CI)**			***p*-value**
Active vs. placebo	0.85 (0.61 to 1.19)			0.348
i.v. vs. nebuliser	0.78 (0.54 to 1.15)			0.210
i.v. vs. placebo	0.75 (0.52 to 1.09)			0.133
Nebuliser vs. placebo	0.96 (0.64 to 1.44)			0.848

a Values in brackets denote per cent of total.

Patient breathlessness is summarised in *Tables 13* (complete case), *14* (complete case, per-protocol) and *15* (imputed). The complete case analysis is also presented graphically in *Figure 4*. The change in VAS at 2 hours was recorded in 976 out of 1084 (90%) members of the cohort. Improvements in breathlessness were observed in all three groups. In the complete case data, the mean change from baseline was largest [34.3 mm; standard deviation (SD) 27.7 mm] in the i.v. group and smallest (28.2 mm; SD 27.4 mm) in the nebulised group, whereas the change in the placebo group was between the two (31.3 mm; SD 29.4 mm). Overall, magnesium sulphate did not reduce breathlessness (mean difference = 0 mm, 95% CI –1.9 to 1.9 mm; $p = 0.999$). Although i.v. magnesium sulphate appeared superior to nebulised magnesium sulphate (mean difference = 5.1 mm; 95% CI 0.8 to 9.4 mm; $p = 0.019$), the magnitude of the difference in clinical terms is small. The post-hoc comparison of i.v. magnesium sulphate against placebo yielded no significant difference (mean difference 2.6 mm; 95% CI –1.6 to 6.8 mm; $p = 0.231$), although this may be partly due to a small imbalance at baseline, as the pretreatment VAS scores were slightly higher in the placebo group than in the i.v. group. Nonetheless, the magnitude of difference between i.v. and placebo is minor when considered in the context that the minimum clinically significant difference for VAS breathlessness has been estimated to be 22 mm.[48]

TABLE 13 Visual analogue scale (mm) – complete case

Measurement	Nebulised magnesium (*n* = 332)	Intravenous magnesium (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
VAS at baseline				
Number of observations	326	386	349	1061
Mean [mm (SD)]	61.6 (23.3)	61.9 (22.8)	63.1 (23.5)	62.2 (23.2)
Median [mm (IQR)]	65.0 (46–80)	65.0 (46–80)	69.0 (46–82)	67.0 (46–80)
Min., max. (mm)	2, 100	4, 100	0, 100	0, 100
VAS at 1 hour				
Number of observations	314	372	344	1030
Mean [mm (SD)]	42.9 (25.7)	37.7 (25.4)	41.9 (25.0)	40.7 (25.4)
Median [mm (IQR)]	42.5 (23–63)	34.5 (16–58)	41.0 (20–62)	39.0 (19–60)
Min., max. (mm)	0, 100	0, 98	0, 99	0, 100
Change in VAS at 1 hour				
Number of observations	314	372	344	1030
Mean [mm (SD)]	–18.4 (22.8)	–24.2 (24.4)	–21.5 (24.7)	–21.5 (24.1)
Median [mm (IQR)]	–15.0 (–32 to –4)	–20.0 (–40 to –7)	–17.0 (–37 to –5)	–18.0 (–35 to –5)
Min., max. (mm)	–86, 63	–96, 39	–93, 60	–96, 63
VAS at 2 hours				
Number of observations	296	357	323	976
Mean [mm (SD)]	32.9 (27.8)	27.7 (26.4)	32.4 (27.5)	30.8 (27.3)
Median [mm (IQR)]	27.5 (8–53)	18.0 (5–45)	25.0 (9–53)	23.0 (7–52)
Min., max. (mm)	0, 99	0, 100	0, 100	0, 100
Change in VAS at 2 hours				
Number of observations	296	357	323	976
Mean [mm (SD)]	–28.2 (27.4)	–34.3 (27.7)	–31.3 (29.4)	–31.5 (28.2)
Median [mm (IQR)]	–28.0 (–47 to –9)	–33.0 (–53 to –14)	–29.0 (–53 to –10)	–30.0 (–52 to –11)
Min., max. (mm)	–94, 90	–99, 45	–98, 63	–99, 90
Comparisons	**Mean difference (95% CI)**			***p*-value**
Active vs. placebo	0.0 (–1.9 to 1.9)			0.999
i.v. vs. nebuliser	–5.1 (–9.4 to –0.8)			0.019
i.v. vs. placebo	–2.6 (–6.8 to 1.6)			0.231
Nebuliser vs. placebo	2.6 (–1.8 to 7.0)			0.253

IQR, interquartile range; max., maximum; min., minimum.

TABLE 14 Visual analogue scale (mm) – complete case, per protocol

Measurement	Nebulised magnesium (*n* = 305)	Intravenous magnesium (*n* = 368)	Placebo (*n* = 333)	Overall (*n* = 1006)
VAS at baseline				
Number of observations	303	362	326	991
Mean [mm (SD)]	61.7 (23.3)	61.6 (22.7)	63.0 (23.5)	62.1 (23.1)
Median [mm (IQR)]	65.0 (46–80)	65.0 (47–80)	69.0 (45–82)	66.0 (46–80)
Min., max. (mm)	2, 100	4, 100	0, 100	0, 100
VAS at 1 hour				
Number of observations	297	354	322	973
Mean [mm (SD)]	43.6 (25.7)	37.9 (25.7)	42.0 (25.0)	41.0 (25.5)
Median [mm (IQR)]	43.0 (24–64)	34.5 (16–59)	41.0 (20–62)	39.0 (19–61)
Min., max. (mm)	0, 100	0, 98	0, 99	0, 100
Change in VAS at 1 hour				
Number of observations	297	354	322	973
Mean [mm (SD)]	–17.9 (22.2)	–23.8 (24.2)	–21.3 (24.5)	–21.2 (23.8)
Median [mm (IQR)]	–15.0 (–30 to –3)	–19.5 (–39 to –7)	–17.0 (–37 to –5)	–17.0 (–34 to –5)
Min., max. (mm)	–86, 63	–96, 39	–93, 60	–96, 63
VAS at 2 hours				
Number of observations	280	341	304	925
Mean [mm (SD)]	33.7 (27.8)	28.0 (26.6)	32.7 (27.7)	31.3 (27.4)
Median [mm (IQR)]	28.5 (10–54)	18.0 (5–45)	25.5 (10–53)	24.0 (7–52)
Min., max. (mm)	0, 99	0, 100	0, 100	0, 100
Change in VAS at 2 hours				
Number of observations	280	341	304	925
Mean [mm (SD)]	–27.7 (27.1)	–34.0 (27.7)	–31.1 (29.4)	–31.1 (28.2)
Median [mm (IQR)]	–27.5 (–46 to –9)	–33.0 (–52 to –14)	–28.5 (–53 to –10)	–30.0 (–51 to –11)
Min., max. (mm)	–88, 90	–99, 45	–98, 63	–99, 90
Comparisons	**Mean difference (95% CI)**			***p*-value**
Active vs. placebo	0.1 (–1.8 to 2.0)			0.950
i.v. vs. nebuliser	–5.2 (–9.6 to –0.8)			0.021
i.v. vs. placebo	–2.5 (–6.8 to 1.8)			0.261
Nebuliser vs. placebo	2.6 (–1.8 to 7.0)			0.253

IQR, interquartile range; max., maximum; min., minimum.

TABLE 15 Visual analogue scale (mm) – results from different imputation strategies

Imputation strategy	Number of participants included	Mean difference (95% CI)	*p*-value
Active vs. placebo			
ITT, no imputation	976	0.0 (–1.9 to 1.9)	0.999
ITT, linear interpolation	981	0.1 (–1.7 to 1.9)	0.956
ITT, multiple imputation	1084	–1.0 (–2.3 to 4.3)	0.549
PP, no imputation	925	0.1 (–1.8 to 2.0)	0.950
i.v. vs. nebuliser			
ITT, no imputation	976	–5.1 (–9.4 to –0.8)	0.019
ITT, linear interpolation	981	–4.8 (–9.0 to –0.5)	0.027
ITT, multiple imputation	1084	–5.2 (–9.1 to 1.3)	0.007
PP, no imputation	925	–5.2 (–9.6 to –0.8)	0.021
i.v. vs. placebo			
ITT, no imputation	976	–2.6 (–6.8 to 1.6)	0.231
ITT, linear interpolation	981	–2.3 (–6.4 to 1.9)	0.279
ITT, multiple imputation	1084	–3.6 (–7.3 to 0.1)	0.059
PP, no imputation	925	–2.5 (–6.8 to 1.8)	0.261
Nebuliser vs. placebo			
ITT, no imputation	976	2.6 (–1.8 to 7.0)	0.253
ITT, linear interpolation	981	2.5 (–1.9 to 6.9)	0.261
ITT, multiple imputation	1084	1.6 (–2.2 to 5.5)	0.401
PP, no imputation	925	2.6 (–1.8 to 7.0)	0.253

ITT, intention to treat; PP, per protocol.

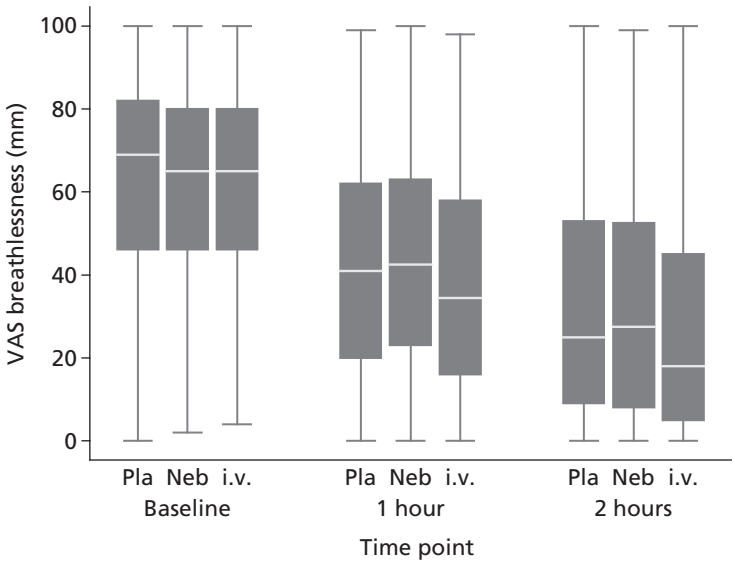

FIGURE 4 Change in VAS breathlessness (complete case analysis). Neb, nebuliser; Pla, placebo.

Secondary outcome analysis

Table 16 and *Figure 5* compare the hospital length of stay after initial attendance for the three groups. The length of stay was not recorded unless the patients had been admitted; these patients are represented by the 'spike' at 3.9 hours in the Kaplan–Meier graph. The length of stay was shorter in the i.v. group, although not significantly so.

Table 17 shows the number of days spent on ICU, HDU and a general medical ward up to 30 days after recruitment. Only 2% of the cohort spent any days on ICU and only 6% spent any days on HDU. There were no significant differences between the three groups in the number of days spent in any location.

Table 18 shows the number of patients requiring invasive or non-invasive ventilatory support. Only 1% of the cohort required ventilatory support and there were no significant differences between the three groups.

TABLE 16 Length of stay

Measurement/ classification	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Total (*n* = 1084)
Time to discharge[a]				
Time not known	3 (1%)	6 (2%)	5 (1%)	14 (1%)
Patient died	1 (< 1%)	1 (< 1%)	0	2 (< 1%)
Patient admitted, duration not known	1 (< 1%)	2 (1%)	4 (1%)	7 (1%)
Nothing recorded	1 (< 1%)	3 (1%)	1 (< 1%)	5 (< 1%)
Time recorded				
n	329	388	353	1070
Mean [hours (SD)]	63.2 (79.7)	57.0 (75.1)	63.3 (84.3)	61.0 (79.6)
Median [hours (IQR)]	35.1 (5–88)	31.5 (4–78)	36.4 (5–87)	34.1 (4–84)
Min., max. (hours)	3, 623	4, 723	1, 694	1, 723
Not admitted/ discharged within 4 hours[a]	80 (24%)	120 (30%)	83 (23%)	283 (26%)
4–6 hours[a]	4 (1%)	11 (3%)	8 (2%)	23 (2%)
6–12 hours[a]	16 (5%)	10 (3%)	15 (4%)	41 (4%)
12–24 hours[a]	33 (10%)	34 (9%)	38 (11%)	105 (10%)
> 24 hours[a]	196 (59%)	213 (54%)	209 (58%)	618 (57%)
Comparisons	**Time ratio (95% CI)**			***p*-value**
Active vs. placebo	0.92 (0.76 to 1.13)			0.432
i.v. vs. nebuliser	0.87 (0.69 to 1.09)			0.230
i.v. vs. placebo	0.86 (0.69 to 1.08)			0.192
Nebuliser vs. placebo	0.99 (0.78 to 1.25)			0.936

IQR, interquartile range; max., maximum; min., minimum.
a Values in brackets denote per cent of total.

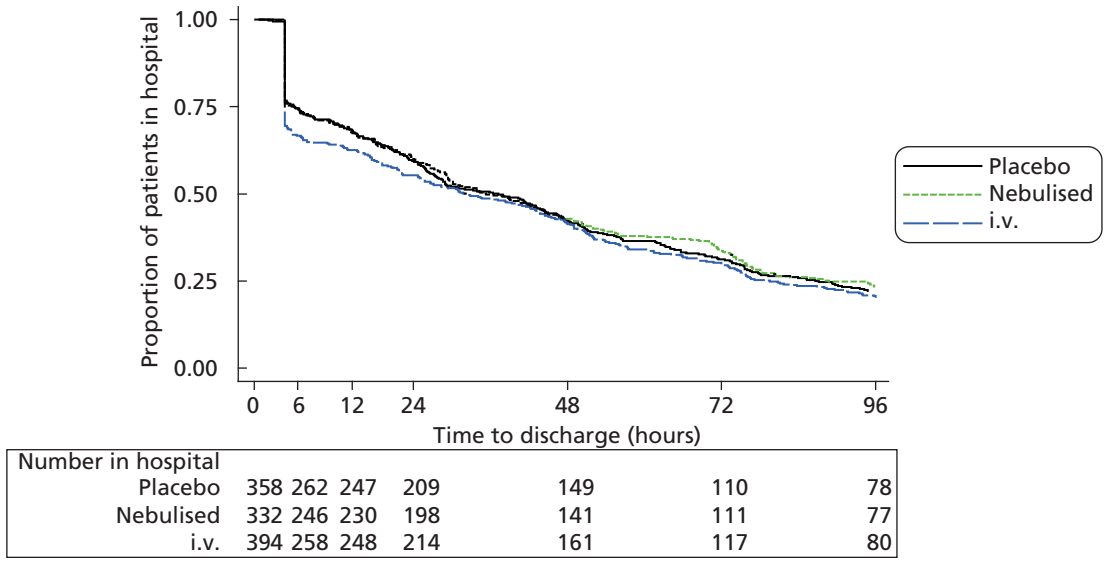

FIGURE 5 Length of stay following initial attendance.

TABLE 17 Number of days on ICU, HDU or ward

Measurement	Nebulised magnesium sulphate ($n = 332$)	Intravenous magnesium sulphate ($n = 394$)	Placebo ($n = 358$)	Total ($n = 1084$)	*p*-values	
					Active vs. placebo	Intravenous vs. nebuliser
Days in hospital at any location						
Number (%) with any stay[a]	253 (76)	278 (71)	267 (75)	798 (74)	0.613	0.087
Mean [days (SD)]	3.3 (4.8)	3.1 (5.0)	2.9 (3.9)	3.1 (4.6)		
Median [days (IQR)][b]	2.0 (1–4)	2.0 (0–4)	2.0 (0–4)	2.0 (0–4)	0.598	0.218
Days on ICU						
Number (%) with any ICU stay[a]	9 (3)	11 (3)	5 (1)	25 (2)	0.161	0.947
Mean [days (SD)]	3.3 (4.8)	3.1 (5.0)	2.9 (3.9)	3.1 (4.6)		
Median [days (IQR)][b]	2.0 (1–4)	2.0 (0–4)	2.0 (0–4)	2.0 (0–4)	0.159	0.941
Days on HDU						
Number (%) with any HDU stay[a]	22 (7)	23 (6)	20 (6)	65 (6)	0.690	0.661
Mean [days (SD)]	3.3 (4.8)	3.1 (5.0)	2.9 (3.9)	3.1 (4.6)		
Median [days (IQR)][b]	2.0 (1–4)	2.0 (0–4)	2.0 (0–4)	2.0 (0–4)	0.715	0.630
Days on ward						
Number (%) with any ward stay[a]	247 (74)	275 (70)	258 (72)	780 (72)	0.954	0.169
Mean [days (SD)]	3.3 (4.8)	3.1 (5.0)	2.9 (3.9)	3.1 (4.6)		
Median [days (IQR)][b]	2.0 (1–4)	2.0 (0–4)	2.0 (0–4)	2.0 (0–4)	0.612	0.323

IQR, interquartile range.
a *p*-values from chi-squared test.
b *p*-values from Mann–Whitney *U*-test.

TABLE 18 Use of ventilation or respiratory support

Classification	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Total (*n* = 1084)
Required ventilation[a]	3 (1%)	6 (2%)	4 (1%)	13 (1%)
Non-invasive ventilation[a]	2 (1%)	2 (1%)	3 (1%)	7 (1%)
Emergency intubation[a]	2 (1%)	4 (1%)	1 (< 1%)	7 (1%)
Comparisons	**Odds ratio (95% CI)**			***p*-value**
Active vs. placebo	1.05 (0.31 to 3.51)			0.936
i.v. vs. nebuliser	1.70 (0.42 to 6.83)			0.458
i.v. vs. placebo	1.37 (0.38 to 4.89)			0.629
Nebuliser vs. placebo	0.81 (0.18 to 3.63)			0.780

a Values in brackets denote per cent of total.
One patient had both non-invasive intubation and emergency intubation.
Model for comparison does not include site due to sparse numbers.

Tables 19–22 show the change in heart rate, respiratory rate and blood pressure (systolic and diastolic) over the first 2 hours after initiation of treatment. These changes are also shown in *Figures 6–9*. Mean values of all four parameters fell during treatment, but there were no significant differences between the treatment groups in the magnitude of change.

TABLE 19 Heart rate (beats per minute) during and after trial treatment

Measurement	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
Pulse at baseline				
Number of observations	331	394	356	1081
Mean [beats per minute (SD)]	111.1 (19.8)	112.0 (19.1)	110.4 (18.9)	111.2 (19.2)
Median [beats per minute (IQR)]	112.0 (97–123)	112.0 (98–124)	110.5 (98–123)	112.0 (98–123)
Min., Max. (beats per minute)	52, 177	60, 168	54, 180	52, 180
Pulse at 1 hour				
Number of observations	326	387	353	1066
Mean [beats per minute (SD)]	106.8 (18.0)	106.2 (18.6)	106.5 (18.1)	106.5 (18.2)
Median [beats per minute (IQR)]	107.0 (95–119)	106.0 (94–119)	106.0 (94–119)	106.0 (94–119)
Min., max. (beats per minute)	61, 162	59, 162	52, 164	52, 164

TABLE 19 Heart rate (beats per minute) during and after trial treatment (*continued*)

Measurement	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
Change in pulse at 1 hour				
Number of observations	326	387	353	1066
Mean [beats per minute (SD)]	–4.4 (13.0)	–5.7 (12.7)	–3.9 (12.3)	–4.7 (12.7)
Median [beats per minute (IQR)]	–4.0 (–12 to 3)	–6.0 (–13 to 1)	–2.0 (–10 to 3)	–4.0 (–12 to 3)
Min., max. (beats per minute)	–50, 54	–42, 46	–45, 44	–50, 54
Pulse at 2 hours				
Number of observations	311	379	340	1030
Mean [beats per minute (SD)]	104.9 (17.3)	105.7 (18.1)	105.9 (17.5)	105.5 (17.7)
Median [beats per minute (IQR)]	104.0 (93–118)	105.0 (92–117)	105.0 (95–118)	105.0 (93–117)
Min., max. (beats per minute)	62, 166	57, 164	52, 160	52, 166
Change in pulse at 2 hours				
Number of observations	311	379	340	1030
Mean [beats per minute (SD)]	–6.3 (15.1)	–6.3 (14.7)	–4.5 (14.4)	–5.7 (14.7)
Median [beats per minute (IQR)]	–5.0 (–16 to 3)	–6.0 (–15 to 2)	–4.0 (–14 to 4)	–5.0 (–15 to 3)
Min., max. (beats per minute)	–60, 34	–50, 53	–52, 40	–60, 53

Comparisons	Mean difference [beats per minute (95% CI)]	*p*-value
Active vs. placebo	–1.8 (–3.7 to 0.1)	0.067
i.v. vs. nebuliser	–0.1 (–2.3 to 2.1)	0.940
i.v. vs. placebo	–1.8 (–4.0 to 0.3)	0.096
Nebuliser vs. placebo	–1.8 (–4.0 to 0.5)	0.130

IQR, interquartile range; max., maximum; min., minimum.

TABLE 20 Respiratory rate (breaths per minute) during and after trial treatment

Measurement	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
Respiratory rate at baseline				
Number of observations	330	392	356	1078
Mean [breaths per minute (SD)]	25.7 (7.2)	25.4 (6.4)	25.2 (6.3)	25.4 (6.6)
Median [breaths per minute (IQR)]	24.0 (20–29)	25.0 (21–28)	24.0 (20–29)	24.0 (20–28)
Min., max. (breaths per minute)	12, 58	10, 48	13, 45	10, 58
Respiratory rate at 1 hour				
Number of observations	323	383	350	1056
Mean [breaths per minute (SD)]	22.7 (6.3)	22.1 (5.9)	21.8 (5.3)	22.2 (5.8)
Median [breaths per minute (IQR)]	21.0 (19–25)	20.0 (18–24)	20.0 (18–24)	20.0 (18–24)
Min., max. (breaths per minute)	8, 50	11, 48	11, 40	8, 50
Change in respiratory rate at 1 hour				
Number of observations	323	381	350	1054
Mean [breaths per minute (SD)]	–3.1 (5.9)	–3.4 (5.6)	–3.3 (5.4)	–3.3 (5.6)
Median [breaths per minute (IQR)]	–2.0 (–6 to 0)	–3.0 (–6 to 0)	–2.0 (–6 to 0)	–2.0 (–6 to 0)
Min., max. (breaths per minute)	–24, 20	–24, 21	–20, 11	–24, 21
Respiratory rate at 2 hours				
Number of observations	307	376	336	1019
Mean [breaths per minute (SD)]	21.3 (5.7)	20.6 (5.3)	21.0 (5.4)	21.0 (5.5)
Median [breaths per minute (IQR)]	20.0 (18–24)	20.0 (18–23)	20.0 (18–24)	20.0 (18–24)
Min., max. (breaths per minute)	10, 60	11, 48	9, 48	9, 60
Change in respiratory rate at 2 hours				
Number of observations	307	374	336	1017
Mean [breaths per minute (SD)]	–4.3 (7.0)	–4.8 (5.9)	–4.2 (6.3)	–4.5 (6.4)
Median [breaths per minute (IQR)]	–4.0 (–8 to 0)	–4.0 (–8 to –1)	–4.0 (–8 to 0)	–4.0 (–8 to 0)
Min., max. (breaths per minute)	–38, 16	–30, 12	–27, 14	–38, 16
Comparisons	**Mean difference [breaths per minute (95% CI)]**			***p*-value**
Active vs. placebo	–0.5 (–1.3 to 0.4)			0.264
i.v. vs. nebuliser	–0.4 (–1.4 to 0.5)			0.396
i.v. vs. placebo	–0.7 (–1.6 to 0.3)			0.154
Nebuliser vs. placebo	–0.3 (–1.3 to 0.7)			0.594

IQR, interquartile range; max., maximum; min., minimum.

TABLE 21 Systolic blood pressure (mmHg) during and after trial treatment

Measurement	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
Systolic BP at baseline				
Number of observations	330	392	356	1078
Mean [mmHg (SD)]	132.5 (20.4)	133.1 (20.6)	130.6 (19.7)	132.1 (20.2)
Median [mmHg (IQR)]	129.5 (118–142)	130.0 (118–145)	129.0 (116–141)	130.0 (118–143)
Min., max.	84, 230	93, 216	86, 235	84, 235
Systolic BP at 1 hour				
Number of observations	323	383	351	1057
Mean [mmHg (SD)]	128.2 (19.4)	125.2 (15.8)	126.6 (17.2)	126.6 (17.4)
Median [mmHg (IQR)]	125.0 (116–140)	124.0 (115–133)	125.0 (114–137)	124.0 (115–137)
Min., max. (mmHg)	80, 215	79, 186	85, 203	79, 215
Change in systolic BP at 1 hour				
Number of observations	322	381	351	1054
Mean [mmHg (SD)]	–4.5 (17.8)	–7.8 (19.4)	–4.2 (18.1)	–5.6 (18.6)
Median [mmHg (IQR)]	–4.5 (–14 to 5)	–6.0 (–17 to 4)	–3.0 (–14 to 6)	–4.0 (–15 to 5)
Min., max. (mmHg)	–65, 74	–82, 92	–71, 48	–82, 92
Systolic BP at 2 hours				
Number of observations	309	373	338	1020
Mean [mmHg (SD)]	127.0 (19.3)	125.5 (16.5)	124.9 (18.5)	125.7 (18.1)
Median [mmHg (IQR)]	124.0 (114–137)	124.0 (114–134)	122.0 (112–134)	123.0 (114–135)
Min., max. (mmHg)	85, 194	88, 187	76, 212	76, 212
Change in systolic BP at 2 hours				
Number of observations	309	371	338	1018
Mean [mmHg (SD)]	–5.6 (19.9)	–7.7 (18.2)	–6.1 (19.5)	–6.5 (19.2)
Median [mmHg (IQR)]	–5.0 (–17 to 6)	–7.0 (–16 to 4)	–5.0 (–17 to 6)	–5.5 (–17 to 5)
Min., max. (mmHg)	–82, 51	–82, 60	–78, 47	–82, 60
Comparisons	**Mean difference [mmHg (95% CI)]**			***p*-value**
Active vs. placebo	–0.6 (–3.1 to 2.0)			0.664
i.v. vs. nebuliser	–1.8 (–4.7 to 1.1)			0.214
i.v. vs. placebo	–1.5 (–4.3 to 1.4)			0.308
Nebuliser vs. placebo	0.4 (–2.6 to 3.3)			0.810

BP, blood pressure; IQR, interquartile range; max., maximum; min., minimum.

TABLE 22 Diastolic blood pressure (mmHg) during and after trial treatment

Measurement	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
Diastolic BP at baseline				
Number of observations	330	391	356	1077
Mean [mmHg (SD)]	76.3 (15.5)	75.7 (14.8)	75.0 (15.1)	75.6 (15.1)
Median [mmHg (IQR)]	75.0 (66–86)	74.0 (66–85)	74.0 (65–84)	74.0 (65–85)
Min., max. (mmHg)	30, 151	38, 135	33, 145	30, 151
Diastolic BP at 1 hour				
Number of observations	323	383	351	1057
Mean [mmHg (SD)]	73.2 (14.4)	69.3 (11.5)	70.8 (13.5)	71.0 (13.2)
Median [mmHg (IQR)]	73.0 (64–81)	69.0 (61–77)	70.0 (62–79)	71.0 (62–78)
Min., max. (mmHg)	36, 135	30, 115	32, 133	30, 135
Change in diastolic BP at 1 hour				
Number of observations	322	380	351	1053
Mean [mmHg (SD)]	–3.4 (14.1)	–6.3 (13.8)	–4.2 (13.6)	–4.7 (13.9)
Median [mmHg (IQR)]	–2.0 (–11 to 5)	–5.0 (–13 to 2)	–4.0 (–12 to 3)	–4.0 (–12 to 3)
Min., max. (mmHg)	–65, 49	–67, 41	–72, 69	–72, 69
Diastolic BP at 2 hours				
Number of observations	309	372	337	1018
Mean [mmHg (SD)]	70.6 (13.9)	68.3 (12.3)	69.7 (14.3)	69.4 (13.5)
Median [mmHg (IQR)]	69.0 (62–80)	68.0 (61–76)	69.0 (61–78)	69.0 (61–78)
Min., max. (mmHg)	35, 117	32, 113	37, 148	32, 148
Change in diastolic BP at 2 hours				
Number of observations	309	369	337	1015
Mean [mmHg (SD)]	–5.8 (14.4)	–7.5 (14.9)	–5.4 (14.6)	–6.3 (14.7)
Median [mmHg (IQR)]	–5.0 (–15 to 4)	–7.0 (–16 to 2)	–5.0 (–14 to 4)	–6.0 (–15 to 3)
Min., max. (mmHg)	–53, 31	–81, 40	–72, 35	–81, 40
Comparisons	**Mean difference [mmHg (95% CI)]**			***p*-value**
Active vs. placebo	–1.1 (–3.0 to 0.8)			0.248
i.v. vs. nebuliser	–1.6 (–3.8 to 0.6)			0.151
i.v. vs. placebo	–1.9 (–4.1 to 0.2)			0.080
Nebuliser vs. placebo	–0.3 (–2.6 to 1.9)			0.782

BP, blood pressure; IQR, interquartile range; max., maximum; min., minimum.

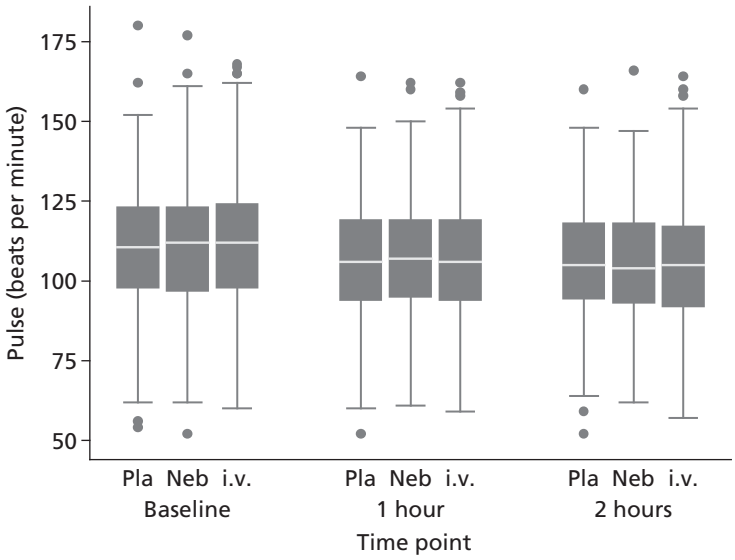

FIGURE 6 Heart rate (beats per minute) during and after trial treatment. Neb, nebuliser; Pla, placebo.

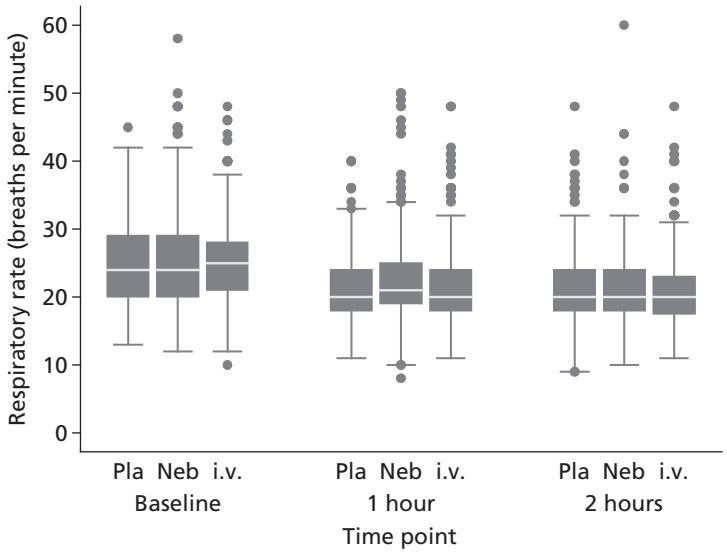

FIGURE 7 Respiratory rate (breaths per minute) during and after trial treatment. Neb, nebuliser; Pla, placebo.

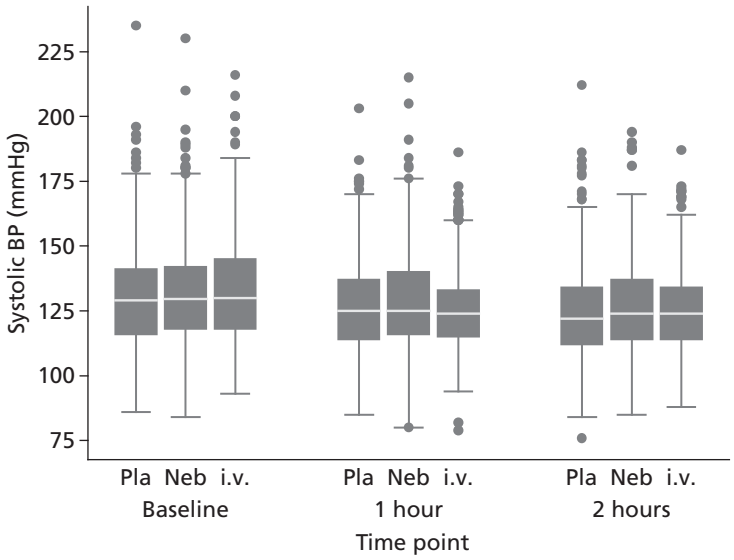

FIGURE 8 Systolic blood pressure (mmHg) during and after trial treatment. Neb, nebuliser; Pla, placebo.

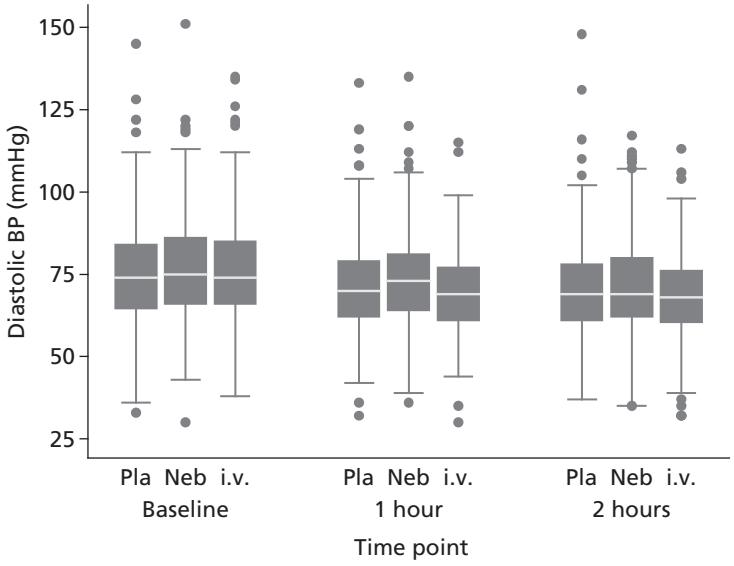

FIGURE 9 Diastolic blood pressure (mmHg) during and after trial treatment. Neb, nebuliser; Pla, placebo.

Table 23 shows the change in peripheral oxygen saturation over the first 2 hours after initiation of treatment. Three-quarters of the cohort were receiving supplemental oxygen at baseline. The proportion of participants receiving supplemental oxygen increased at 1 hour and then decreased at 2 hours. This means that the analysis of peripheral oxygen saturation, shown separately for those receiving and not receiving supplemental oxygen, includes different patients at different times. Unsurprisingly, there is little change in the peripheral oxygen saturation over time and little difference between groups, since administration of oxygen is likely to be titrated in response to demand and/or peripheral oxygen saturation. Patients receiving supplemental oxygen had a mean peripheral oxygen saturation of around 98%, whereas those patients not receiving supplemental oxygen had a peripheral oxygen saturation of 96–97%.

If the trial treatment had influenced oxygenation then this might have been apparent in terms of reduced requirement for inspired oxygen. *Table 24* and *Figure 10* show the change in inspired oxygen flow rate over the first 2 hours after initiation of treatment. Patients not receiving oxygen were analysed as having a flow rate of 0 l/minute. Patients allocated to i.v. magnesium sulphate had a slightly lower oxygen flow rate at 2 hours than patients allocated to nebulised magnesium sulphate, but there were no significant differences between either treatment arm and placebo.

TABLE 23 Peripheral oxygen saturation during and after trial treatment

Measurement	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
Mode of delivery at baseline[a]				
On oxygen	256 (77%)	294 (75%)	259 (72%)	809 (75%)
On air	75 (23%)	99 (25%)	95 (27%)	269 (25%)
Not recorded	1 (< 1%)	1 (< 1%)	4 (1%)	6 (1%)
Mode of delivery at 1 hour[a]				
On oxygen	285 (86%)	338 (86%)	299 (84%)	922 (85%)
On air	39 (12%)	45 (11%)	51 (14%)	135 (12%)
Not recorded	8 (2%)	11 (3%)	8 (2%)	27 (2%)
Mode of delivery at 2 hours[a]				
On oxygen	213 (64%)	224 (57%)	199 (56%)	636 (59%)
On air	99 (30%)	154 (39%)	138 (39%)	391 (36%)
Not recorded	20 (6%)	16 (4%)	21 (6%)	57 (5%)
Patients on oxygen				
Oxygen saturation at baseline (%)				
Number of observations	256	294	259	809
Mean [% (SD)]	97.8 (2.1)	97.9 (2.3)	98.0 (2.2)	97.9 (2.2)
Median [% (IQR)]	98.0 (97–100)	98.5 (97–100)	99.0 (97–100)	98.0 (97–100)
Min., max. (%)	91, 100	88, 100	90, 100	88, 100
Oxygen saturation at 1 hour (%)				
Number of observations	285	338	299	922
Mean [% (SD)]	98.2 (1.9)	98.3 (1.9)	98.3 (1.9)	98.2 (1.9)
Median [% (IQR)]	99.0 (97–100)	99.0 (97–100)	99.0 (97–100)	99.0 (97–100)
Min., max. (%)	91, 100	89, 100	90, 100	89, 100
Change in oxygen saturation at 1 hour (%)				
Number of observations	235	266	234	735
Mean [% (SD)]	0.3 (2.0)	0.3 (2.0)	0.3 (1.9)	0.3 (2.0)
Median [% (IQR)]	0.0 (–1 to 1)	0.0 (–1 to 1)	0.0 (–1 to 1)	0.0 (–1 to 1)
Min., max. (%)	–5, 6	–5, 9	–5, 7	–5, 9
Oxygen saturation at 2 hours (%)				
Number of observations	213	224	199	636
Mean [% (SD)]	97.7 (2.3)	97.7 (2.1)	97.8 (2.2)	97.7 (2.2)
Median [% (IQR)]	98.0 (96–100)	98.0 (97–99)	98.0 (96–100)	98.0 (96–100)
Min., max. (%)	90, 100	90, 100	90, 100	90, 100

continued

TABLE 23 Peripheral oxygen saturation during and after trial treatment (*continued*)

Measurement	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
Change in oxygen saturation at 2 hours (%)				
Number of observations	176	181	164	521
Mean [% (SD)]	–0.0 (2.3)	–0.1 (2.3)	–0.2 (2.1)	–0.1 (2.2)
Median [% (IQR)]	0.0 (–1 to 1)	0.0 (–1 to 1)	0.0 (–1 to 1)	0.0 (–1 to 1)
Min., max. (%)	–6, 6	–8, 7	–7, 7	–8, 7
Patients on air				
Oxygen saturation at baseline (%)				
Number of observations	75	99	95	269
Mean [% (SD)]	96.3 (2.6)	95.9 (2.5)	95.9 (2.6)	96.0 (2.6)
Median [% (IQR)]	96.0 (95–98)	96.0 (94–98)	96.0 (94–98)	96.0 (94–98)
Min., max. (%)	88, 100	87, 100	85, 100	85, 100
Oxygen saturation at 1 hour (%)				
Number of observations	39	45	51	135
Mean [% (SD)]	96.6 (2.6)	96.6 (2.9)	97.1 (2.4)	96.8 (2.7)
Median [% (IQR)]	98.0 (95–98)	97.0 (95–99)	98.0 (95–99)	98.0 (95–99)
Min., max. (%)	92, 100	88, 100	92, 100	88, 100
Change in oxygen saturation at 1 hour (%)				
Number of observations	24	25	30	79
Mean [% (SD)]	0.0 (2.0)	1.0 (2.1)	1.5 (2.6)	0.9 (2.3)
Median [% (IQR)]	0.0 (–2 to 2)	1.0 (0 to 3)	1.0 (–1 to 4)	1.0 (–1 to 3)
Min., max. (%)	–6, 3	–4, 4	–2, 7	–6, 7
Oxygen saturation at 2 hours (%)				
Number of observations	99	154	138	391
Mean [% (SD)]	96.4 (2.6)	96.3 (2.7)	96.4 (2.4)	96.4 (2.6)
Median [% (IQR)]	96.0 (95–99)	97.0 (95–98)	96.0 (95–98)	96.0 (95–98)
Min., max. (%)	87, 100	86, 100	85, 100	85, 100
Change in oxygen saturation at 2 hours (%)				
Number of observations	34	52	56	142
Mean [% (SD)]	–0.0 (2.6)	–0.1 (2.4)	0.5 (2.6)	0.2 (2.5)
Median [% (IQR)]	0.0 (–1 to 1)	0.0 (–1 to 1)	0.0 (–1 to 2)	0.0 (–1 to 1)
Min., max. (%)	–7, 6	–9, 4	–4, 10	–9, 10

IQR, interquartile range; max., maximum; min., minimum.
a Values in brackets denote per cent of total.

TABLE 24 Inspired oxygen flow rate (l/minute) during and after trial treatment

Measurement	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
Oxygen flow at baseline				
Number of observations	324	387	344	1055
Mean [l/minute (SD)]	5.1 (3.5)	5.3 (4.0)	4.8 (3.6)	5.1 (3.7)
Median [l/minute (IQR)]	6.0 (2–6)	6.0 (0–6)	6.0 (0–6)	6.0 (0–6)
Min., max. (l/minute)	0, 15	0, 15	0, 15	0, 15
Oxygen flow at 1 hour				
Number of observations	315	377	339	1031
Mean [l/minute (SD)]	5.6 (2.6)	5.6 (2.6)	5.3 (2.7)	5.5 (2.6)
Median [l/minute (IQR)]	6.0 (5–6)	6.0 (6–6)	6.0 (5–6)	6.0 (5–6)
Min., max. (l/minute)	0, 15	0, 15	0, 15	0, 15
Change in oxygen flow at 1 hour				
Number of observations	312	372	331	1015
Mean [l/minute (SD)]	0.5 (3.4)	0.4 (3.9)	0.5 (3.7)	0.5 (3.7)
Median [l/minute (IQR)]	0.0 (0–1)	0.0 (0–2)	0.0 (0–2)	0.0 (0–2)
Min., max. (l/minute)	–10, 10	–11, 10	–15, 10	–15, 10
Oxygen flow at 2 hours (l/minute)				
Number of observations	301	364	326	991
Mean [l/minute (SD)]	4.4 (3.7)	3.6 (3.5)	3.6 (3.5)	3.8 (3.5)
Median [l/minute (IQR)]	6.0 (0–6)	5.0 (0–6)	5.0 (0–6)	5.0 (0–6)
Min., max. (l/minute)	0, 15	0, 15	0, 15	0, 15
Change in oxygen flow at 2 hours (l/minute)				
Number of observations	299	361	320	980
Mean [l/minute (SD)]	–0.7 (4.3)	–1.6 (4.8)	–1.3 (4.2)	–1.2 (4.5)
Median [l/minute (IQR)]	0.0 (–4 to 0)	0.0 (–6 to 0)	0.0 (–5 to 0)	0.0 (–5 to 0)
Min., max. (l/minute)	–15, 10	–15, 10	–15, 10	–15, 10
Comparisons	**Mean difference [l/minute (95% CI)]**			***p*-value**
Active vs. placebo	0.0 (–0.6 to 0.6)			0.942
i.v. vs. nebuliser	–0.9 (–1.6 to –0.2)			0.008
i.v. vs. placebo	–0.4 (–1.1 to 0.2)			0.196
Nebuliser vs. placebo	0.5 (–0.2 to 1.2)			0.173

IQR, interquartile range; max., maximum; min., minimum.

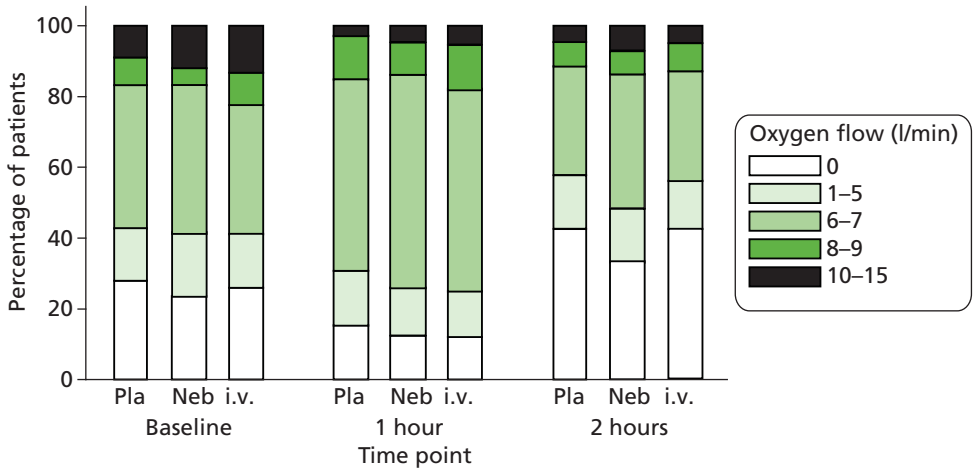

FIGURE 10 Oxygen flow rate (l/minute) during and after trial treatment. Neb, nebuliser; Pla, placebo.

Table 25 and *Figure 11* show the change in PEFR over the first 2 hours after initiation of treatment, and *Table 26* and *Figure 12* show these data as percentage of predicted PEFR. Mean PEFR and percentage predicted PEFR improved markedly in all three treatment groups over the 2 hours. The IQR for percentage predicted PEFR at 2 hours indicates that after treatment only around one-quarter of the cohort were recording a PEFR < 50% of predicted. Comparison of the three groups shows no evidence of any effect from i.v. or nebulised magnesium sulphate on PEFR.

Adverse events and side effects

Table 27 shows the adverse events recorded up to 30 days and *Table 28* shows those adverse events which were classified as being SAEs. There were very few adverse events in the prespecified categories: seven patients required intubation, seven patients required non-invasive ventilation, two patients suffered an arrhythmia, one patient suffered a cardiac arrest and two patients died. However, the definition of an adverse event used in the trial included any subsequent hospitalisation. A substantial number of patients were therefore recorded as having an adverse event by virtue of subsequent admission to hospital, either due to worsening of their asthma or other unrelated problems.

TABLE 25 Peak expiratory flow rate (l/minute) during and after trial treatment

Measurement	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
PEFR at baseline				
Number of observations	312	379	336	1027
Mean [l/minute (SD)]	209.1 (92.3)	226.8 (92.3)	214.5 (84.0)	217.4 (89.9)
Median [l/minute (IQR)]	200.0 (150–250)	210.0 (150–270)	200.0 (150–255)	200.0 (150–260)
Min., max. (l/minute)	50, 620	50, 530	50, 520	50, 620
PEFR at 1 hour				
Number of observations	293	358	324	975
Mean [l/minute (SD)]	255.2 (109.8)	275.6 (104.9)	259.0 (100.2)	263.9 (105.2)
Median [l/minute (IQR)]	240.0 (170–330)	260.0 (190–350)	250.0 (180–330)	250.0 (180–340)
Min., max. (l/minute)	50, 590	50, 650	60, 700	50, 700
Change in PEFR at 1 hour				
Number of observations	284	351	312	947
Mean [l/minute (SD)]	43.3 (63.9)	48.2 (66.0)	45.3 (65.1)	45.8 (65.0)
Median [l/minute (IQR)]	30.0 (0–70)	30.0 (0–90)	30.0 (3–70)	30.0 (0–70)
Min., max. (l/minute)	–110, 330	–100, 350	–60, 580	–110, 580
PEFR at 2 hours				
Number of observations	281	348	310	939
Mean [l/minute (SD)]	270.4 (117.4)	288.1 (111.2)	278.9 (105.5)	279.8 (111.4)
Median [l/minute (IQR)]	250.0 (190–350)	280.0 (200–355)	270.0 (200–350)	270.0 (200–350)
Min., max. (l/minute)	50, 800	50, 650	50, 600	50, 800
Change in PEFR at 2 hours				
Number of observations	272	339	298	909
Mean [l/minute (SD)]	58.3 (77.3)	61.0 (73.6)	62.5 (69.4)	60.7 (73.3)
Median [l/minute (IQR)]	40.0 (5–95)	40.0 (10–90)	50.0 (20–100)	40.0 (10–100)
Min., max. (l/minute)	–89, 500	−140, 410	−80, 390	–140, 500
Comparisons	**Mean difference [l/minute (95% CI)]**			***p*-value**
Active vs. placebo	–2.5 (–12.5 to 7.5)			0.625
i.v. vs. nebuliser	0.3 (–11.2 to 11.7)			0.964
i.v. vs. placebo	–2.4 (–13.6 to 8.8)			0.680
Nebuliser vs. placebo	–2.6 (–14.5 to 9.2)			0.664

IQR, interquartile range; max., maximum; min., minimum.

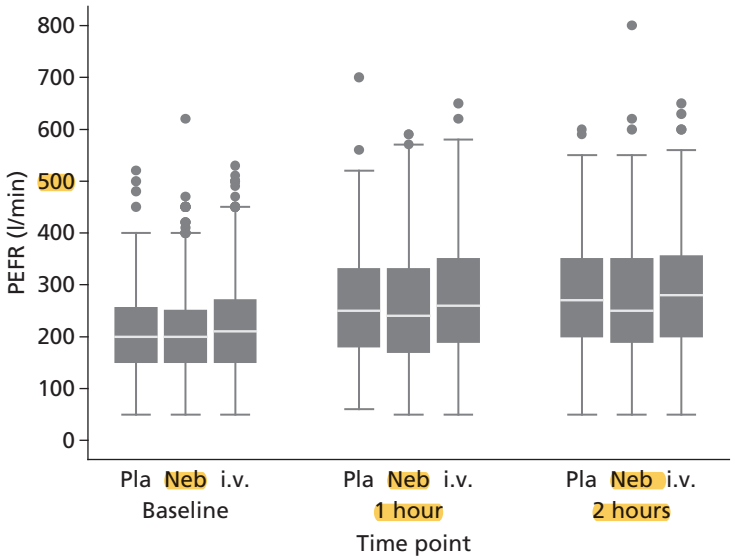

FIGURE 11 Peak expiratory flow rate (l/minute) during and after trial treatment. Neb, nebuliser; Pla, placebo.

TABLE 26 Peak expiratory flow rate (% of predicted) during and after trial treatment

Measurement	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
% PEFR at baseline				
Number of observations	308	375	327	1010
Mean [% of predicted (SD)]	50.0 (19.6)	54.3 (20.2)	50.5 (19.1)	51.7 (19.7)
Median [% of predicted (IQR)]	47.5 (35–61)	50.0 (40–67)	48.0 (37–63)	50.0 (38–63)
Min., max. (% of predicted)	11, 116	12, 160	9, 112	9, 160
% PEFR at 1 hour				
Number of observations	290	356	315	961
Mean [% of predicted (SD)]	60.3 (22.8)	65.5 (22.7)	60.1 (20.9)	62.1 (22.3)
Median [% of predicted (IQR)]	57.1 (43–77)	63.0 (50–80)	60.0 (44–73)	60.0 (45–78)
Min., max. (% of predicted)	17, 125	13, 140	13, 125	13, 140
% change in PEFR at 1 hour				
Number of observations	282	349	304	935
Mean [% of predicted (SD)]	9.9 (15.0)	11.4 (15.7)	10.2 (14.7)	10.6 (15.2)
Median [% of predicted (IQR)]	7.0 (0–17)	6.8 (0–20)	7.5 (0–16)	7.0 (0–17)
Min., max. (% of predicted)	–40, 63	–24, 75	–27, 97	–40, 97

TABLE 26 Peak expiratory flow rate (% of predicted) during and after trial treatment (*continued*)

Measurement	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
% PEFR at 2 hours				
Number of observations	278	346	301	925
Mean [% of predicted (SD)]	63.1 (24.0)	68.6 (23.3)	65.0 (22.7)	65.8 (23.5)
Median [% of predicted (IQR)]	60.0 (46–78)	68.3 (52–86)	64.9 (47–80)	64.0 (49–81)
Min., max. (% of predicted)	16, 160	13, 144	10, 164	10, 164
% change in PEFR at 2 hours				
Number of observations	270	337	291	898
Mean [% of predicted (SD)]	13.4 (18.0)	14.4 (17.4)	14.4 (16.3)	14.1 (17.2)
Median [% of predicted (IQR)]	9.8 (1–22)	10.9 (3–23)	10.9 (4–22)	10.4 (3–22)
Min., max. (% of predicted)	–36, 100	–30, 83	–18, 103	–36, 103
Comparisons	**Mean difference [% of predicted (95% CI)]**			***p*-value**
Active vs. placebo	–0.5 (–2.9 to 1.9)			0.676
i.v. vs. nebuliser	0.3 (–2.4 to 3.0)			0.841
i.v. vs. placebo	–0.4 (–3.0 to 2.3)			0.786
Nebuliser vs. placebo	–0.6 (–3.4 to 2.1)			0.652

IQR, interquartile range; max., maximum; min., minimum.

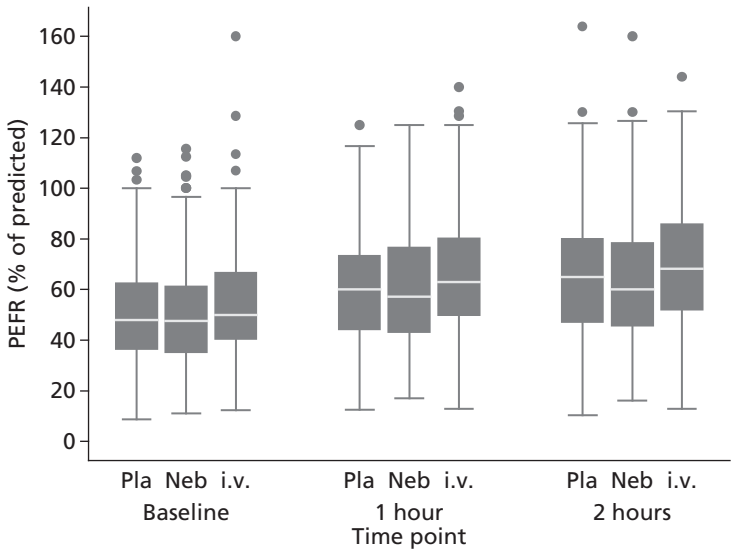

FIGURE 12 Peak expiratory flow rate (% of predicted) during and after trial treatment. Neb, nebuliser; Pla, placebo.

TABLE 27 Adverse events up to 30 days

Adverse event	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 395)	Placebo (*n* = 358)	Overall (*n* = 1085)
Any adverse event	41 (12.3%)	53 (13.4%)	36 (10.1%)	130 (12.0%)
Arrhythmia	0	1 (0.3%)	1 (0.3%)	2 (0.2%)
Cardiac arrest	0	1 (0.3%)	0	1 (0.1%)
Death	1 (0.3%)	1 (0.3%)	0	2 (0.2%)
Intubation	2 (0.6%)	4 (1.0%)	1 (0.3%)	7 (0.6%)
Non-invasive ventilation	2 (0.6%)	2 (0.5%)	3 (0.8%)	7 (0.6%)
Other asthma related	26 (7.8%)	25 (6.3%)	22 (6.1%)	73 (6.7%)
Other non-asthma related	14 (4.2%)	20 (5.1%)	12 (3.4%)	46 (4.2%)

Numbers refer to patients experiencing an event of each type.
Values in brackets denote per cent of total.
Total number of events will not equal the sum of events per individual if a patient experiences multiple events.

TABLE 28 Serious adverse events up to 30 days

Adverse event	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 395)	Placebo (*n* = 358)	Overall (*n* = 1085)
Any serious adverse event	35 (10.5%)	45 (11.4%)	28 (7.8%)	108 (10.0%)
Arrhythmia	0	1 (0.3%)	0	1 (0.1%)
Cardiac arrest	0	1 (0.3%)	0	1 (0.1%)
Death	1 (0.3%)	1 (0.3%)	0	2 (0.2%)
Intubation	2 (0.6%)	4 (1.0%)	1 (0.3%)	7 (0.6%)
Non-invasive ventilation	0	1 (0.3%)	3 (0.8%)	4 (0.4%)
Other asthma related	24 (7.2%)	23 (5.8%)	21 (5.9%)	68 (6.3%)
Other non-asthma related	8 (2.4%)	14 (3.6%)	5 (1.4%)	27 (2.5%)

Numbers refer to patients experiencing an event of each type.
Values in brackets denote per cent of total.
Total number of events will not equal the sum of events per individual if a patient experiences multiple events.

Table 29 shows the potential side effects recorded during or after trial treatment. The rate of side effects that have previously been reported in association with administration of magnesium sulphate (flushing, hypotension, nausea and vomiting) were generally low and were only slightly higher in the active treatment arms than the placebo arm. Overall, side effects were a little more common in the active treatment arms than the placebo arm [15.6% vs. 10.1%, odds ratio (OR) 1.68 (95% CI 1.11 to 2.52; $p = 0.014$)].

Thirty-day outcomes

Overall, 504 (47%) of the 30-day outcome questionnaires were returned. *Table 30* shows the 30-day questionnaire response rate by age group and sex. Females were more likely to respond than males and the percentage response increased with participant age.

Figure 13 shows the overall distribution of EQ-5D scores and *Table 31* shows patient-reported health utility, at baseline and 30 days, measured on the EQ-5D survey. The placebo group had a slightly higher

TABLE 29 Side effects recorded during or after trial treatment

Side effect	Nebulised magnesium sulphate ($n = 332$)	Intravenous magnesium sulphate ($n = 394$)	Placebo ($n = 358$)	Overall ($n = 1085$)
Any side effect[a]	52 (15.7%)	61 (15.5%)	36 (10.1%)	149 (13.7%)
Flushing[a]	3 (0.9%)	7 (1.8%)	2 (0.6%)	12 (1.1%)
Hypotension[a]	31 (9.3%)	31 (7.8%)	22 (6.1%)	84 (7.7%)
Nausea[a]	5 (1.5%)	14 (3.5%)	7 (2.0%)	26 (2.4%)
Vomiting[a]	6 (1.8%)	6 (1.5%)	3 (0.8%)	15 (1.4%)
Other[a]	12 (3.6%)	15 (3.8%)	5 (1.4%)	32 (2.9%)
Comparisons[b]	**Odds ratio (95% CI)**			***p*-value**
Active vs. placebo	1.68 (1.11 to 2.52)			0.014
i.v. vs. nebuliser	1.00 (0.66 to 1.52)			0.988
i.v. vs. placebo	1.68 (1.07 to 2.63)			0.025
Nebuliser vs. placebo	1.67 (1.05 to 2.66)			0.031

a Value in brackets denotes per cent of total.
b Comparison is any side effect (yes/no).
Numbers refer to patients experiencing a side effect of each type.
The total number of events will not equal the sum of side effects per individual if a patient experiences multiple side effects.

TABLE 30 Response rate according to sex and age group

	n (%) response	
Age group (years)	Males	Females
< 25	22 (28)	87 (43)
25–34	23 (30)	91 (47)
35–44	25 (35)	79 (49)
45–54	35 (59)	73 (55)
55–64	11 (55)	34 (62)
65–74	6 (55)	12 (86)
≥ 75	3 (60)	3 (60)

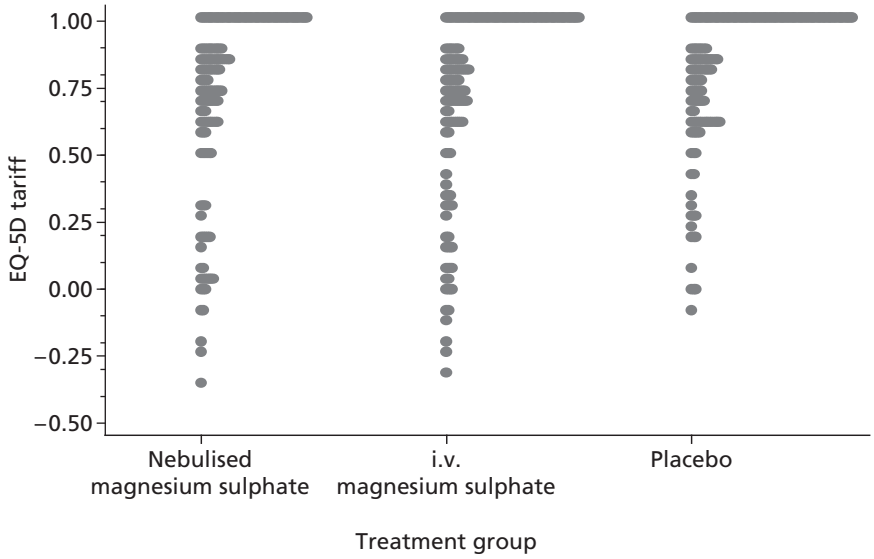

FIGURE 13 Distribution of EQ-5D scores. EQ-5D values at 30 days.

TABLE 31 Patient-reported health utility (EQ-5D)

Measurement	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
Baseline				
Number (%) of responses	282 (84.9)	341 (86.5)	309 (86.3)	932 (86.0)
Mean (SD)	0.734 (0.327)	0.726 (0.354)	0.746 (0.323)	0.735 (0.336)
Median (IQR)	0.814 (0.69–1.00)	0.814 (0.69–1.00)	0.883 (0.69–1.00)	0.848 (0.64–1.00)
Min., max.	–0.35, 1.00	–0.59, 1.00	–0.35, 1.00	–0.59, 1.00
One month				
Number (%) of responses	160 (48.2)	169 (42.9)	173 (48.3)	502 (46.3)
Mean (SD)	0.721 (0.326)	0.731 (0.329)	0.810 (0.250)	0.755 (0.305)
Median (IQR)	0.814 (0.62–1.00)	0.814 (0.62–1.00)	0.883 (0.69–1.00)	0.848 (0.64–1.00)
Min., max.	–0.35, 1.00	–0.32, 1.00	–0.08, 1.00	–0.35, 1.00
Change in EQ-5D score at 1 month				
Number (%) of responses	140 (42.2)	146 (37.1)	151 (42.2)	437 (40.3)
Mean (SD)	0.037 (0.377)	0.035 (0.357)	0.041 (0.341)	0.038 (0.358)
Median (IQR)	0.00 (–0.10 to 0.20)	0.00 (–0.15 to 0.19)	0.00 (–0.12 to 0.15)	0.00 (–0.11 to 0.19)
Min., max.	–1.07, 1.09	–1.02, 1.48	–1.02, 1.32	–1.07, 1.48
Comparisons	**Difference (95% CI)**			***p*-value**
Active vs. placebo	–0.01 (–0.08 to 0.06)			0.842
i.v. vs. nebuliser	–0.00 (–0.09 to 0.08)			0.961
i.v. vs. placebo	–0.01 (–0.09 to 0.07)			0.884
Nebuliser vs. placebo	–0.01 (–0.09 to 0.08)			0.844
Comparison of baseline scores (responders vs. non-responders)				
Difference	–0.10	–0.05	0.03	–0.04
(95% CI)	–0.17 to –0.02	–0.13 to 0.02	–0.04 to 0.10	–0.08 to 0.01
p-value	0.014	0.179	0.456	0.085

IQR, interquartile range; max., maximum; min., minimum.

baseline mean score than the nebulised group, which was in turn higher than the i.v. group. There were only small changes in EQ-5D score from baseline to 30 days and no significant differences between the groups. Health utility data for the normal UK population were used to calculate a regional age- and sex-adjusted expected normal value for each patient.[68] The results are shown in *Figure 14*. At 30 days, the responders had a significantly lower EQ-5D than age- or sex-matched UK norms (mean loss = –0.14, 95% CI –0.17 to –0.11; $p < 0.001$).

The 30-day questionnaire also asked patients to describe which NHS resources they had used in the 30 days following randomisation and these are described in *Table 32*. No obvious differences were noted between the groups, but most patients (74%) had at least one GP contact and reattendances at hospital were common, either as an outpatient (36%) or as an admission (29%).

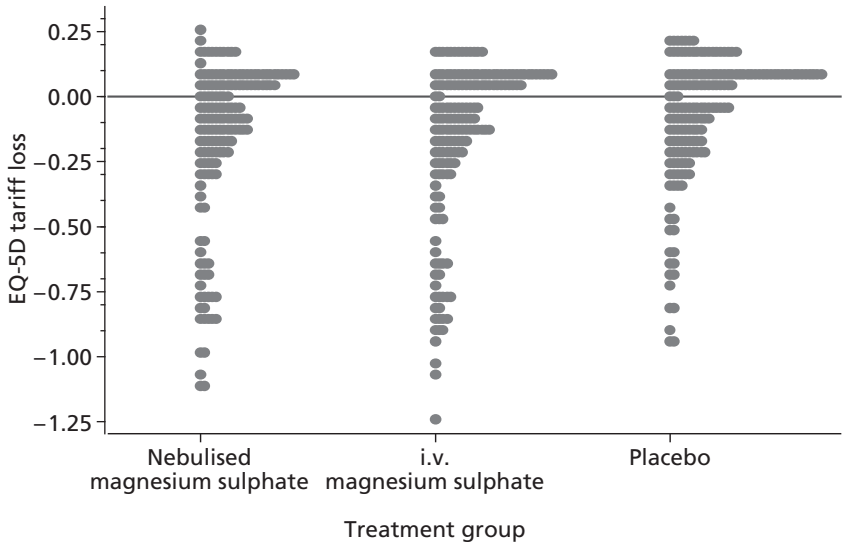

FIGURE 14 EQ-5D score loss at 30 days compared with age- or sex-matched UK norms.

TABLE 32 Use of health and social services over the following month

Health or social service	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Total (*n* = 1084)
Number (%) of responders	138 (42%)	151 (38%)	144 (40%)	433 (40%)
Use of telephone health advice				
None	97 (70%)	103 (68%)	107 (74%)	307 (71%)
1	19 (14%)	22 (15%)	17 (12%)	58 (13%)
2	6 (4%)	8 (5%)	11 (8%)	25 (6%)
3 or more	16 (12%)	18 (12%)	9 (6%)	43 (10%)
Use of GP surgery consultations				
None	39 (28%)	43 (28%)	39 (27%)	121 (28%)
1	37 (27%)	33 (22%)	31 (22%)	101 (23%)
2	24 (17%)	28 (19%)	35 (24%)	87 (20%)
3	16 (12%)	17 (11%)	18 (13%)	51 (12%)
4 or more	22 (16%)	30 (20%)	21 (15%)	73 (17%)
GP home visits				
None	131 (95%)	141 (93%)	140 (97%)	412 (95%)
1 or more	7 (5%)	10 (7%)	4 (3%)	21 (5%)
Nurse home visits				
None	131 (95%)	145 (96%)	141 (98%)	417 (96%)
1 or more	7 (5%)	6 (4%)	3 (2%)	16 (4%)
Social worker visits				
None	130 (94%)	145 (96%)	143 (99%)	418 (97%)
1 or more	8 (6%)	6 (4%)	1 (1%)	15 (3%)
Outpatient attendances				
None	83 (60%)	90 (60%)	103 (72%)	276 (64%)
1	35 (25%)	38 (25%)	28 (19%)	101 (23%)
2	14 (10%)	15 (10%)	6 (4%)	35 (8%)
3 or more	6 (4%)	8 (5%)	7 (5%)	21 (5%)
Inpatient nights				
None	89 (64%)	106 (70%)	113 (78%)	308 (71%)
1	8 (6%)	5 (3%)	3 (2%)	16 (4%)
2	8 (6%)	5 (3%)	5 (3%)	18 (4%)
3 or more	33 (24%)	35 (23%)	23 (16%)	91 (21%)
Any self-reported medication use				
Yes	131 (96%)	144 (97%)	138 (97%)	413 (96%)

Table 33 describes the time taken off work in the month following randomisation. Despite the groups being well matched in respect to age and sex, both at baseline and among responders, the placebo group contained a lower percentage of patients not in paid employment (31%) than the active groups (i.v. 43%; nebulised 45%). Restricting the analysis just to those in paid employment, 47% of responders in the placebo group took time off, compared with 55% in the i.v. magnesium sulphate group and 62% in the nebulised magnesium sulphate group, although this comparison was not statistically significant (comparison of active vs. placebo: $\chi^2 = 3.1$, $p = 0.08$). Likewise, the number of days taken off was not significantly different between groups (Mann–Whitney *U*-test, $p = 0.21$). Among patients who had taken time off work, typically this entailed more than 1 week (median 9 days).

Table 34 shows the results of the 11 questions in the satisfaction with care questionnaire. In general, satisfaction with care was high across all three treatment groups and across most dimensions of care, with over 70% rating care as very good or excellent on 8 of the 11 dimensions. The dimensions of care relating to personal interest in the patient and their medical problems, the amount of time given by hospital staff and especially advice given about ways to avoid illness and stay healthy were generally rated lower. There were no significant differences in any of the primary contrasts between the treatment groups.

Table 35 shows the results of questions asking the participants to guess whether they received active treatment or placebo. Most patients in the active treatment arms (61% of patients in the nebulised group and 60% of patients in the i.v. group) believed they had received active treatment, compared with 45% of patients in the placebo group. When asked how they thought they had received magnesium sulphate, 39% of patients in the nebuliser group and 26% of patients in the i.v. group correctly identified the route of administration. These findings suggest that participants had some ability to correctly identify whether or not they had received active treatment, but their guessing was only moderately better than that expected due to chance.

TABLE 33 Time taken off work over the following month

Classification	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Total (*n* = 1084)
Number (%) of responders	138 (42%)	151 (38%)	144 (40%)	433 (40%)
Any time taken off work				
Yes	47 (34%)	45 (31%)	46 (32%)	138 (33%)
No	29 (21%)	37 (26%)	52 (37%)	118 (28%)
Not in paid employment	61 (45%)	63 (43%)	44 (31%)	168 (40%)
Number of days if yes:				
≤ 1 day	3 (8%)	0	4 (9%)	7 (6%)
2–3 days	4 (10%)	9 (22%)	7 (15%)	20 (16%)
4–5 days	3 (8%)	5 (12%)	7 (15%)	15 (12%)
6–10 days	6 (15%)	5 (12%)	9 (20%)	20 (16%)
11–15 days	11 (28%)	6 (15%)	6 (13%)	23 (18%)
≥ 16 days	12 (31%)	16 (39%)	13 (28%)	41 (33%)

TABLE 34 Patient satisfaction with care

Classification	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
Number (%) of questionnaires returned	138 (42%)	151 (38%)	145 (41%)	434 (40%)
The urgency with which you were assessed				
Poor	1 (1%)	4 (3%)	1 (1%)	6 (1%)
Fair	8 (6%)	5 (3%)	10 (7%)	23 (5%)
Good	22 (16%)	19 (13%)	25 (17%)	66 (15%)
Very good	42 (30%)	52 (34%)	42 (29%)	136 (31%)
Excellent	65 (47%)	71 (47%)	67 (46%)	203 (47%)
Comparisons				p-*value*
Active vs. placebo				0.592
i.v. vs. nebuliser				0.781
The thoroughness of your assessment				
Poor	1 (1%)	1 (1%)	0	2 (< 1%)
Fair	4 (3%)	7 (5%)	9 (6%)	20 (5%)
Good	24 (17%)	20 (13%)	25 (17%)	69 (16%)
Very good	52 (38%)	51 (34%)	51 (35%)	154 (36%)
Excellent	57 (41%)	71 (47%)	60 (41%)	188 (43%)
Comparisons				p-*value*
Active vs. placebo				0.400
i.v. vs. nebuliser				0.368
Explanations given to you about medical procedures and tests				
Poor	2 (1%)	5 (3%)	4 (3%)	11 (3%)
Fair	6 (4%)	8 (5%)	9 (6%)	23 (5%)
Good	23 (17%)	15 (10%)	23 (16%)	61 (14%)
Very good	58 (42%)	55 (36%)	46 (32%)	159 (37%)
Excellent	49 (36%)	68 (45%)	63 (43%)	180 (41%)
Comparisons				p-*value*
Active vs. placebo				0.960
i.v. vs. nebuliser				0.157
Attention given to what you have to say				
Poor	1 (1%)	6 (4%)	3 (2%)	10 (2%)
Fair	12 (9%)	9 (6%)	15 (10%)	36 (8%)
Good	26 (19%)	26 (17%)	27 (19%)	79 (18%)
Very good	45 (33%)	58 (38%)	53 (37%)	156 (36%)
Excellent	53 (39%)	52 (34%)	47 (32%)	152 (35%)

continued

TABLE 34 Patient satisfaction with care (*continued*)

Classification	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
Comparisons				p-*value*
Active vs. placebo				0.342
i.v. vs. nebuliser				0.666
Advice you got about ways to avoid illness and stay healthy				
Poor	13 (10%)	14 (9%)	9 (6%)	36 (8%)
Fair	28 (21%)	23 (15%)	19 (13%)	70 (16%)
Good	38 (28%)	36 (24%)	39 (27%)	113 (26%)
Very good	30 (22%)	38 (25%)	39 (27%)	107 (25%)
Excellent	26 (19%)	39 (26%)	36 (25%)	101 (24%)
Comparisons				p-*value*
Active vs. placebo				0.143
i.v. vs. nebuliser				0.112
Friendliness and courtesy shown to you by hospital staff				
Poor	2 (1%)	1 (1%)	0	3 (1%)
Fair	7 (5%)	7 (5%)	4 (3%)	18 (4%)
Good	21 (15%)	25 (17%)	26 (18%)	72 (17%)
Very good	41 (30%)	43 (28%)	38 (26%)	122 (28%)
Excellent	66 (48%)	75 (50%)	77 (53%)	218 (50%)
Comparisons				p-*value*
Active vs. placebo				0.407
i.v. vs. nebuliser				0.812
Personal interest in you and your medical problems				
Poor	1 (1%)	4 (3%)	4 (3%)	9 (2%)
Fair	12 (9%)	19 (13%)	11 (8%)	42 (10%)
Good	35 (25%)	28 (19%)	32 (22%)	95 (22%)
Very good	43 (31%)	49 (33%)	51 (35%)	143 (33%)
Excellent	47 (34%)	50 (33%)	47 (32%)	144 (33%)
Comparisons				p-*value*
Active vs. placebo				0.887
i.v. vs. nebuliser				0.733
Respect shown to you and attention to your privacy				
Poor	3 (2%)	2 (1%)	0	5 (1%)
Fair	10 (7%)	8 (5%)	8 (6%)	26 (6%)
Good	28 (20%)	30 (20%)	32 (22%)	90 (21%)
Very good	45 (33%)	47 (31%)	41 (28%)	133 (31%)
Excellent	52 (38%)	64 (42%)	64 (44%)	180 (41%)

TABLE 34 Patient satisfaction with care (*continued*)

Classification	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Overall (*n* = 1084)
Comparisons				p-*value*
Active vs. placebo				0.484
i.v. vs. nebuliser				0.363
Reassurance and support offered to you by hospital staff				
Poor	5 (4%)	7 (5%)	4 (3%)	16 (4%)
Fair	14 (10%)	13 (9%)	13 (9%)	40 (9%)
Good	28 (20%)	23 (15%)	25 (17%)	76 (18%)
Very good	39 (28%)	57 (38%)	45 (31%)	141 (33%)
Excellent	51 (37%)	51 (34%)	58 (40%)	160 (37%)
Comparisons				p-*value*
Active vs. placebo				0.373
i.v. vs. nebuliser				0.922
Amount of time the hospital staff gave you				
Poor	4 (3%)	4 (3%)	3 (2%)	11 (3%)
Fair	20 (14%)	22 (15%)	15 (10%)	57 (13%)
Good	30 (22%)	35 (23%)	37 (26%)	102 (24%)
Very good	42 (30%)	47 (31%)	46 (32%)	135 (31%)
Excellent	42 (30%)	43 (28%)	44 (30%)	129 (30%)
Comparisons				p-*value*
Active vs. placebo				0.539
i.v. vs. nebuliser				0.790
Overall, how satisfied are you with the service you received				
Poor	4 (3%)	1 (1%)	1 (1%)	6 (1%)
Fair	8 (6%)	13 (9%)	6 (4%)	27 (6%)
Good	23 (17%)	19 (13%)	25 (17%)	67 (16%)
Very good	45 (33%)	54 (36%)	51 (35%)	150 (35%)
Excellent	57 (42%)	63 (42%)	62 (43%)	182 (42%)
Comparisons				p-*value*
Active vs. placebo				0.645
i.v. vs. nebuliser				0.741

Values in brackets denote per cent of total.

TABLE 35 Responses to the request for patients to guess their treatment

Response	Nebulised magnesium sulphate (*n* = 332)	Intravenous magnesium sulphate (*n* = 394)	Placebo (*n* = 358)	Total (*n* = 1084)
Number of responses	140	156	148	444
Believed they had received magnesium sulphate	85 (61%)[a]	94 (60%)[a]	66 (45%)[a]	245 (55%)
How do you think magnesium sulphate was given?				
Nebuliser	55 (39%)[a]	35 (22%)	28 (19%)	118 (27%)
i.v.	21 (15%)	40 (26%)[a]	28 (19%)	89 (20%)
Both	7 (5%)	13 (8%)	7 (5%)	27 (6%)
Do not know/not answered	2 (1%)	6 (4%)	3 (2%)	11 (2%)
NA	55 (39%)	62 (40%)	82 (55%)	199 (45%)

NA, not applicable.
a Correctly guessed.

Subgroup analysis

The protocol prespecified three key factors for subgroup analyses: age, baseline PEFR and previous receipt of salbutamol. *Table 36* shows the impact of these factors on the primary outcomes. In each case, the factor (age, PEFR or previous receipt of salbutamol) was added to a model that also contained treatment group and site. For change in VAS, the VAS at baseline was also included. Older age and lower PEFR at baseline were both highly associated with an increase in admissions and also a greater reduction from baseline in VAS. The latter is presumably a reflection of the greater severity (i.e. higher VAS at baseline) among those with lower percentage PEFR. The use of salbutamol in the ED or ambulance prior to randomisation was compromised by relatively small numbers without prior usage ($n = 59$), but those with previous use were more likely to be admitted than those who had not (77% vs. 56%; $p = 0.001$).

TABLE 36 Impact of age, PEFR at baseline and previous use of salbutamol on outcomes

	Hospital admission		Change in VAS (mm)	
Factor	OR (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value
Age (per 10 year increase)	1.27 (1.13 to 1.43)	< 0.001	2.3 (1.1 to 3.4)	< 0.001
PEFR at baseline (per 10% of predicted increase)	0.81 (0.75 to 0.88)	< 0.001	–1.4 (–2.2 to –0.6)	0.001
Previous use of salbutamol (yes vs. no)	2.83 (1.57 to 5.12)	0.001	–2.3 (–9.3 to 4.7)	0.520

The consistency of the treatment effect was assessed for each of the factors separately, specifically (a) age above or below 50 years; (b) baseline PEFR above the median value for the cohort (50%), below the BTS criteria for life-threatening asthma (< 33%) or inbetween (33–50%): and (c) previous receipt of salbutamol in the ambulance or ED.

The results are displayed graphically in *Figures 15* and *16*. As the primary analysis showed no difference between the nebulised and placebo arms, the graphical displays focus on the comparison of i.v. and placebo. *Figure 15* shows the ORs for admission to hospital for each subgroup and overall and, likewise, *Figure 16* shows the mean differences in VAS. The results appear consistent across all subgroups. The subgroup of patients who had not previously received salbutamol appeared to have worse outcomes with active treatment, but this analysis is limited by small numbers and wide CIs.

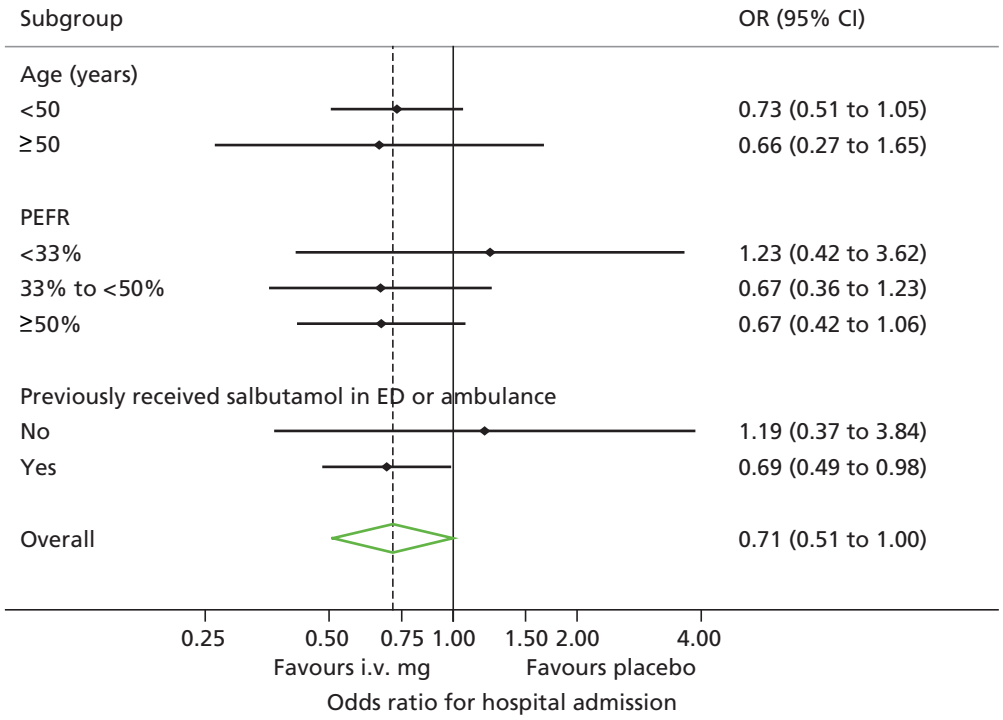

FIGURE 15 Hospital admission, i.v. vs. placebo, by subgroup.

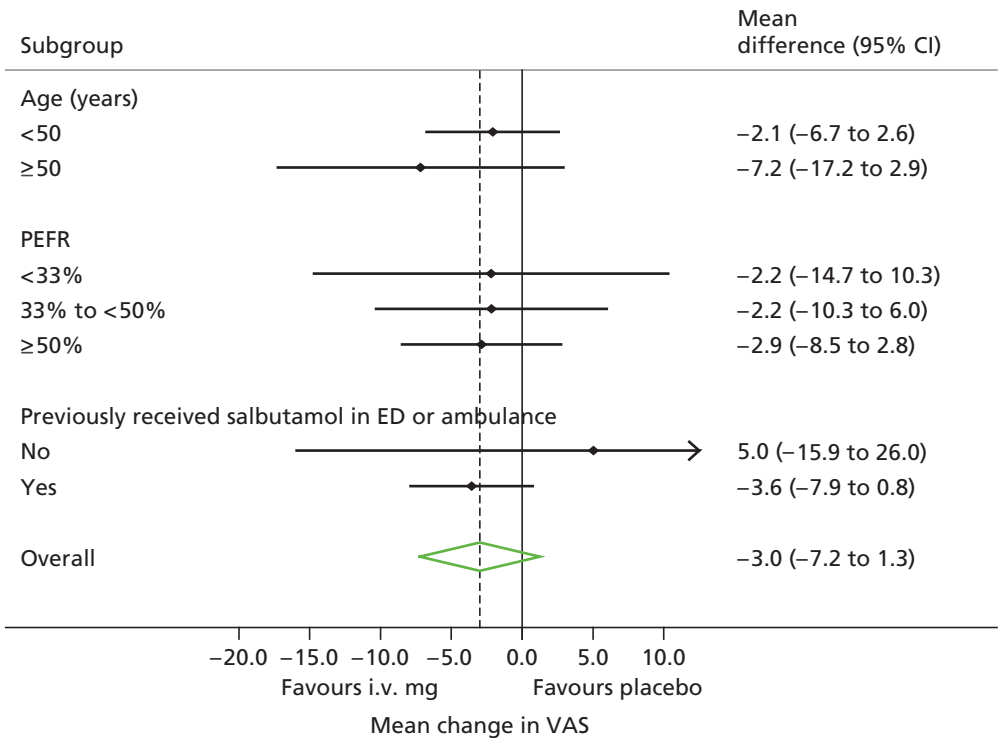

FIGURE 16 Change in VAS by subgroup.

Economic analysis

Table 37 presents the results of the cost-effectiveness analysis of the QALY and cost data excluding productivity costs. The placebo-treated population have the highest population mean QALY and there was no apparent difference between the population mean QALYs associated with nebulised magnesium sulphate and i.v. magnesium sulphate; there is a 67% chance that placebo is associated with the highest population mean QALY. Nebulised magnesium sulphate has the highest population mean cost and placebo has the lowest population mean cost; there is a 95% chance that placebo is associated with the lowest population mean cost.

Figure 17 presents the cost-effectiveness frontiers for willingness to pay in the range £0 to £100,000. There is a 97% and 96% chance that placebo has the highest net benefit at thresholds of £20,000 and £30,000 respectively.

Table 38 presents the results of the cost-effectiveness analysis of the QALY and cost data, including productivity costs. Nebulised magnesium sulphate has the highest population mean cost and placebo has the lowest population mean cost; there is a 90% chance that placebo is associated with the lowest population mean cost.

TABLE 37 Quality-adjusted life-years: summary of cost-effectiveness analysis excluding productivity costs

Treatment	QALYs, mean (SD)	Incremental QALYs (95% CrI)	Cost, (£) mean (SD)	Incremental cost, £ (95% CrI)	ICER
Placebo	0.063 (0.0030)	–	1610 (89.7)	–	
Nebulised magnesium	0.060 (0.0033)	–0.011 to 0.006	1974 (115.3)	77 to 651	Dominated
i.v. magnesium	0.060 (0.0028)	–0.011 to 0.005	1870 (110.8)	–20 to 540	Dominated

CrI, credible interval; ICER, incremental cost-effectiveness ratio.

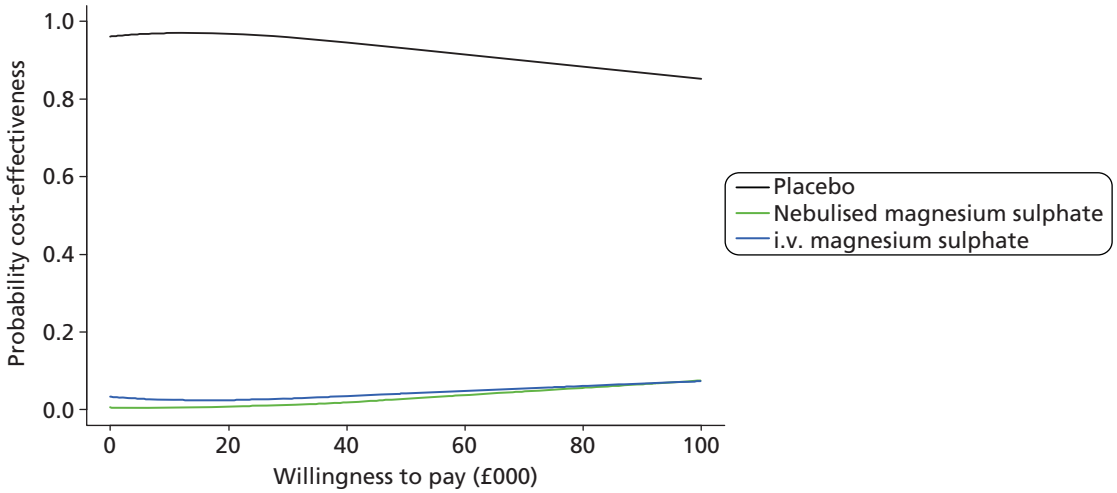

FIGURE 17 Cost-effectiveness frontiers for willingness to pay, main QALY analysis.

TABLE 38 QALYs: summary of cost-effectiveness analysis including productivity costs

Treatment	QALYs, mean (SD)	Incremental QALYs (95% CrI)	Cost (£), mean (SD)	Incremental cost (95% CrI)	ICER
Placebo	0.063 (0.0030)	–	2007 (107.4)	–	
Nebulised magnesium sulphate	0.060 (0.0033)	–0.011 to 0.006	2401 (120.9)	78 to 712	Dominated
i.v. magnesium sulphate	0.060 (0.0028)	–0.011 to 0.005	2219 (120.5)	–104 to 530	Dominated

CrI, credible interval.

Figure 18 presents the cost-effectiveness frontiers for willingness-to-pay in the range £0 to £100,000. There is a 93% chance that placebo has the highest net benefit at thresholds of both £20,000 and £30,000.

Table 39 presents the results of the cost-effectiveness analysis of the 2-hour breathlessness (change from baseline) and cost data excluding productivity costs. Intravenous magnesium sulphate has the greatest population mean change from baseline in 2-hour breathlessness, whereas nebulised magnesium sulphate has the smallest population mean change from baseline in 2-hour breathlessness; there is a 97% chance that i.v. magnesium sulphate is associated with the greatest population mean change from baseline 2-hour breathlessness score.

Figure 19 presents the cost-effectiveness frontiers for willingness to pay in the range £0 to £1000. The incremental cost-effectiveness ratio (ICER) for i.v. magnesium sulphate relative to placebo was £61.70/mm.

Table 40 presents the results of the cost-effectiveness analysis of the 2-hour breathlessness (change from baseline) and cost data including productivity costs. *Figure 20* presents the cost-effectiveness frontiers for willingness to pay in the range of £0 to £1000. The ICER for i.v. magnesium sulphate relative to placebo was £50.48/mm.

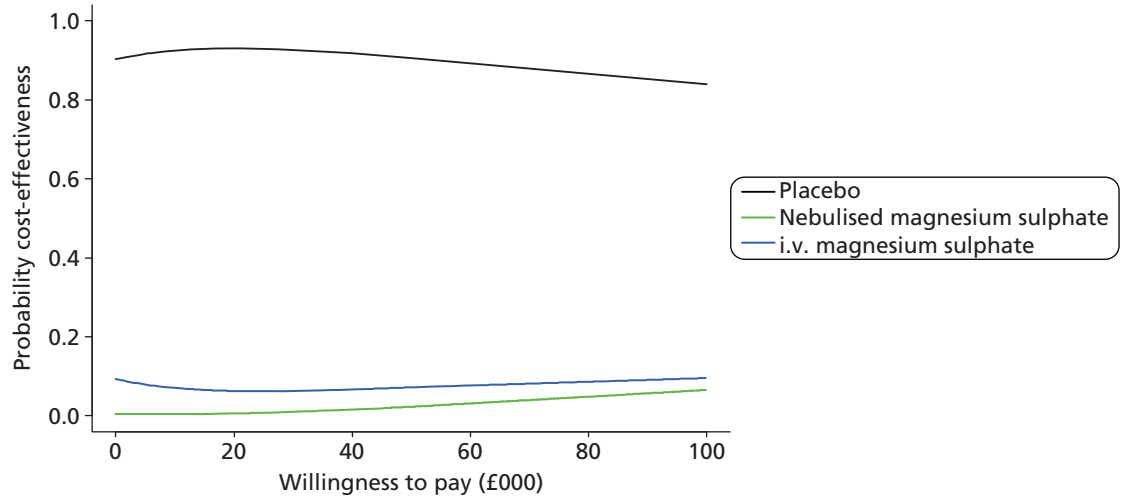

FIGURE 18 Cost-effectiveness frontiers for willingness to pay, QALY analysis including productivity costs.

TABLE 39 Breathlessness: 2-hour change from baseline (VAS) – summary of cost-effectiveness analysis excluding productivity costs

Treatment	Breathlessness (VAS), mean (SD)	Incremental breathlessness (95% CrI)	Cost (£), mean (SD)	Incremental Cost (95% CrI)	ICER
Placebo	29.5 (1.57)	–	1610 (89.8)	–	
Nebulised magnesium sulphate	27.8 (1.57)	–6.0 to 2.7	1974 (115.3)	77 to 651	Dominated
i.v. magnesium sulphate	33.7 (1.43)	0 to 8.4	1870 (110.9)	–20 to 540	£61.7/mm

CrI, credible interval.

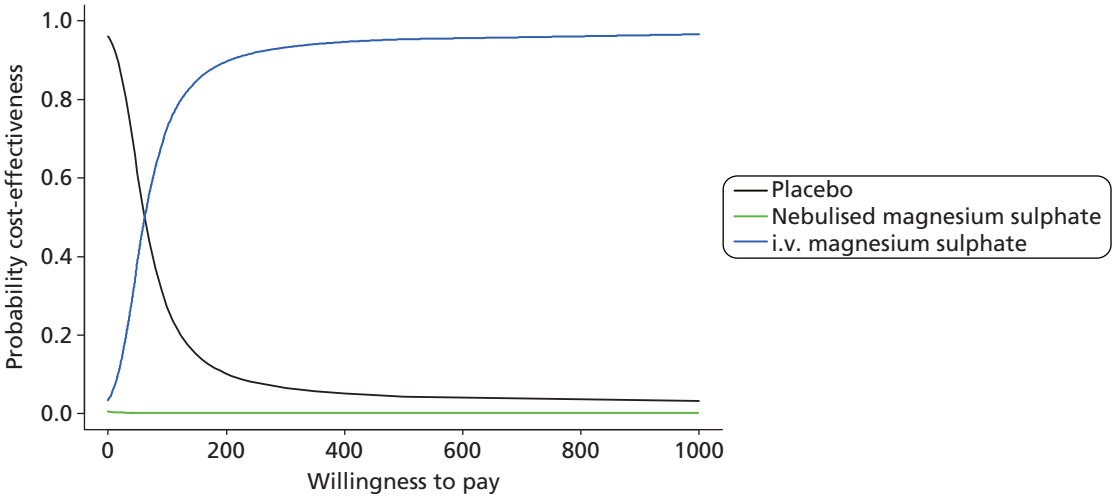

FIGURE 19 Cost-effectiveness frontiers for willingness to pay, main breathlessness analysis.

TABLE 40 Breathlessness: 2-hour change from baseline (VAS) – summary of cost-effectiveness analysis including productivity costs

Treatment	Breathlessness (VAS), mean (SD)	Incremental breathlessness (95% CrI)	Mean cost, £ (SD)	Incremental cost, £ (95% CrI)	ICER
Placebo	29.6 (1.57)	–	2007 (107.4)	–	
Nebulised magnesium sulphate	28.0 (1.57)	–6.0 to 2.7	2401 (120.9)	78 to 712	Dominated
i.v. magnesium sulphate	33.7 (1.43)	0.0 to 8.4	2219 (120.5)	–104 to 530	£50.48/mm

CrI, credible interval.

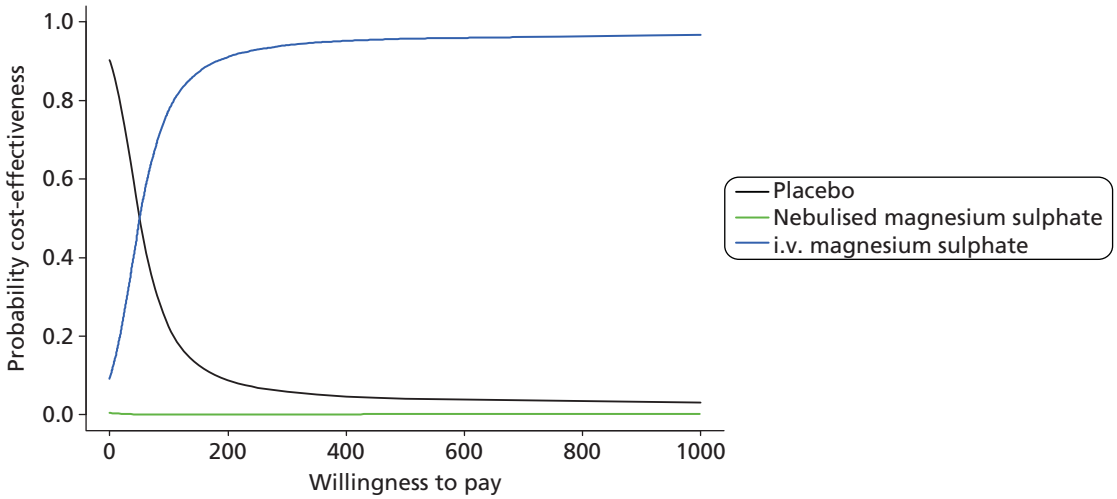

FIGURE 20 Cost-effectiveness frontiers for willingness to pay, breathlessness analysis including productivity costs.

Additional analysis: predictors of unsuccessful treatment

Overall, 81 (7%) participants required critical care and 157 (14%) required emergency medical treatment (including critical care) within 7 days of initial attendance. *Table 41* shows the criteria behind these classifications.

Tables 42 and *43* show the results of univariate analysis. *Table 42* shows the association between baseline characteristics or categorised baseline physiological variables and each outcome. *Table 43* shows the *p*-values for the associations between fractional polynomials of continuous variables (as used in the model) and for each outcome. There was some evidence that previous asthma admission, previous ITU admission, other serious illness and percentage predicted PEFR, heart rate, respiratory rate, oxygen flow rate and VAS breathlessness at baseline or after treatment were associated with unsuccessful treatment. Although percentage predicted PEFR at presentation was associated with unsuccessful treatment it did not provide very useful prognostic value (AUROC < 0.6).

TABLE 41 Criteria for unsuccessful treatment

Criterion	Number (%) of patients
Critical care	81 (7.5)
Emergency medical treatment	157 (14.5)
Reason	
Stay on HDU or ICU	77 (7.1)
Arrhythmia	2 (0.2)
Emergency intubation	8 (0.7)
Non-invasive ventilation	7 (0.6)
Other event	4 (0.4)
Reattendance at ED/unscheduled inpatient review[a]	111 (10.2)

a Contributes to definition 2 only.
The total numbers do not add up to 'overall' as some patients had more than one reason.

TABLE 42 Association between baseline characteristics or categorised baseline physiological variables and each outcome

Factor	Requiring critical care	Requiring emergency medical treatment
Overall	81 (7%)	157 (14%)
Age group (years)	($p = 0.921$)	($p = 0.722$)
16–24	21 (8%)	43 (15%)
25–34	20 (7%)	42 (16%)
35–44	16 (7%)	27 (12%)
45–54	13 (7%)	26 (14%)
55–64	7 (9%)	13 (17%)
65+	4 (11%)	6 (17%)
Sex	($p = 0.798$)	($p = 0.396$)
Female	56 (7%)	115 (15%)
Male	25 (8%)	42 (13%)
Ethnic category	($p = 0.121$)	($p = 0.180$)[a]
White	77 (8%)	140 (14%)
Mixed	2 (25%)	4 (50%)
Asian or Asian British	0 (0%)	6 (16%)
Black or black British	0 (0%)	1 (9%)
Other	0 (0%)	0 (0%)
Not stated	2 (4%)	6 (12%)
Smoker	($p = 0.639$)	($p = 0.822$)
Never	31 (7%)	63 (14%)
Current	28 (8%)	54 (15%)
Previous	22 (9%)	39 (16%)
Missing	0 (0%)	1 (4%)
Previous asthma admission	($p = 0.061$)	($p = 0.034$)
No	21 (5%)	44 (11%)
Yes	60 (9%)	113 (16%)
Previous ITU asthma admission	($p = 0.002$)	($p = 0.070$)
No	60 (6%)	127 (14%)
Yes	21 (13%)	30 (19%)
Previous serious lung disease	($p = 0.348$)	($p = 0.719$)
No	75 (8%)	142 (15%)
Yes	5 (5%)	13 (13%)
Missing	1 (7%)	2 (14%)

TABLE 42 Association between baseline characteristics or categorised baseline physiological variables and each outcome (*continued*)

Factor	Requiring critical care	Requiring emergency medical treatment
Other serious illness	($p = 0.002$)	($p = 0.001$)
No	55 (6%)	111 (13%)
Yes	26 (13%)	44 (22%)
Missing	0 (0%)	2 (17%)
% of predicted PEFR at baseline	($p = 0.153$)	($p = 0.042$)
≤ 35	22 (10%)	42 (20%)
> 35–45	13 (6%)	27 (13%)
> 45–54	13 (7%)	24 (12%)
> 54–67	11 (6%)	26 (14%)
> 67	9 (4%)	20 (10%)
Missing	13 (18%)	18 (24%)
Pulse at baseline (beats per minute)	($p < 0.001$)	($p < 0.001$)
≤ 95	6 (3%)	26 (11%)
95–107	15 (7%)	22 (11%)
107–115	18 (9%)	31 (16%)
115–125	11 (5%)	23 (11%)
> 125	31 (14%)	55 (25%)
Missing	0 (0%)	0 (0%)
Respiratory rate at baseline (breaths per minute)	($p < 0.001$)	($p < 0.001$)
≤ 20	10 (4%)	31 (11%)
> 20–23	12 (8%)	21 (14%)
> 23–26	20 (8%)	29 (11%)
> 26–30	11 (5%)	27 (13%)
> 30	28 (15%)	49 (26%)
Missing	0 (0%)	0 (0%)
Systolic BP at baseline (mmHg)	($p = 0.220$)	($p = 0.634$)
≤ 114	14 (7%)	31 (15%)
> 114–125	12 (5%)	27 (11%)
> 125–135	16 (7%)	35 (16%)
> 135–147	16 (8%)	30 (15%)
> 147	23 (11%)	34 (16%)
Missing	0 (0%)	0 (0%)

continued

TABLE 42 Association between baseline characteristics or categorised baseline physiological variables and each outcome (*continued*)

Factor	Requiring critical care	Requiring emergency medical treatment
Diastolic BP at baseline (mmHg)	($p = 0.238$)	($p = 0.192$)
≤ 63	17 (7%)	30 (13%)
> 63–70	13 (7%)	32 (16%)
> 70–78	11 (5%)	23 (10%)
> 78–86	17 (8%)	34 (16%)
> 86	23 (11%)	38 (18%)
Missing	0 (0%)	0 (0%)
Oxygen flow at baseline (l/minute)	($p = 0.027$)	($p = 0.054$)
0	11 (4%)	34 (13%)
1–5	15 (9%)	26 (15%)
6	38 (10%)	62 (16%)
7–10	10 (6%)	21 (12%)
≥ 10	7 (14%)	14 (29%)
Missing	0 (0%)	0 (0%)

BP, blood pressure.
a *p*-value from Fisher's exact test.
p-values from chi-squared test unless stated otherwise.
Physiology factors were modelled as non-linear terms in the logistic regression model, but for ease of display are presented here in quintiles.

TABLE 43 *p*-values for associations between baseline or post-treatment physiology measures and outcome

	Requiring critical care		Requiring emergency medical treatment	
Variable	Baseline	Post treatment	Baseline	Post treatment
Heart rate	< 0.001	< 0.001	< 0.001	< 0.001
Respiratory rate	< 0.001	< 0.001	< 0.001	< 0.001
Systolic BP	0.074	0.211	0.390	0.604
Diastolic BP	0.164	0.420	0.086	0.819
Oxygen saturation (on oxygen)	0.428	0.001	0.333	0.001
Oxygen saturation (on air)	0.549	0.945	0.283	0.272
Oxygen flow rate	0.009	< 0.001	0.041	< 0.001
VAS breathlessness	0.028	< 0.001	0.003	< 0.001
% predicted PEFR	0.008	< 0.001	0.012	< 0.001

BP, blood pressure.

Tables 44 and *45* show the results of multivariate analysis for prediction of need for critical care and need for any emergency medical treatment respectively. The effect of PEFR on hospitalisation remained similar in the three models and with both outcomes, but the addition of physiological features and the presence of serious comorbidity improved prognostic ability. The presence of other serious illness, raised heart rate and raised oxygen flow requirement were all associated with increased need for critical care. Change in physiology measures over the 2-hour observation period increased the predictive ability of the model further, with a decrease in heart rate or increase in PEFR predicting reduced need for critical care. The derived model was robust and produced comparable fits to the subgroups (temporal, season and teaching/non-teaching hospital). Nonetheless, the resultant model had limited predictive ability (model incorporating change in physiology: AUROC = 0.77), suggesting that there is limited means to predict events for individual patients.

A similar theme emerged from the analysis of prediction of need for any medical treatment, although more terms were identified. There was a quadratic relationship between pretreatment heart rate and needing emergency medical treatment, with the outcome being least likely when the heart rate was in the range 90–100 beats per minute. In addition, pretreatment respiratory rate was significantly associated with the need for emergency medical treatment (higher rate meaning a greater probability of the outcome). The derived model incorporating 2-hour change in physiology was robust and comparable in the subgroups, but again predictive ability remained low (AUROC = 0.69).

TABLE 44 Prediction of need for critical care

	Model 1 (pretreatment PEFR)		Model 2 (pretreatment characteristics and physiology)		Model 3 (pretreatment characteristics and physiology, and 2-hour changes in physiology)	
Factor	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Number of patients with data	1010		999		956	
PEFR (% of predicted)[a]	0.82 (0.72 to 0.95)	0.007	0.82 (0.71 to 0.95)	0.008	0.83 (0.71 to 0.97)	0.017
Other serious illness			2.15 (1.24 to 3.73)	0.006	2.04 (1.12 to 3.70)	0.019
Heart rate (beats per minute)[a]			1.27 (1.12 to 1.45)	< 0.001	1.45 (1.23 to 1.70)	< 0.001
Oxygen flow (l/minute)[a]			2.08 (1.08 to 4.00)	0.028	2.11 (0.99 to 4.49)	0.054
Change in PEFR (% of predicted)[a]					0.77 (0.63 to 0.95)	0.015
Change in pulse (beats per minute)[a]					1.70 (1.35 to 2.12)	< 0.001
Model AUROC	0.60		0.70		0.77	

a The ORs for physiological variables are presented per 10-unit increase.

TABLE 45 Prediction of need for emergency medical treatment

	Model 1 (pretreatment PEFR)		Model 2 (pretreatment characteristics and physiology)		Model 3 (pretreatment characteristics and physiology, and 2-hour changes in physiology)	
Factor	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Number of patients with data	1010		997		954	
PEFR (% of predicted)[a]	0.87 (0.79 to 0.96)	0.008	0.88 (0.79 to 0.97)	0.010	0.87 (0.78 to 0.97)	0.010
Other serious illness			1.77 (1.16 to 2.71)	0.009	1.67 (1.07 to 2.61)	0.023
Heart rate (beats per minute)[a]				< 0.001		< 0.001
Linear term			0.48 (0.25 to 0.95)		0.57 (0.28 to 1.17)	
Quadratic term			1.04 (1.01 to 1.07)		1.03 (1.00 to 1.07)	
Respiratory rate (breaths per minute)[a]			1.34 (1.03 to 1.76)	0.032	1.42 (1.06 to 1.88)	0.017
Change in PEFR (% of predicted)[a]					0.82 (0.71 to 0.93)	0.003
Change in pulse (beats per minute)[a]					1.30 (1.12 to 1.52)	0.001
Model AUROC	0.57		0.64		0.69	

a The ORs for physiological variables are presented per 10-unit increase.

Chapter 4 Discussion

Main findings

Analysis of this three-arm trial involved two preplanned contrasts: (1) active treatment (i.v. and nebulised magnesium sulphate combined) compared with placebo and (2) i.v. compared with nebulised magnesium sulphate. This was based on a systematic review and meta-analysis of previous trials of magnesium sulphate in adults,[11] which suggested that both i.v. and nebulised magnesium sulphate had a potential effect on respiratory function and hospital admission but found no direct comparisons between i.v. and nebulised magnesium sulphate. We found no evidence that active treatment was more effective than placebo, but we did find some evidence that active treatment was associated with a slightly higher risk of side effects [15.6% vs. 10.1%, OR 1.68 (95% CI 1.11 to 2.52; $p = 0.014$)].

Our choice of preplanned comparisons could be criticised if it was thought that one mode of administration was superior to the other, especially if the inferior mode of administration was associated with worse outcomes than placebo. We therefore reported comparisons between i.v. treatment and placebo, and between nebulised treatment and placebo, although it should be recognised that these comparisons were not those originally specified. We found no evidence that nebulised magnesium sulphate was more effective than placebo. In fact, any non-significant trends in the outcomes tended to favour placebo. The only significant effect of nebulised magnesium sulphate compared with placebo was a small increase in the risk of side effects [15.7% vs. 10.1%, OR 1.67 (95% CI 1.05 to 2.66; $p = 0.031$)]. Intravenous magnesium sulphate was associated with a lower rate of hospital admission than placebo, but the difference was not significant [OR 0.73 (95% CI 0.51 to 1.04, $p = 0.083$)], and there was no evidence of an effect on VAS breathlessness [mean difference 2.6 mm (95% CI –1.6 to 6.8 mm; $p = 0.231$)] compared with placebo. Although i.v. magnesium sulphate appeared superior to nebulised magnesium sulphate [mean difference = 5.1 mm, (95% CI 0.8 to 9.4 mm)], the magnitude of the difference in clinical terms is small when considered in the context of a minimum clinically significant difference for VAS breathlessness of 22 mm.[48] There was also no evidence of any clinically worthwhile effect from i.v. magnesium sulphate compared with placebo on secondary outcome measures, including change in PEFR [2.4 l/minute (95% CI –8.8 to 13.6 l/minute; $p = 0.680$)]. Overall, therefore, we were unable to demonstrate a clinically worthwhile benefit from i.v. magnesium sulphate.

Given the failure to demonstrate clinical effectiveness of magnesium sulphate it is not surprising that the economic analysis showed a corresponding lack of cost-effectiveness, with high probabilities that placebo is associated with the highest net benefit at conventionally used thresholds for willingness to pay on the cost per QALY analysis. The analysis of incremental cost per unit change in VAS breathlessness is more difficult to interpret as it showed that i.v. magnesium sulphate could provide a non-significant improvement in outcome at a higher cost, compared with placebo. The ICER was around £50–£60/mm improvement in VAS, but both cost and effectiveness estimates were surrounded by considerable uncertainty.

Our additional analysis to explore the predictive value of baseline characteristics and response to treatment showed that the percentage predicted PEFR at baseline predicted the need for critical care or emergency medical treatment, but that the predictive value was limited (AUROC 0.60 and 0.57 respectively). The presence of other serious illnesses, heart rate, the oxygen flow rate required, change in the percentage predicted PEFR and change in heart rate all predicted the need for critical care, and a predictive model based on these variables had a reasonable predictive value (AUROC 0.77). The presence of other serious illnesses, increased heart rate, increased respiratory rate, change in the percentage predicted PEFR and change in heart rate all predicted the need for emergency medical treatment within the next week (including critical care), but a predictive model based on these variables had only a limited predictive value (AUROC 0.69).

Current BTS/SIGN guidance[2] uses PEFR and a number of other parameters to guide hospital admission decisions, but does not recommend the use of any decision rule or predictive model. Our findings confirm that PEFR is a useful, albeit limited, predictor of adverse outcome. Taking the heart rate, other serious illnesses and the required oxygen flow rate into account could improve prediction, but the predictive model based on these values was unlikely to be adequate for guiding practice. This was a secondary analysis, however, and the sample size was determined by the trial and recruitment constraints. A larger number of outcomes would be required to analyse the predictor variables with sufficient statistical power to ensure an optimal model.

Comparison with previous trials

The most recent meta-analysis of magnesium sulphate for acute asthma[11] showed some heterogeneity among existing trials, but concluded that overall there was uncertain evidence suggesting that both i.v. and nebulised magnesium sulphate could have a clinically worthwhile effect on respiratory function and admission to hospital. It is not unusual for the results of meta-analyses of small trials to be negated or even overturned in large scale, robust trials and there are a number of potential reasons why the findings of the 3Mg trial and the meta-analysis are inconsistent. Meta-analyses may be subject to publication bias if positive trials are preferentially submitted and accepted for publication, and some previous trials may have been limited by inadequate allocation concealment or blinding that inflated estimates of treatment effects. All three arms of the 3Mg trial received treatment with nebulised beta-agonists, ipratropium bromide and corticosteroids in accordance with BTS/SIGN guidance,[2] which may have limited the potential for magnesium sulphate to provide additional bronchodilatation, whereas it was not always clear that all patients received optimal standard treatment in previous trials. It is worth noting that patients in the placebo arm showed marked improvements in PEFR and VAS breathlessness, and few required respiratory support, indicating a good response to standard treatment alone.

One potential explanation that can probably be discounted is that the trial treatment was inadequate in the 3Mg trial. The protocol specified doses of i.v. and nebulised magnesium sulphate that were at the top end of those used in previous trials. Data presented in the supplemental tables show high adherence to the trial protocol, with most patients receiving the full dose of the relevant drugs. Pragmatic trials carry an inevitable risk that trial treatment will be delivered in a suboptimal manner, but we found no significant evidence of this in the 3Mg trial.

Strengths and weaknesses

The 3Mg trial was designed as a pragmatic trial to determine the effectiveness of using magnesium sulphate alongside other treatments as part of routine ED practice. As such it can tell us whether or not magnesium sulphate is an effective treatment for typical patients presenting to the ED with acute severe asthma. However, it cannot tell us whether magnesium sulphate may have benefits in a more narrowly defined patient population or a more specialised setting. The study population was pragmatically defined using information routinely available to ED staff. This means that the findings are generalisable to typical patients attending hospital with acute asthma, but also means that the study population could have included some patients with other diagnoses. In particular, the study population included a proportion of older patients and those who had smoked for a number of years in whom a diagnosis of chronic obstructive pulmonary disease may be more likely than asthma. We evaluated magnesium sulphate in combination with standard treatment rather than assessing it alone. This may have reduced the potential for magnesium sulphate to make a difference, but withholding standard treatment would have been unethical and would not have reflected typical practice. We selected primary outcomes that measured the effect of treatment on symptoms (VAS breathlessness) and clinical management (hospital admission). We also measured physiological parameters and PEFR as secondary outcomes. It is possible that other

measures, such as FEV_1, might have been more sensitive to changes in respiratory function, but these are not usually measured in the ED and are of uncertain clinical relevance.

We deliberately excluded patients with life-threatening asthma and were unable to power the study to detect differences in serious adverse outcomes (including death), therefore we are unable to determine whether or not magnesium sulphate may have an effect on serious adverse outcomes in life-threatening asthma.

Although 3Mg is the largest trial undertaken of magnesium sulphate in acute asthma it is still possible that i.v. magnesium sulphate has a modest effect on admission to hospital that was not proven in this trial. Some of the differences in outcome between i.v. magnesium sulphate and placebo showed trends towards benefit, most notably hospital admission, and the CI includes the possibility of a worthwhile effect (albeit also including the possibility of no effect or even a slightly increased admission rate). The recruitment rate was slower than expected and this meant that, despite additional funding, increasing the number of recruiting centres and prolonging recruitment, we fell short of our recruitment target of 1200 participants. This reduced the power of the trial from 90% to 87% to detect a 10% difference in admission rate. The effect on the power to detect other outcomes was minimal. The sample size was mainly determined by the primary health service outcome, so the trial was powered to detect an 8-mm change in VAS breathlessness despite the minimum clinically significant difference being estimated to be 22 mm. We also assumed a conservative attrition rate of 20% for VAS breathlessness, whereas it was actually only 10% and, therefore, power to detect differences in VAS breathlessness was maintained.

The trial was double blinded to reduce the potential for placebo effects and measurement bias. The responses to the questionnaire suggested that more patients in the active treatment arms than in the placebo arm thought that they had received active treatment, suggesting that blinding did not completely overcome the patient's ability to detect that they had received active treatment. However, given the overall negative findings and pragmatic nature of the trial, this does not seem to be an important source of bias.

Although the attrition rates for the primary outcomes and physiological secondary outcomes were low, the response rate to the questionnaire was lower than anticipated. Previous trials in ED patients have achieved response rates of around 70%,[69,70] but our response rate was 40%. The reasons for this are not clear but may reflect a younger age group, general population disengagement with traditional mailing over time or recognised associations between presentation with asthma at the ED and lower willingness to engage with health care. The low response rate means that the findings of the EQ-5D analysis, health-care resource use survey and patient satisfaction survey should be treated with caution. However, the lack of evidence of clinical effectiveness demonstrated in the primary outcomes and physiological secondary outcomes undermines the potential mechanism for changes in the questionnaire outcomes, while the lack of any important differences between the trial groups means that there is little to be gained from speculating about the potential effect of responder bias.

Chapter 5 Conclusions

Implications for health care

The findings of this trial suggest that there is no role for nebulised magnesium sulphate in the management of acute severe asthma in adults and only a limited potential role for i.v. magnesium sulphate. Patients receiving placebo alongside standard treatment showed marked improvements in breathlessness and PEFR, and few required respiratory support. Although most were admitted to hospital, we found no evidence that nebulised magnesium sulphate reduced the admission rate and the effect on admission rates from i.v. magnesium sulphate was not significant. The low rate of side effects and adverse events (other than those related to the underlying illness) suggests a low risk of harm from i.v. magnesium sulphate administration, but the corresponding evidence of benefit is modest and uncertain.

The findings of the trial do not apply to patients with life-threatening asthma, who were excluded from the trial. The low rate of adverse events associated with i.v. magnesium sulphate treatment may reassure clinicians who feel that in life-threatening asthma any weak evidence of benefit extrapolated from this trial or other sources provides a justification for administering i.v. magnesium sulphate. However, given the failure to demonstrate evidence of benefit, it is important to ensure that magnesium sulphate is not used as an alternative to effective treatments or as a way of delaying the provision of respiratory support.

The BTS/SIGN guidelines[2] do not currently recommend routine use of i.v. or nebulised magnesium sulphate in the management of acute severe asthma, but recommend considering a single dose of i.v. magnesium sulphate (following consultation with senior medical staff) for patients with severe acute asthma who have not had a good initial response to inhaled bronchodilator therapy or patients with life-threatening or near fatal asthma. Our findings do not suggest any reliable expectation of clinical benefit from i.v. or nebulised magnesium sulphate.

The BTS/SIGN guidance recommends using PEFR to guide decision-making in acute asthma. Our secondary analysis suggests that PEFR predicts adverse outcome. Heart rate, other serious illnesses and the required oxygen flow rate could also be used to predict adverse outcome, but the predictive value of a model based on these parameters is not high.

Recommendations for research

Further clinical trials of magnesium sulphate in adults with acute asthma are very unlikely to be worthwhile. It is possible that i.v. treatment could have a modest effect on admission to hospital that was not detected by 3Mg, but a much larger trial would be needed to detect this. Despite having extensive experience of undertaking trials in the emergency setting, an excellent network of supporting hospitals and a simple, pragmatic trial protocol we failed to achieve our recruitment targets and took longer to complete the trial than expected. Undertaking a larger trial to obtain a more precise estimate of treatment effect would therefore require international collaboration and incur substantial costs. It is very unlikely that this could be justified given the low probability of detecting a worthwhile benefit.

The results of the 3Mg trial show that, although standard treatment for acute severe asthma produces marked improvements in breathlessness and PEFR, with a low rate of adverse outcome or requirement for respiratory support, most patients were admitted to hospital after ED treatment. This suggests there is still scope for new treatments or other changes in clinical practice, to improve the management of acute severe asthma.

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Contributions

Membership of the 3Mg research team is outlined below. The co-applicants designed the trial and wrote the grant application. The Project Management Group and local investigators undertook the trial with independent oversight from the Trial Steering Committee and Data Monitoring Committee.

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Steve Goodacre, **Judith Cohen**, **Mike Bradburn**, **John Stevens**, **Alasdair Gray**, **Jonathan Benger** and **Tim Coats** contributed to drafting the report and approved the final draft.

Mike Bradburn undertook the statistical analysis.

John Stevens undertook the economic analysis.

All members of the writing group contributed to redrafting and approved the final draft.

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Appendix 1 Patient recruitment form

The 3Mg Study — Patient Recruitment Form

Candidate Number (for office use only) ☐

Form completed retrospectively ☐

Please complete this side of the form for all adults (age>16) attending the ED with acute severe asthma

Recruiting Hospital: _____ Recruiting Doctor: _____

Date: d d m m y y y y Time: h h m m

Patient Details Sex: Male ☐ Female ☐ Age: ☐

Please answer the following questions to determine whether the patient is eligible for the trial:

1) **Is the patient aged 16 years or over?** Yes ☐ No ☐

2) **Does the patient have acute severe asthma?** Yes ☐ No ☐
If yes, tick at least one of these criteria:

PEFR < 50% of best or predicted	☐	Respiratory rate > 25/min	☐
Heart rate > 110/min	☐	Inability to complete sentences in one breath	☐

If the answer to either of the questions above is NO, the patient is not eligible - do not proceed

If the answer to both of the questions above is YES, please answer the following questions to check for exclusion criteria:

3) **Does the patient have life-threatening asthma?** Yes ☐ No ☐
If yes, tick at least one of these criteria:

Oxygen saturation < 92%	☐	Arrhythmia	☐	Hypotension	☐
Silent chest, cyanosis	☐	Bradycardia	☐	Coma or confusion	☐
Poor respiratory effort	☐	Exhaustion	☐		

4) **Does the patient have a contraindication to either nebulised or intravenous magnesium sulphate?** Yes ☐ No ☐
If yes, tick at least one contraindication:

Known pregnancy	☐	Hepatic Failure	☐	Renal Failure	☐
Heart Block	☐	Known Hypermagnesaemia	☐		

5) **Has the patient received IV or nebulised magnesium sulphate in the past 24 hours?** Yes ☐ No ☐

6) **Has the patient previously participated in the 3Mg Trial?** Yes ☐ No ☐

If the answer to ANY of the three previous questions is YES, the patient is excluded from the trial.
If the answer to ALL of the three previous questions is NO, the patient is eligible for the trial.
Please determine whether the patient is able and willing to give written or oral consent.

Has the patient given consent? Yes ☐ No ☐ **If no reason:** _____

If the patient is unable or unwilling to provide consent then they must not be included in the trial. If patient is excluded, please file this form on the non-recruitment section of the site file. If the patient has provided consent, please contact the randomisation system (contact details overleaf: phone or web-system).

P.T.O and complete the participant details

3Mg Patient Recruitment Form, v6, 28SEPT11

RANDOMISATION

You will need a username (SIN) and password (PIN) to allow access. A general randomisation SIN and PIN is printed in the front of your site file.

To access the randomisation system through your web browser:
Click the 3Mg icon on your desktop if installed

Otherwise, go to www.ctru-rs.shef.ac.uk
Click 3Mg - Access Randomisation System
Add your SIN and PIN and submit. If successfully logged in you should see the option to 'randomise a participant'. Click this and follow the on-screen instructions.

To access the system by telephone call: [redacted]
Enter your SIN and PIN from the telephone keypad when prompted, then follow the verbal instructions.

If you are having problems with the randomisation system please contact Judith Cohen or Katie Biggs
Email: [redacted] or [redacted] Tel: [redacted]

RANDOMISATION DETAILS

Eligibility Criteria Checked by Completion of Patient Recruitment Form Yes ☐ No ☐

Form of consent obtained: Oral ☐ Written ☐ **RANDOMISATION NUMBER:**

PARTICIPANT DETAILS:

AFFIX PATIENT LABEL HERE

If patient label is not available or incomplete the details below **MUST** be completed

Ethnic Category: (✓ one only)
White ☐ Mixed ☐ Asian or Asian British ☐ Black or Black British ☐ Other Ethnic Groups ☐ Not Stated ☐

Name: Title _____ Forename _____ Surname _____

Address:

Postcode:

Date of Birth: d d m m y y y y **Telephone number:** (mobile and/or home)

Hospital Number/ CHI Number: **A&E Number:**

Once the patient is randomised, trial treatment can commence
All details should be recorded on the CRF

Appendix 2 Brief information sheet

Initial patient information sheet for the 3Mg study

(Is magnesium sulphate, in addition to standard treatment, effective in patients with an asthma attack?)

You are being invited to take part in a research study. The purpose of the study is to find out whether treating an asthma attack with magnesium sulphate, in addition to standard treatment, relieves symptoms of breathlessness and reduces the chances that people with acute asthma will need to be admitted to hospital. The study will compare standard treatment for asthma to standard treatment and magnesium sulphate, given either into a vein or through a nebuliser.

Why have I been chosen?

You have come to hospital with an asthma attack. The doctors treating you think that magnesium sulphate, if it is effective, may ease your symptoms of breathlessness and improve your chances of avoiding hospital admission.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be asked to sign a consent form. You will be free to withdraw at any time, without giving a reason. A decision to withdraw at any time or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

If you agree to take part you will be given the standard treatment for asthma. You will also be given an infusion into a vein in your arm and three nebulisers. Along with the standard treatments you will be given one of the following three alternatives:

- magnesium sulphate added to the nebuliser but not the infusion
- magnesium sulphate added to the infusion but not the nebuliser
- nothing added to either the infusion or the nebuliser (just standard treatment).

We will then monitor your symptoms for up to 4 hours, after which the doctor will advise whether you should be admitted to hospital or go home. Neither you, nor the doctors will know which treatment you have been given.

What do I have to do?

All the treatments will be given by the doctors and nurses. You will to need answer some questions and do a Peak Flow recording (breathing test).

Are there any side effects to treatment?

Magnesium sulphate can cause feelings of nausea, vomiting, thirst or facial flushing, particularly when given through a vein. In rare cases overdose of magnesium sulphate can cause weakness, coma or heart problems. The doctors will monitor your heartbeat during treatment.

We will give you more information shortly, when you are feeling better.

Version 004: 16 June 2009

Appendix 3 Full information sheet

Headed notepaper from XXX Hospital

PATIENT INFORMATION SHEET FOR THE 3Mg STUDY

(Is magnesium sulphate, in addition to standard treatment, effective in patients with an asthma attack?)

You are being invited to take part in a research study that is organised by the University of Sheffield and undertaken at XXX Hospital. Before you decide it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

The purpose of the study is to find out whether treating an asthma attack with magnesium sulphate relieves symptoms of breathlessness and reduces the chances that people with acute asthma will need to be admitted to hospital.

Magnesium sulphate has been used to treat asthma attacks for several years. It can be given either as an infusion into a vein or by being inhaled using a nebuliser. We know that treatment with magnesium sulphate can improve the results of breathing tests, but we do not yet know whether it improves patient's symptoms of breathlessness or reduces their chances of needing hospital admission. We also do not know whether it works better by infusion into a vein or inhaled through a nebuliser.

The study will compare standard treatment for asthma, with the addition of magnesium sulphate (given either into a vein or through a nebuliser), to standard treatment without magnesium sulphate.

Why have I been chosen?

You have come to hospital with an asthma attack. The doctors treating you think that magnesium sulphate, if it is effective, may ease your symptoms of breathlessness and improve your chances of avoiding hospital admission.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

If you agree to take part you will be given standard treatment for asthma with oxygen, nebulisers and steroids (prednisolone or hydrocortisone). In addition you will also be given an infusion of saline (salt and water) into a vein in your arm. Along with the standard treatments you will be given one of the following three alternatives:

- magnesium sulphate added to the nebuliser but not the infusion
- magnesium sulphate added to the infusion but not the nebuliser
- nothing added to either the infusion or the nebuliser (i.e. just standard treatment on its own).

After you have been given the treatment we will monitor your symptoms for up to 4 hours. Depending upon your response to treatment the doctor will then advise whether you should be admitted to hospital or go home.

One month from now we will examine all of your hospital records and then send you a questionnaire in the post or telephone you asking you about your health, your recent use of health services and what you thought about the care you received.

You will be put into one of the three treatment groups by chance (randomly). Neither you, the staff nor the researchers will know which treatment you have been given (this is known as a 'blind trial'). At the end of the trial the researchers will compare patients in the three groups and then reveal which treatment was which to find out which treatment helped patients most.

If it may affect your care then the doctors treating you can find out which treatment you have been given.

What do I have to do?

All the treatments will be given by the doctors and nurses. You will to need answer some questions and do a peak flow recording (breathing test) to monitor your progress, and then complete a questionnaire in 1 month's time.

Are there any side effects to treatment?

Magnesium sulphate can cause feelings of nausea, vomiting, thirst or facial flushing, particularly when given through a vein. In rare cases overdose of magnesium sulphate can cause weakness, coma or heart problems. The doctors will monitor your heartbeat during treatment.

What are the possible benefits of taking part?

We cannot promise that the study will help you but doing the study may help to improve the treatment of people with an asthma attack.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (contact details below). 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 does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Sheffield or XXX Hospital but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study be kept confidential?

We will inform your GP that you have taken part in this study. We will record information about your treatment over the next few hours and a member of the research team will record information from your hospital notes and computer records in 1 month's time. All information that is collected about you during the course of this study will be kept strictly confidential. The information will be stored in a secure area of the hospital. A copy of the information will be sent to the University of Sheffield where it will be stored in a secure area and also kept as a password-protected computer file, both of which can only be accessed by the research team and regulatory authorities. We will destroy all identifiable information 5 years after the end of the study. An anonymised copy of the computer file (with any details that might identify you removed) will be retained and made available to other researchers for use in future studies.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time. We will need to keep the information you have given up to the time you withdraw but will not collect any new information or send you the questionnaire.

What will happen to the results of the research study?

We will publish the results in a scientific journal and produce a report that is freely available to anyone who wishes to read it. You will not be personally identified in any report or publication we produce. Please contact us using the details below if you would like to see a summary of the results when the trial is completed.

Who is organising and funding the research?

The research is organised by the University of Sheffield and funded by the Department of Health.

Who has reviewed the study?

This study was given a favourable ethical opinion for conduct in the NHS by the Scotland A Research Ethics Committee.

Further information can be obtained from: Prof SW Goodacre

Medical Care Research Unit

University of Sheffield

Regent Court, 30 Regent Street

Sheffield S1 4DA

[redacted]

Version 004: 16 June 2009

Appendix 4 Patient consent form

PATIENT CONSENT FORM FOR 3Mg STUDY

(Is magnesium sulphate effective in patients with an asthma attack?)

Lead Researcher:

	Please tick to confirm
I confirm that I have read the information sheet dated 16/6/09 (version 4) for the above study. I have had the opportunity to ask questions and have had them answered satisfactorily.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from the University of Sheffield, 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 records.	☐
I agree to my GP being informed of my participation in the study.	☐
I understand and accept that, as explained in the information sheet the treatment I am given may have some side effects	☐
I agree to take part in the above study	☐

Patient name: _____ Date:__/__/__ Signature: _____

Verbal consent recorded (tick box) ☐

Person taking consent: _____ Date:__/__/__ Signature: _____

Witness name: _____ Date:__/__/__ Signature:_____

Version 004, 16Jun09

Appendix 5 Clinical protocol

3Mg Clinical Guidelines Version 3, 10AUG2010

When patients present at the Emergency Department (ED) with acute severe asthma they may be eligible for the 3Mg Trial. Please keep the trial in mind and complete the Patient Recruitment Form for all acute severe asthma patients.

The aim of this trial is to measure the effectiveness of intravenous and nebulised magnesium sulphate in relieving symptoms of acute severe asthma and preventing hospital admission. The trial should determine whether magnesium sulphate should be standard first-line treatment for patients presenting to the ED with acute severe asthma.

We are not asking you to with-hold standard treatment from any patients. Standard treatment should be administered as detailed in the BTS/SIGN guidelines. The following protocol outlines the process of assessing patient eligibility, and the procedures to be completed if the patient is entered into the trial. It is split into two sections: Pre-randomisation and Post-randomisation. The full 3Mg protocol and more detailed guidance on each procedure can be found in the working file and site file.

Pre-Randomisation (Flow chart 1)

Please follow this section of the protocol for ALL patients presenting at the emergency department with acute severe asthma.

Immediate management
Make a rapid clinical assessment and attempt PEFR recording
Give urgent treatment according to BTS/SIGN guidelines:

- Commence salbutamol 5mg via oxygen-driven nebuliser or continue prehospital nebulisation
- Consider adding ipratropium 500mcg
- Give prednisolone 40-50mg orally or hydrocortisone 100-200mg IV

Assess for eligibility using the Patient Recruitment Form

- Take a patient pack from the working file (this contains all required paperwork)
- Complete the Patient Recruitment Form for all adults with acute severe asthma
- They must have features of severe asthma
- They must have NO life-threatening features
- They must have NO contraindication to magnesium sulphate
- They must not have received magnesium sulphate (IV or nebulised) in the previous 24 hours
- They cannot be a known previous participant in the 3Mg Trial

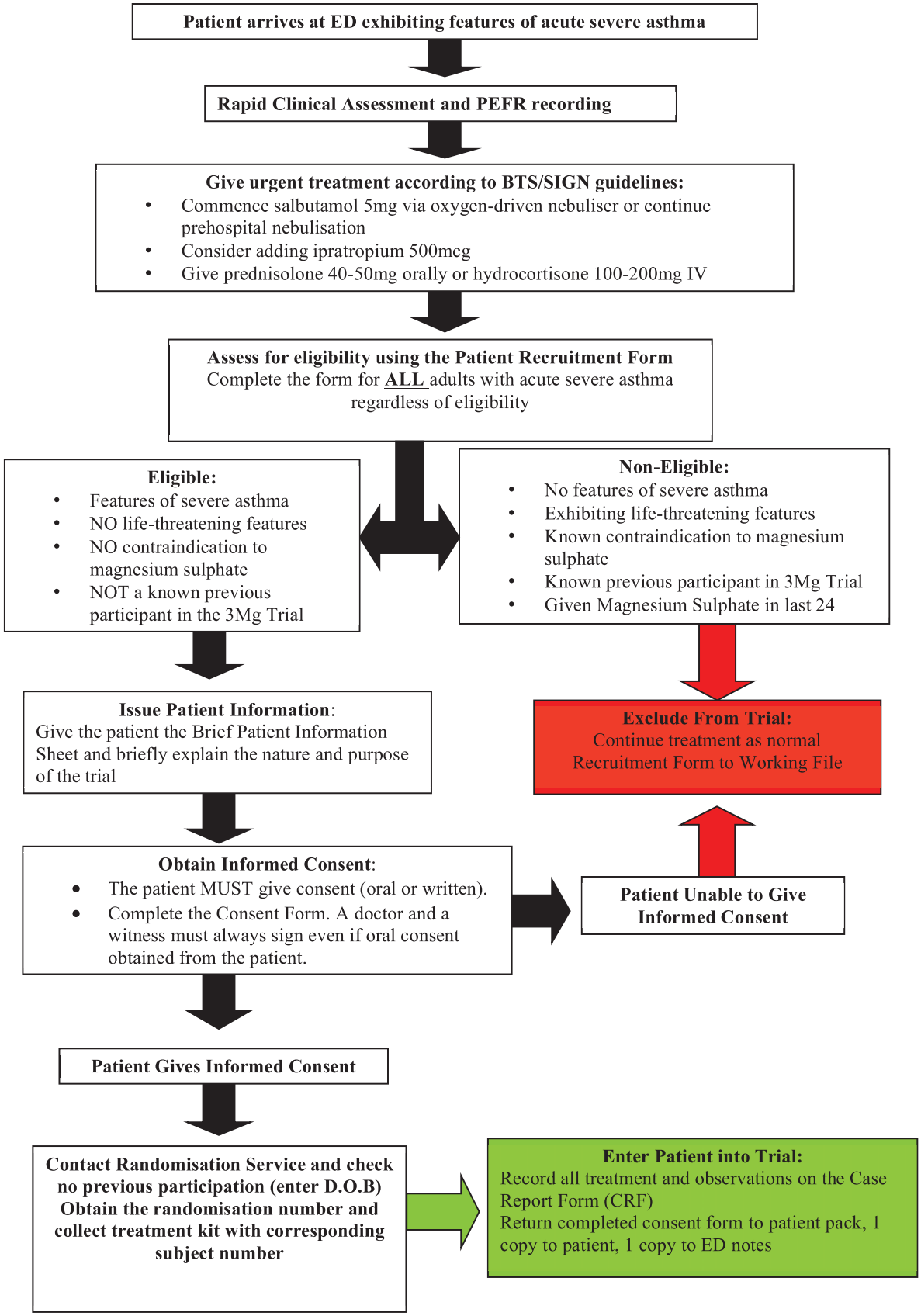
Information, consent and randomisation

- If eligible, give the patient the Brief Patient Information Sheet and briefly explain the nature and purpose of the trial
- Complete the first side of the randomisation form to check eligibility
- The patient MUST give consent (oral or written) before entry to the trial. Please complete the Consent Form and place original top copy in the patient pack. Give a copy of the consent form to the patient, and file a third copy in the ED notes.
- If the patient provides consent, contact the randomisation service (SIN and PIN printed in working file). Check for previous participation by entering D.O.B

on web system and then continue to obtain the treatment kit number. Complete the second side of the randomisation form and return it to the patient pack.

- If the patient is ineligible or does not give consent, only complete the front page of Patient Recruitment Form and file the in the non-recruited section of the working file. Add a blank Patient Recruitment Form to the patient pack and return it to the working file.

Flow Chart 1 – Pre-Randomisation to 3Mg Trial



Post-Randomisation (Flow Chart 2)

Please follow this section of the protocol for all patients who have been recruited into the trial.
Once participants have been randomised they immediately enter the trial and all details of treatment and any observations must be recorded on the case report form (CRF). However, participants are free to withdraw at any time, and the treatment can be unblinded if life-threatening features develop. If the patient withdraws or the treatment is unblinded, ensure this is recorded on page 4 of the CRF.

Baseline measurements
Record pulse, respiratory rate, blood pressure, temperature, oxygen saturation, oxygen flow rate, PEFR, and breathlessness VAS before starting treatment

Trial treatment
Participants are randomly allocated to one of three treatments. Treatment kits are labelled with a subject number (this is the same as randomisation number). Please ensure you use the correctly numbered kit. Before taking the kit from the cupboard, check the temperature log – if the temperature has exceeded 30ºC and a temperature excursion report has not been filed, you must not use until this has been done and the production unit have confirmed kits are safe to use (see temperature excursion section in working file).

Write a prescription (or use sticker if provided) of the 3Mg treatment kit in the patient notes, including the randomisation number and your signature:

3Mg IMP, randomisation number …..
- 1 x IV solution 100mls, over 20 mins
- 3 x nebulisers 7.5ml, started at 20 minute intervals

Each treatment kit contains one intravenous and three nebulised treatments, all of which must be used. Collapse the treatment kit box, write the patient initials and date on the box and place in the patient pack.
- Give the 100ml IV trial infusion over 20 minutes
- Give continuous trial nebulisers over at least one hour
- Record the total volume of trial treatment given on the Case Report Form

Nebulisation
- Continuous nebulisation should be provided using three consecutive nebulisers, each given over at least 20 minutes.
- For each nebuliser you should use one 7.5ml vial from the treatment kit.
- Up to 2.5ml of either 2.5mg or 5mg salbutamol, or saline can be added to each nebuliser, depending upon the patients' condition.
- Nebulisation should be driven by 6L/minute oxygen

Subsequent measurements
- Record the pulse, respiratory rate, blood pressure, oxygen saturation, oxygen flow rate, PEFR, and breathlessness VAS one hour and two hours after starting treatment

Concurrent and further management
- Patients should be reassessed frequently and the BTS/SIGN guidelines used to guide management

- Record any Adverse Events on the CRF and in ED notes and contact the PI as outlined in SAE reporting protocol.
- If the patient develops any life-threatening features or if their PEFR remains below 50% of best or predicted after trial treatment, then obtain arterial blood gases, chest X-ray and senior/ITU help. If appropriate, the trial treatment should be unblinded and intravenous magnesium sulphate considered.

Reassessment

- As soon as the patients' condition allows, give them the full Patient Information Sheet and ask them to complete the EQ-5D questionnaire (on the back of VAS scoring sheet). Place the completed questionnaire in the patient pack.
- If oral consent was given at entry to the trial, obtain written consent on a new consent form and place the completed consent form (original top copy) in the patient pack. Give a copy of the signed consent form for the patient to take home, and file another copy in the ED notes.

Admission or discharge

- Your decision to admit or discharge the patient should not be influenced by their participation in the trial.
- The patient should only be discharged home if, after a period of observation, they are stable and the PEFR is preferably above 75% (and definitely above 50%)
- The decision to admit or discharge can be made any time up to four hours after randomisation.
- If the decision has not been made by four hours, then the patient will be recorded as having been admitted to hospital.
- If the patient is admitted, please ensure that a ward admission letter (enclosed in patient pack) accompanies the patient to the ward so that staff are made aware of their participation in the trial.

Post-discharge care

- Prescribe steroids (BTS guidelines suggest prednisolone 40-50mg daily for 5 days)
- Ensure supply of inhaled beta agonist and steroid, and check inhaler technique
- Arrange GP follow-up
- Local research nurse will send GP letter

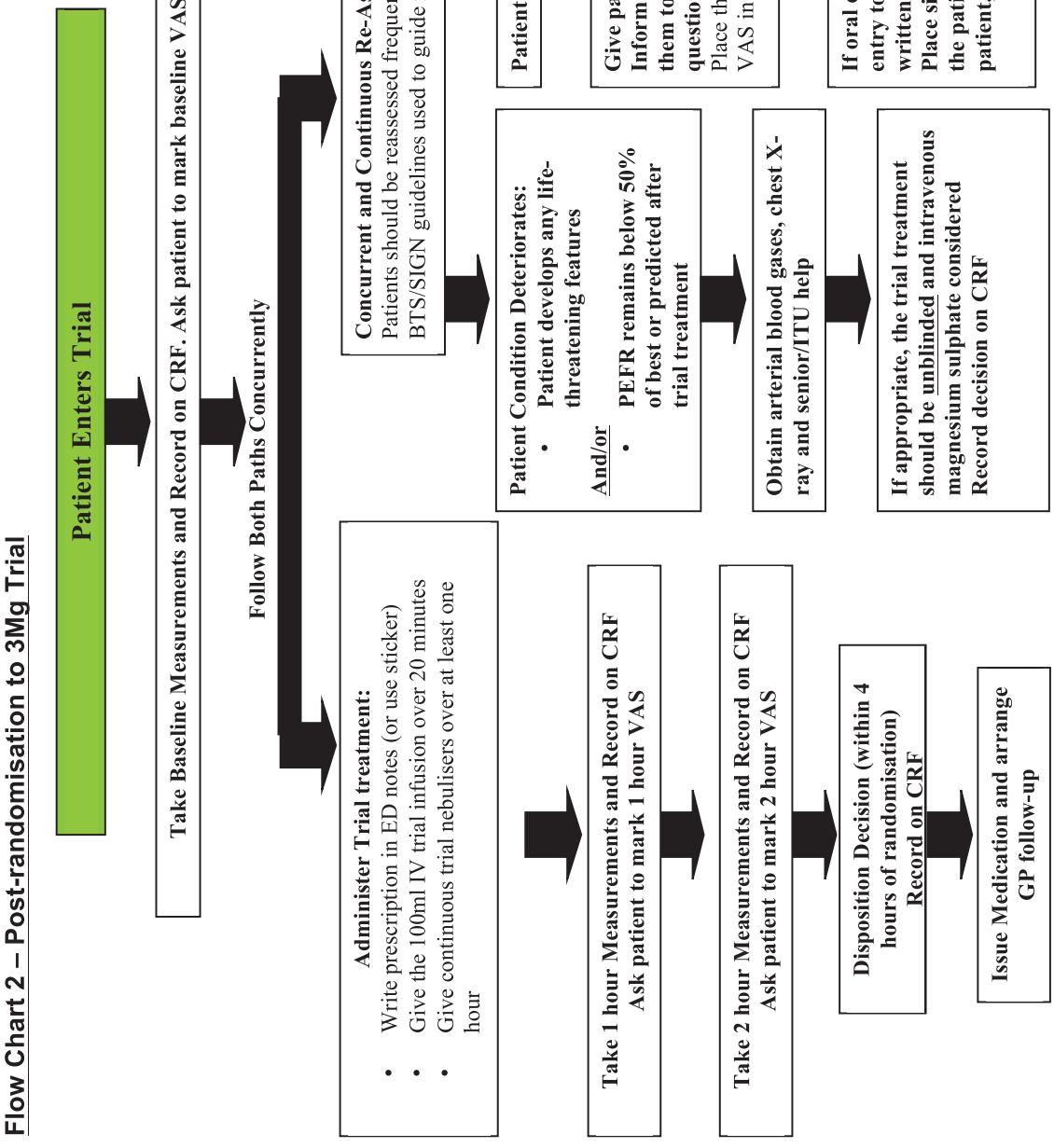
Trial paperwork

- Please complete the Case Report Form, especially any adverse events and side effects in the emergency department (page 4), and details of departure from the emergency department (page 3)
- Please put all paperwork in the patient pack and return to the Working File – ensure the EQ-5D questionnaire and VAS breathlessness scores have been completed
- Please ensure that the patient has a copy of both the brief and full Patient Information Sheet and a copy of their signed consent form

Thank you for recruiting a patient to the 3Mg Study.

Your local research nurse will have been alerted via the randomisation system and will visit the department in the next few days. The research nurse will complete the follow-up of the patient.

Flow Chart 2 – Post-randomisation to 3Mg Trial



Appendix 6 Case report form

Case Report Form (CRF)
Recruiting Hospital:

RANDOMISATION NUMBER

The 3Mg Study

Randomised controlled trial of intravenous or nebulised magnesium sulphate or standard therapy for acute severe asthma

Please complete ALL sections up to AEs in ED. Research Nurse to complete 30 day follow-up	
	Page 1: ○ Prior to entry into the trial
	Pages 2 & 3: ✚ During trial treatment in the Emergency Department (ED)
	Page 4: △ Adverse Events - during treatment in the ED, 30-day follow-up
	Page 4: ★ Local PI signature (sign once all sections complete)

○ PARTICIPANT DETAILS

Please ensure that the participant has been randomised and enter number in box at top of this sheet.
Full participant details should be completed on the randomisation form – please ensure this is done.

Physician responsible for patient: (print name) _____

Admission to ED d d m m 2 0 y y h h : m m

○ MEDICATION TAKEN IN LAST 24 HRS PRIOR TO HOSPITALISATION

Salbutamol: Inhaler ☐ Dose ____ Number of times given ____ Nebuliser ☐ Dose ____ Number of times given ____	Steroids: Oral ☐ Dose ____ Number of times given ____ IV ☐ Dose ____ Number of times given ____
Ipratropium: Inhaler ☐ Dose ____ Number of times given ____ Nebuliser ☐ Dose ____ Number of times given ____	Other: Drug ____ Route ____ Dose ____ Number of times given ____

○ TREATMENTS GIVEN IN AMBULANCE OR ED PRIOR TO TRIAL TREATMENTS

Treatment Name	Dose (e.g. 1mg, 500mcg)	Route (eg oral, IV)	Number of doses given (e.g. x3)
Salbutamol		nebuliser	
Ipratropium		nebuliser	
Prednisolone			
Hydrocortisone			

✚ PREDICTED PEFR

1) Known normal PEFR (when patient can specify) _____ (L/min)

or 2) Estimate of height _____ Calculated PEFR _____ (L/min)

3Mg Case Report Form: Version 5 25FEB09 Page 1 of 4

OBSERVATIONS DURING TRIAL TREATMENT : 0 – 2 Hours

COMPLETE AT 3 TIME-POINTS	Baseline (just prior to initiation of trial treatment)	1 Hour (after initiation of study treatment)	2 Hours (after initiation of study treatment)
	Time:	Time:	Time:
Pulse	(beats/min)	(beats/min)	(beats/min)
Respiratory Rate	(breaths/min)	(breaths/min)	(breaths/min)
Blood Pressure	Systolic/Diastolic / (mmHg)	Systolic/Diastolic / (mmHg)	Systolic/Diastolic / (mmHg)
Temperature	(°C)	Baseline only	Baseline only
Supplemental oxygen flow rate	(O_2%) (L/min)	(O_2%) (L/min)	(O_2%) (L/min)
Oxygen Saturations	(%)	(%)	(%)
PEFR	Take 3 peak flow recordings per time-point, 30 seconds apart, and record the best reading below.		
	(L/min)	(L/min)	(L/min)
VAS Breathlessness	Ask participant to mark breathlessness on the VAS – provided on separate sheet. Add VAS score here.		
	(mm)	(mm)	(mm)

TRIAL TREATMENTS

Trial IV Infusion: Estimate of total volume given (max 100ml) (ml)

Trial Nebulisers:

Nebuliser	Salbutamol (Ventolin) Added (✓)	Total Salbutamol Added		Total Volume of Trial Nebuliser Given (estimate – max 7.5ml or 10ml if salbutamol added)
		Amount (ml)	Dose (mg)	
1				
2				
3				

ADDITIONAL TREATMENTS GIVEN DURING AND AFTER TRIAL TREATMENTS

Treatment Name	Dose (e.g. 1mg, 500mcg)	Route (e.g. oral, IV)	Number of doses given (e.g. x3)

3Mg Case Report Form: Version 5 25FEB09 Page 2 of 4

BACKGROUND INFORMATION

Time since last admission with asthma: ☐ Years ☐ Months ☐ Days ☐ No previous admission

Previous ITU admission with asthma: Yes ☐ No ☐

Admission Date	Discharge Date	Details (Major complications / Interventions)
dd/mm/yyyy	dd/mm/yyyy	
dd/mm/yyyy	dd/mm/yyyy	
dd/mm/yyyy	dd/mm/yyyy	

Has participant ever smoked? Yes ☐ No ☐

If yes: ☐ Current Smoker Number of cigarettes per day ☐ yrs mths

☐ Previous Smoker Number of cigarettes per day ☐ Length of time stopped ☐ ☐

Regular Medication:

Salbutamol Inhaler/nebuliser ☐	Long-acting beta-agonist inhaler ☐	Leukotriene antagonist ☐	Short-term oral steroid therapy (<1 month) ☐
Ipratropium Inhaler/nebuliser ☐	Other inhaler/nebuliser ☐	Long-term oral steroid therapy (>1 month) ☐	Aminophylline or theophylline ☐

Other illness:		If Yes please give details:
Previous serious lung disease (e.g. TB, pneumonia)	Yes ☐ No ☐	
Other serious illness requiring regular medication or impairing daily activities	Yes ☐ No ☐	

If there are any further details on medical history please complete on a continuation sheet ✓ if used ☐

DEPARTURE FROM THE EMERGENCY DEPARTMENT

CHECKLIST PRIOR TO PATIENT DEPARTURE FROM ED

- Consent obtained: Oral Yes ☐ No ☐ if Yes - please obtain written consent on a separate form before pt departs
- Consent obtained: Written Yes ☐ No ☐ (all consent must be undertaken by a trained doctor and witnessed)
- EQ-5D Questionnaire and VAS Completed: Yes ☐ No ☐ (please complete separate sheet and file with the CRF)

4 Hours After Arrival at Emergency Department

Status: Alive ☐ Dead ☐

If Alive -

Discharge Decision at 4 Hours – Admitted ☐ Discharged ☐ No Decision Made ☐

If Admitted:

Destination: ITU ☐ HDU ☐ Ward ☐ Other ☐ (specify) _____

If Discharged:

Treatment	✓	Name	Dose (e.g. 1mg)	Frequency (e.g. bd, monthly)	Number of days
Steroids					
Inhaler					

Follow-up Arranged: GP ☐ outpatient ☐ other ☐ (specify) _____

3Mg Case Report Form: Version 5 25FEB09 Page 3 of 4

ADVERSE EVENTS

If tables are full, please record any further events on a continuation sheet ☐ if used

Blinding removed: Yes ☐ No ☐ If yes, details MUST be completed:

Date: d d m m 2 0 y y Time: h h : m m Doctor: _____

Reason for Unblinding: ☐ Suspected reaction to treatment ☐ Needed to administer IV Magnesium Sulphate to patient

Details: _____

Side Effects (only for initial acute episode): Flushing, Nausea, Vomiting, Hypotension (systolic <100mmHg), Other (specify)

Effect (chosen from types above)	Date	Details (include time of event if known)
	dd/mm/20yy	
	dd/mm/20yy	
	dd/mm/20yy	

Adverse Events:

Cardiac arrest, Respiratory arrest, Non-invasive ventilation, Pneumothorax, Intubation, Arrhythmia, Death, Other (specify)

Event (chosen from types above)	Date	Details (include time of event if known)
	dd/mm/20yy	
	dd/mm/20yy	

30-DAY FOLLOW-UP

Please record any adverse events in table above or on continuation sheet ☐ if used

Status: Alive ☐ Dead ☐ → Date of death d d m m 2 0 y y

1st Week After Randomisation

If admitted (after initial trial treatment):

Discharge date & time	ICU days	HDU days	Ward days
dd/mm/20yy hh:mm			

In the first week did the patient receive any unscheduled medical review for asthma? Yes ☐ No ☐

If yes, detail: i.e. Unscheduled review by doctor or ED attendance – include any unscheduled medication

In the last 30 days (since randomisation) – include only regular medication NOT unscheduled

Asthma treatments taken:

Date started	Treatment Name	Dose (e.g. 1mg)	Route (e.g. oral, IV)	Frequency (e.g. bd, daily)	Number of days

Number of Asthma related outpatient appointments: ☐

Has the participant had any further hospital admissions? Yes ☐ No ☐

Admission date/time	Discharge date/time	ICU days	HDU days	Ward days	Reason for attendance 1 = Asthma-related 2=Other	
dd/mm/20yy hh:mm	dd/mm/20yy hh:mm					
dd/mm/20yy hh:mm	dd/mm/20yy hh:mm					
dd/mm/20yy hh:mm	dd/mm/20yy hh:mm					

☆ LOCAL PI SIGNATURE: _____ DATE: / /

Appendix 7 Health-care resource use questionnaire

YOUR USE OF HEALTH SERVICES OVER THE LAST MONTH

1. Please could you tell us how many times you have used the following services for any problems (not just breathing problems) in the last month. If you cannot remember the exact number, please give an estimate. For example, if you think it was between 4 and 6 times, please put 5. If you haven't used the service, please enter 0.

SERVICE	Number of times used
Telephone health advice (e.g. GP, NHS Direct)	
GP surgery consultations	
GP home visits	
Nurse home visits	
Social worker visits	
Accident and emergency attendances	
Attendance at hospital as an outpatient	

2. Have you spent any nights as a hospital inpatient in the last month?

YES [ ] NO [ ]

If YES, how many nights were you in hospital for? _____

3. Please could you tell us what medications you have taken for your asthma over the last month?

MEDICATION (including inhalers and tablets)	DOSE	NUMBER OF TIMES PER DAY	NUMBER OF DAYS TAKEN*

*If you have been taking the medication continuously since you left hospital, just write "continuous".

4. Have you used any other treatments for your asthma over the last month? For example, have you had any other health services, private treatments or alternative treatments? If you have, please provide details in the space below.

YOUR WORK OVER THE LAST MONTH

Have you taken any time off work (from your usual paid job) in the last month?

YES [ ]
NO [ ]
I'M NOT IN PAID EMPLOYMENT [ ]

If YES- how many days did you take off in the last month

_____

FINALLY – What treatment do you think you had?

You took part in a blinded trial of magnesium sulphate. This means that you should not have known whether you were given magnesium sulphate or not. However, it is sometimes possible in a blinded trial for patients to guess, or work out, which treatment they had.

Do you think you were given magnesium sulphate?

YES [ ] NO [ ]

If you think you were given magnesium sulphate, do you think you were given it through the intravenous drip or through the nebuliser?

THE INTRAVENOUS DRIP [ ]

THE NEBULISER [ ]

PLEASE ADD ANY OTHER COMMENTS YOU HAVE IN THE SPACE BELOW OR OVER THE PAGE, THEN PUT THE QUESTIONNAIRE IN THE ENVELOPE AND RETURN IT TO US.

THANK YOU FOR YOUR HELP

Version 002, dated 11/07/2008

Appendix 8 Satisfaction with care questionnaire

PATIENT SATISFACTION WITH CARE

We are interested in your honest opinions, whether they are positive or negative, regarding the care you received when you arrived at the hospital one month ago. **Your answers will be confidential and will not be seen by any of the doctors or nurses who were caring for you.**

Please answer all of the questions. We also welcome your comments and suggestions.

Thinking about your treatment when you attended the hospital one month ago, how would you rate the following? (Please circle **one** number on each line)

1. The urgency with which you were assessed

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

2. The thoroughness of your assessment

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

3. Explanations given to you about medical procedures and tests

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

4. Attention given to what you have to say

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

5. Advice you got about ways to avoid illness and stay healthy

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

6. Friendliness and courtesy shown to you by hospital staff

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

7. Personal interest in you and your medical problems

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

8. Respect shown to you, and attention to your privacy

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

9. Reassurance and support offered to you by hospital staff

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

10. Amount of time the hospital staff gave you

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

11. Overall, how satisfied are you with the service you received?

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

Appendix 9 Investigational Medical Products Dossier

TAYSIDE PHARMACEUTICALS

Ninewells Hospital & Medical School
Dundee DD1 9SY
Tel No: (01382) 632273
Fax No. (01382) 632060

Abbreviated IMP dossier (Revised January 2010)
(to reflect change in manufacturer of IMP)

Study name: **The 3Mg Trial: A randomised controlled trial of intravenous or nebulised magnesium sulphate versus standard therapy for acute severe asthma**

Sponsor: **Sheffield Teaching Hospitals NHS Foundation Trust**

Principal Investigator: **Prof. Steve Goodacre**

EUDRACT number: **2007-001187-78**

Introduction and study outline

This study is a large scale, collaborative, Investigator led non-commercial study to evaluate the effects of nebulised or intravenous magnesium sulphate in patients attending for treatment for acute exacerbations of asthma.

The study sets out to compare three arms: intravenous magnesium sulphate with a placebo nebuliser solution, intravenous placebo with placebo nebuliser solution, and placebo intravenous solution with nebulised magnesium sulphate. It is intended to treat 1200 patients in the study. Details of the study background and rationale and a review of existing literature are given in the study protocol.

The study will be conducted in a number of treatment centres around the UK. The medication will be manufactured into blinded treatment packs by Tayside Pharmaceuticals, Dundee. The solutions will be delivered to the Pharmacy Department at the Royal Hallamshire Hospital, Sheffield for randomisation and distribution on to the study sites.

This abbreviated IMP dossier describes the formulations and production methodologies for the products required for the study.

IMP rationale

The study requires the preparation of four solutions for administration:

1. Active iv – a sterile solution containing 8mmol Mg^{2+} in 100ml Water for Injections, adjusted to isotonicity with sodium chloride.
2. Placebo iv – a sterile solution containing 0.9%w/v Sodium Chloride in Water for Injections
3. Active nebuliser solution – a sterile solution containing 2mmol in 7.5ml Water for Injections
4. Placebo nebuliser solution – a sterile solution containing 0.9% w/v Sodium Chloride in Water for Injections

All solutions are calculated to be isotonic with physiological solutions. This is of particular relevance with the nebulised solutions as both hyper- and hypotonic solutions have been shown to cause bronchoconstriction and increased airways resistance.

All raw materials have previously been used for the manufacture of pharmaceutical products under the Manufacturer's 'Specials' licence MS 14074. Similar products have been made by the unit over a number of years, utilising the same methodologies, equipment and staff. Container and closure systems have been used previously, as have the proposed analytical methodologies. All raw materials are certificated as TSE free.

It is proposed to check the actual osmolarity of the solutions during the product development process using equipment located in the hospital's clinical chemistry department. It is recognised that this equipment is not covered by the GMP accreditation of the manufacturer, however this is intended as a confirmation of calculated osmolarity and will not form a part of the product release specification – product release being based on analytical methodologies covered by the manufacturers licence.

Given the state of knowledge relating to the materials and processes used, it is not proposed to manufacture test batches of product. Bacterial endotoxin and sterility tests will be carried out following validated methods used with previous products.

Product: **Magnesium Sulphate intravenous infusion 8mmol Mg2+ in 100ml (Active IV)**

Drug Substance

Magnesium Sulphate heptahydrate Ph Eur is purchased from Fagron via Spodefel (importers). Sodium Chloride Ph Eur is purchased from Merck Chemicals. Distilled Water is obtained from the distillation plant with Tayside Pharmaceuticals. All raw materials are subjected to quality control testing on receipt to demonstrate compliance with the relevant Pharmacopoeial monograph (see appendix 1 & 2).

Manufacture

Bulk solution is prepared by dissolving weighed materials in Distilled Water and making to volume. Solution is filtered through a 0.45µ filter before filling into empty 250ml PVC infusion pouches and sealed. Solutions are sterilised by autoclaving at 121°C Sterilising parameters and conditions are validated according to HTM 2010 and the British Pharmacopoeia.

All production conditions, processes and systems used in the manufacture of this product are as stated in the application resulting in the grant of Manufacturing Licence (IMP) 14076.

Shelf life and retesting

The product is allocated a one year shelf life from the date of manufacture. This is based on previous products manufactured.

It is anticipated that the product will be used within the shelf life allocated, however in the event that product is not used by the shelf life originally allocated the shelf life may be extended by a further period not exceeding one year, following satisfactory retesting, subject to the agreement of the study Sponsor, the head of quality control, and the QP (IMP). Samples from all batches manufactured will be retained to permit full retesting if required.

Product: **Sodium Chloride intravenous infusion 0.9%w/v in 100ml (Placebo IV)**

Drug Substance

Sodium chloride Ph Eur is purchased from Merck Chemicals. Distilled Water is obtained from the distillation plant with Tayside Pharmaceuticals. All raw materials are subjected to quality control testing on receipt to demonstrate compliance with the relevant Pharmacopoeial monograph.

Manufacture

Bulk solution is prepared by dissolving weighed materials in Distilled Water and making to volume. Solution is filtered through a 0.45µ filter before filling into empty 250ml PVC infusion pouches and sealed. Solutions are sterilised by autoclaving at 121°C. Sterilising parameters and conditions are validated according to HTM 2010 and the British Pharmacopoeia.

All production conditions, processes and systems used in the manufacture of this product are as stated in the application resulting in the grant of Manufacturing Licence (IMP) 14076.

Shelf life and retesting

The product is allocated a one year shelf life from the date of manufacture. This is based on previous products manufactured.

It is anticipated that the product will be used within the shelf life allocated, however in the event that product is not used by the shelf life originally allocated the shelf life may be extended by a further period not exceeding one year, following satisfactory retesting, subject to the agreement of the study Sponsor, the head of quality control, and the QP (IMP). Samples from all batches manufactured will be retained to permit full retesting if required.

Product: **Magnesium sulphate nebuliser solution 2mmol Mg2+ in 7.5ml (Active nebuliser solution)**

Drug Substance

Magnesium sulphate heptahydrate Ph Eur is purchased from Fagron via Spodefel (importers). Distilled Water is obtained from the distillation plant with Tayside Pharmaceuticals. All raw materials are subjected to quality control testing on receipt to demonstrate compliance with the relevant Pharmacopoeial monograph.

Manufacture

Bulk solution is prepared by dissolving weighed materials in Distilled Water and making to volume. Solution is filtered through a 0.45µ filter before filling into 10ml amber glass bottles fitted with rubber bung and cap. Solutions are sterilised by autoclaving at 121°C. Sterilising parameters and conditions are validated according to HTM 2010 and the British Pharmacopoeia.

All production conditions, processes and systems used in the manufacture of this product are as stated in the application resulting in the grant of Manufacturing Licence (IMP) 14076.

Shelf life and retesting

The product is allocated a 2 year shelf life from the date of manufacture. This is based on previous products manufactured.

It is anticipated that the product will be used within the shelf life allocated, however in the event that product is not used by the shelf life originally allocated the shelf life may be extended by a further period not exceeding one year, following satisfactory retesting, subject to the agreement of the study Sponsor, the head of quality control, and the QP (IMP). Samples from all batches manufactured will be retained to permit full retesting if required.

Product: **Sodium Chloride nebuliser solution 0.9% w/v in 7.5ml (Placebo nebuliser solution)**

Drug Substance

Sodium Chloride BP is purchased from Merck Chemicals. Distilled Water is obtained from the distillation plant with Tayside Pharmaceuticals. All raw materials are subjected to quality control testing on receipt to demonstrate compliance with the relevant Pharmacopoeial monograph.

Manufacture

Bulk solution is prepared by dissolving weighed materials in Distilled Water and making to volume. Solution is filtered through a 0.45µ filter before filling into 10ml amber glass bottles fitted with rubber bung and cap. Solutions are sterilised by autoclaving at 121°C. Sterilising parameters and conditions are validated according to HTM 2010 and the British Pharmacopoeia.

All production conditions, processes and systems used in the manufacture of this product are as stated in the application resulting in the grant of Manufacturing Licence (IMP) 14076.

Shelf life and retesting

The product is allocated a 2 year shelf life from the date of manufacture. This is based on previous products manufactured.

It is anticipated that the product will be used within the shelf life allocated, however in the event that product is not used by the shelf life originally allocated the shelf life may be extended by a further period not exceeding one year, following satisfactory retesting, subject to the agreement of the study Sponsor, the head of quality control, and the QP (IMP). Samples from all batches manufactured will be retained to permit full retesting if required.

Packaging and labelling

Primary packaging for the products will be as described in individual IMP production outlines above. Following production, batches will be inspected for particulates as per standard procedures and samples taken for quality control

A set of blinded treatment kits will be assembled and labelled by Tayside pharmaceuticals as per ECGMP annex 13 requirements to enable the treatment to be identified and the batch source of the materials traced. Labelling is carried out using standard procedures to ensure traceability and separateness of active and placebo products. Treatment kits will consist of a box containing an infusion bag and 3 x nebuliser solution vials. Boxes will carry an outer label identifying the trial and kit number.

The kits will be delivered to the Pharmacy Department at the Royal Hallamshire Hospital, Sheffield with an unblinding kit number list to allow them to identify to which arm of the trial each kit belongs. The Pharmacy Department at Sheffield will label the kits with a randomisation code in accordance with a randomisation schedule supplied by the Clinical Trials Research Unit, Sheffield. This will enable the kits to be supplied on a demand basis to the participating sites with minimal waste of trial kits. The Pharmacy Department at Sheffield does not hold a current MIA licence, but this assembly service is permitted under the exemption for hospitals (regulation 37, UK SI 2004/1031).

Product testing and release

All batches will be tested in accordance with the attached technical specifications prior to release (see appendix 3, 4 & 5).

All products will be released by the QP (IMP).

Dossier compiled by:

Simon Bath
Production Manager
Tayside Pharmaceuticals
Dundee

January 2010

Appendix 1
Sheet 1 of 2

Tayside Pharmaceuticals - Quality Assurance Department
Raw Material Specification

SODIUM CHLORIDE BP

Supplier: Merck

Pack size: 25 kg

TP Code: X0174/25K

Description: White, crystalline powder or colourless crystals or white pearls..

Sampling and testing.

See Raw Material Sampling and Testing Sheet (QC2.2).

Test.

Identification:

a) Sodium. Yellow flame.

b) Chloride. Dissolve a few mg in 2 ml Distilled Water. Add 1 ml Nitric Acid 2M and 400 µl Silver Nitrate 5%. A curdled white precipitate forms which is soluble in 1.5 ml Ammonia 5M.

Loss on Drying (A%)

Dry about 1 g in the oven at 100 - 105°C for 2 hours.

Limit: Not more than 0.5%.

Assay: (Based on BP 2002 assay method – Ammonium Thiocyanate assay).

TS1 Sodium Chloride BP Approx 1 g (accurately weighed X g)
Distilled Water to 100 ml

Pipette 10ml of TS1 into a conical flask. Add 50 ml Distilled Water, 5 ml Nitric Acid 2M, 25 ml Silver Nitrate 0.1M and 2 ml Dibutyl Phthalate. Shake. Titrate with Ammonium Thiocyanate 0.1M using 2 ml of Ammonium Iron Sulphate Solution 10% (*) as indicator. Shake vigorously towards the end point. Use the 10 ml burette.

(*) – prepared by dissolving 1 g of Ammonium Iron Sulphate in 10 ml Distilled Water.

Each ml Silver Nitrate 0.1M = 0.005844 g Sodium Chloride.

$$\% \text{ Sodium Chloride} = \frac{[(25 \times SF_{AgNO_3}) - (\text{titre} \times SF_{NH_4SCN})] \times 0.005844 \times 1000}{X - (X \times A/100)}$$

Limits: 99.0 - 100.5%

Potassium Limit Test (see page 2).

Tayside Pharmaceuticals - Quality Assurance Department Sheet 2 of 2

Raw Material Specification

SODIUM CHLORIDE BP

Potassium Limit Test. See IC Sheet (QC5.19)

SS1	Potassium Standard Solution (1000mg/l)		1 ml
	Distilled Water	to	200 ml
SS2	SS1		1 ml
	Distilled Water	to	50 ml
TS2	TS1 (from assay above)		1 ml
	Distilled Water	to	50 ml

Standard Potassium value for IC = 500

Manually highlight the small Potassium peaks.

$$\text{ppm Potassium} = \frac{\text{TS2 amount}}{\text{Xg}}$$

Limit: Not more than 500 ppm

Ensure a certificate of analysis is received.

Label as enclosed.

Tayside Pharmaceuticals - Quality Assurance Department

Raw Material Specification

MAGNESIUM SULPHATE Ph Eur (Magnesii Sulfas Heptahydricus)

Supplier: Fagron

Pack size: 10 kg

TP Code: X0109/10K

Description: Brilliant, colourless crystals, or a white crystalline powder, odourless.

Sampling and testing.

See Raw Material Sampling and Testing Sheet (QC2.2).

Tests.

Identification.

a) Magnesium. Dissolve 15 mg in 2 ml Distilled Water. Add 1 ml Ammonia 5M a white precipitate forms that is redissolved by adding 1 ml Ammoniun Chloride 10.7%. Add 1 ml Disodium Hydrogen Phosphate Solution; a whit crystalline precipitate forms.

b) Sulphate. Dissolve 50 mg in 5 ml Distilled Water. Add 1 ml Hydrochloric Acid 2M and 1 ml Barium Chloride 0.25M, a white precipitate forms.

Loss on Drying

Use 500 mg.
Dry in the oven at 110°C for 1 hour then increase to 400°C for 4 hours (note temperature needle on oven will not rise above 200°C). Turn oven down to 110°C and leave for at least 30 mins. VERY CAREFULLY stopper the vessel and transfer to the dessicator and allow to cool.

Limits: 48.0 – 52.0%

Assay. (Based on BP 2008).

Dissolve 450 mg Magnesium Sulphate Ph Eur accurately weighed (X g), in 100 ml Distilled Water. Add 10 ml Ammonia Buffer pH 10.0 and 50 mg Solochrome Black Triturate. Heat to 40°C and titrate with Disodium Edetate 0.1M at this temperature. Use a 25 ml burette. Avoid overtitration by ensuring slow dropwise addition of titre with good mixing in the flask when approaching the endpoint.

$$\% \text{ Magnesium Sulphate} = \frac{\text{Titre} \times 0.01204 \times 100}{X - (X \times A/100)}$$

where A = Loss on drying above.

Tayside Pharmaceuticals - Quality Assurance Department Sheet 2 of 2

Raw Material Specification

MAGNESIUM SULPHATE Ph Eur (Magnesii Sulfas Heptahydricus)

Limits: 99.0 - 100.5%

Ensure a Certificate of Analysis is received.

Label as enclosed.

Appendix 3

Tayside Pharmaceuticals - Quality Assurance Department Sheet 1 of 2
TP Code:

MAGNESIUM SULPHATE 8MMOL IN 100ml INTRAVENOUS INFUSION SOLUTION FOR CLINICAL TRIAL

Sodium Chloride BP		g
Magnesium Sulphate BP		g
Distilled Water	to	litres (including overage)
	(Formula to prepare appropriate quantity)	

Sterilised by autoclaving at 121°C for 15 minutes

Shelf Life: One year
Shelf life based on previous products prepared

1. Check label (title, batch no., expiry date). Check worksheet and formulation.

2. Check method of sterilisation, tape etc. If satisfactory proceed to following tests.

3. Report any unusual characteristics, e.g. defect in container, particulate matter, cloudiness, or colour in solution to Quality Controller.

4. Weigh sample bag. Limits 126.5 – 138.5 g.

5. Identification.

   a) Sodium: See 8a below.

   b) Magnesium: See 8b below.

   c) Chloride: See 8c below.

   d) Sulphate: To 5 ml add 1 ml Hydrochloric Acid 2M and 1 ml Barium Chloride Solution 6.1%. A white precipitate forms.

6. pH. See pH Meter Sheet (QC5.12). Limits 4.5 - 7.0.

7. Particulate Matter. See Liquid Sampler LS-200/Liquilaz E20P Sheet (QC5.23).

   Determine the number of particles equal to or greater than 10 µm and 25 µm per ml.

   Counts per container = counts per ml x 100

   Limits: 10 µm not more than 6000 per container, 25 µm not more than 600 per container

Tayside Pharmaceuticals - Quality Assurance Department Sheet 2 of 2
TP Code:

MAGNESIUM SULPHATE 8MMOL IN 100ml INTRAVENOUS INFUSION SOLUTION FOR CLINICAL TRIAL

8. Assay.

For assay a) and b) see IC Sheet (QC5.19). Use Solutions SS2 and TS1.

SS1	Sodium Chloride BP		582 mg
	Magnesium Sulphate BP		**1.97 g**
	Distilled Water	to	100 ml
SS2	SS1		1 ml
	Distilled Water	to	50 ml
TS1	Infusion		1 ml
	Distilled Water	to	50 ml

a) Sodium.
Standard Sodium Value for IC: 0.582

% Sodium Chloride in sample = average TS1 amount

In-house release limits: 0.553 - 0.594%
Product specification: 0.553 - 0.611%

b) Magnesium.
Standard Magnesium Value for IC: 8.00

mmol Magnesium in 100ml = average TS1 amount

In-house release limits: 7.60 – 8.16 mmol in 100 ml
Product specification: 7.60 – 8.40 mmol in 100 ml

c) Chloride. See Chloride Meter Sheet (QC5.4).

Use the infusion. Sample Volume 100 µl.

In-house release limits: 95 - 102 mEq/litre
Product specification: 95 - 105 mEq/litre

9. Bacterial Endotoxins. See Test for Endotoxins Sheet.

10. Sterility. See Sterility Test Sheet.

11. Complete Certificate of Analysis and record sheet, initial and pass to quality controller.

12. Release follows Procedure QC3.8. All details and compliance with Production Worksheet and QA Specifications are checked including randomisation and specific patient numbering. Batch is approved for release by a Quality Assurance Pharmacist who is a QP(IMP) and a record of release is kept in the Register of Clinical Trial Batches.

Appendix 4

Tayside Pharmaceuticals - Quality Assurance Department Sheet 1 of 2

PLACEBO INFUSION FOR CLINICAL TRIAL (MATCHING MAGNESIUM SULPHATE 8MMOL IN 100ml SODIUM CHLORIDE 0.9% INTRAVENOUS INFUSION)

Sodium Chloride BP	g	
Distilled Water	to	litres (including overage)
	(Formula to prepare appropriate quantity)	

Shelf Life: One year.

1. Check label. See overleaf, batch number and expiry date. Check worksheet. If satisfactory proceed to following tests.

2. Check method of sterilistion, tape etc. If satisfactory proceed to following tests.

3. Report any unusual characteristics, e.g. defect in container, particulate matter, cloudiness or colour in solution to Quality Controller.

4. Weigh sample bag. Limits: 125.5 – 138.5 g.

5. Identification.

   (a) Sodium. Yellow flame test.

   (b) Chloride. See 8 below.

6. pH. See pH Meter Sheet (QC5.12).

9. Particulate Matter. See Liquid Sampler LS-200/Liquilaz E20P Sheet (QC5.23).

   Determine the number of particles equal to or greater than 10 µm and 25 µm per ml.

   Counts per container = counts per ml x 100

   Limits: 10 µm not more than 6000 per container, 25 µm not more than 600 per container

10. Assay.

    Chloride. See Chloride Meter Sheet (QC5.4).

    Use the infusion. Sample Volume 100 µl.

    In-house release limits: 146 - 157 mEq/litre
    Product specification: 146 - 162 mEq/litre

9. Bacterial Endotoxins. See Test for Endotoxins Sheet.

10. Sterility. See Sterility Test Sheet.

Tayside Pharmaceuticals - Quality Assurance Department Sheet 2 of 2

PLACEBO INFUSION FOR CLINICAL TRIAL (MATCHING MAGNESIUM SULPHATE 8MMOL IN 100ml SODIUM CHLORIDE 0.9% INTRAVENOUS INFUSION)

11. Complete Certificate of Analysis and record sheet, initial and pass to Quality Controller.

12. Release follows Procedure QC3.8. All details and compliance with Production Worksheet and QA Specifications are checked including randomisation and specific patient numbering. Batch is approved for release by a Quality Assurance Pharmacist who is a QP(IMP) and a record of release is kept in the Register of Clinical Trial Batches.

Appendix 5

Tayside Pharmaceuticals - Quality Assurance Department Sheet 1 of 3

PLACEBO NEBULISER SOLUTION FOR CLINICAL TRIAL (SODIUM CHLORIDE 0.9%) 7.5 ml Fill 10 ml bottles

TP Code:

Sodium Chloride BP g
Distilled Water to ml (including overage)
(Formula to prepare appropriate quantity)

Sterilised by autoclaving at 121°C for 15 minutes.
Shelf Life: Two years

1. Check label. See overleaf, batch number and expiry date. Check worksheet and formulation.

2. Check method of sterilisation, tape, etc. If satisfactory proceed to following tests.

3. Report any unusual characteristics, e.g. defect in container, particulate matter, cloudiness or colour in solution to Quality Controller.

4. Measure the Volume. Limits: 7.5 – 7.8 ml

5. Identification.
   a) Sodium: Yellow flame test.
   b) Chloride: See 7 below.

6. pH. See pH Meter Sheet (QC5.12).

7. Assay.

   Chloride: See Chloride Meter Sheet (QC5.4).

   Sample volume 100 µl of TS1

   Limits: 146 - 162 mEq/L

8. Sterility. See Sterility Test Sheet.

9. Complete Certificate of Analysis and record sheet, initial and pass to Quality Controller.

10. Release follows Procedure QC3.8. All details and compliance with Production Worksheet and QA Specifications are checked including randomisation and specific patient numbering. Batch is approved for release by a Quality Assurance Pharmacist who is a QP(IMP) and a record of release is kept in the Register of Clinical Trial Batches.

Appendix 5

Tayside Pharmaceuticals - Quality Assurance Department Sheet 2 of 3

MAGNESIUM SULPHATE 2MMOL NEBULISER SOLUTION FOR CLINICAL TRIAL 7.5 ml Fill 10 ml bottles
TP Code:

Magnesium Sulphate BP g
Distilled Water to ml (including overage)
(Formula to prepare appropriate quantity)

Sterilised by autoclaving at 121°C for 15 minutes.
Shelf Life: Two years

1. Check label. See overleaf, batch number and expiry date. Check worksheet and formulation.

2. Check method of sterilisation, tape, etc. If satisfactory proceed to following tests.

3. Report any unusual characteristics, e.g. defect in container, particulate matter, cloudiness or colour in solution to Quality Controller.

4. Measure the Volume. Limits: 7.5 – 7.8 ml

5. Identification.
   a) Magnesium: See 7a below.
   b) Sulphate: To 5 ml add 1 ml Hydrochloric Acid 2M and 1 ml Barium Chloride Solution 6.1%. A white precipitate forms.

6. pH. See pH Meter Sheet (QC5.12).

8. Assay.

   a) Magnesium: See IC Sheet (QC5.19). Use Solutions SS2 and TS1.

SS1	Magnesium Sulphate BP		6.567 g
	Distilled Water	to	100 ml
SS2	SS1		1.33 ml
	Distilled Water	to	200 ml
TS1	Nebuliser Solution		1.33 ml
	Distilled Water	to	200 ml

Standard Magnesium Value for IC: 2.00

mmol Magnesium in 7.5ml = average TS1 amount

Limits: 1.90 – 2.10 mmol in 7.5 ml

MAGNESIUM SULPHATE 2MMOL NEBULISER SOLUTION FOR CLINICAL TRIAL 7.5 ml Fill 10 ml bottles
TP Code:

8. Sterility. See Sterility Test Sheet.

10. Complete Certificate of Analysis and record sheet, initial and pass to Quality Controller.

10. Release follows Procedure QC3.8. All details and compliance with Production Worksheet and QA Specifications are checked including randomisation and specific patient numbering. Batch is approved for release by a Quality Assurance Pharmacist who is a QP(IMP) and a record of release is kept in the Register of Clinical Trial Batches.

Appendix 10 Investigator's brochure

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

The 3Mg Trial

HTA 06/01/02: Magnesium Sulphate for treatment of severe acute asthma

Investigator's Brochure

Version 2.00

5th January 2009

Introduction

This study compares the effectiveness and cost-effectiveness of intravenous (IV) and nebulised magnesium sulphate in severe acute asthma, in order to determine whether either should be standard first line treatment for patients presenting to the emergency department with acute severe asthma.

Previous studies have compared IV magnesium sulphate with placebo and have shown some improvement in pulmonary function, but the clinical significance of this effect in uncertain. Similarly nebulised magnesium has been shown to have benefit in some studies but the results are inconclusive. No studies comparing the two treatments have been identified. The study protocol contains a detailed account of the prior studies reviewed. One further randomised trial of IV magnesium sulphate has been published in the Iranian journal of allergy, asthma, and immunology in the past year (Singh AK et al, 2008). Patients presenting to the Emergency Department with acute severe asthma received standard therapy (IV hydrocortisone, 3 x nebulised salbutamol and ipratropium) and then either 2g IV Magnesium Sulphate or IV normal saline (N=30 in each arm). IV magnesium sulphate was associated with greater change in %predicted FEV1 from baseline (Mean Difference= 6.07%, C.I.1.87-10.62, $p<0.01$) and discharge rates (log rank.=6.8, $p<0.05$). We are currently seeking full details of this study to incorporate it into the existing meta-analysis. We anticipate that the addition of 60 cases from this study to the 1137 in the meta-analysis is unlikely to alter the overall findings. There have been no further publications assessing the use of nebulised magnesium sulphate.

Confidentiality statement

The information contained within the Investigator's Brochure is provided for the use of Investigators and participants in the study including relevant Independent Review Boards / Independent Ethics Committees.

Physical, chemical and pharmaceutical properties and formulation

Magnesium chloride is an inorganic salt with a long history of usage as a pharmaceutical material. Presentations of magnesium sulphate for oral or topical use are available for sale to the public. Other preparations containing magnesium sulphate are used for a variety of purposes including the treatment of hypomagnesaemia, arrhythmias, as an anticonvulsant for eclampsia and pre-eclampsia, and for the prevention of premature labour. There are a number of licensed injectable preparations suitable for intravenous or intramuscular use, which are formulated as simple solutions in water for injections and sterilised by autoclaving. Magnesium sulphate and magnesium sulphate injection are subject to monographs in the European Pharmacopoeia.

The presentations used in this study are formulated as solutions either for intravenous infusion or for nebulisation. Both formulations are adjusted to isotonicity by the addition of an appropriate quantity of sodium chloride. Details of the formulations in use are given in the Investigational Medicinal Products Dossier.

Non clinical safety studies

No non-clinical safety studies have been conducted in support of this study.

Clinical safety and efficacy

Historical use of magnesium sulphate has identified the following adverse events:

Hypermagnesaemia – symptoms of hypermagnesaemia include nausea, vomiting, flushing of the skin, thirst, hypotension due to neuromuscular blockade, muscle weakness, respiratory depression, cardiac arrhythmias, coma and cardiac arrest.

Hypersensitivity – cases of hypersensitivity reactions to magnesium sulphate have been reported.

Cautions and interactions:

Magnesium sulphate must be used with caution in patients suspected of or known to have renal impairment. Magnesium Sulphate should not be used in hepatic coma if there is a risk of renal failure.

Administer with caution to patients receiving digitalis glycosides. Magnesium sulphate should not be administered concomitantly with high doses of barbiturates, opioids or hypnotics due to the risk of respiratory depression.

The action of non-depolarising muscle relaxants such as tubocurarine is potentiated and prolonged by parenteral magnesium salts.

Profound hypotension has been reported with concomitant use of nifedipine.

Safety in human pregnancy and during breastfeeding has not been established, therefore, as with all drugs it is not advisable to administer magnesium sulphate during pregnancy or breastfeeding unless considered essential, and it must be administered under medical supervision.

No specific clinical safety studies have been conducted in support of this study.

Marketing experience

No presentations are currently marketed for the indication under investigation in this study, hence there is no relevant marketing experience to draw on. There is, however a significant volume of clinical experience in using magnesium salts by both the intravenous and nebulised route, to the extent that these indications are described in the current British National Formulary (Volume 54, September 2007, page 146).

Summary

Magnesium sulphate is a well understood pharmaceutical material commonly used in a variety of forms for the treatment of a broad range of conditions. Adverse events associated with the IV use of magnesium salts are well described and clearly associated with the known properties of magnesium and its role in physiological processes.

No non-clinical or clinical safety studies have been conducted in support of this study. Safety information presented in this brochure has been taken from reference texts and SPCs for licensed injectable preparations of magnesium sulphate.

Appendix 11 Trial protocol

Version 7, 28MARCH11

This was the current version of the protocol at the end of the trial.

HTA 06/01/02: Magnesium sulphate for treatment of severe acute asthma

Project Title: The 3Mg Trial

Planned investigation

Research objectives
We aim to measure the effectiveness and cost-effectiveness of intravenous (IV) and nebulised magnesium sulphate in acute severe asthma and thus determine whether either should be standard first-line treatment for patients presenting to the emergency department with acute severe asthma.

We plan to test the following specific hypotheses:

1. IV or nebulised magnesium sulphate will reduce the proportion of patients who require admission at initial presentation or during the following week
2. IV or nebulised magnesium sulphate will improve patient's assessment of their breathlessness over two hours after initiation of treatment

We will also measure the effect of IV or nebulised magnesium sulphate upon:

1. Length of hospital stay and use of high-dependency or intensive care
2. Mortality, adverse events and use of respiratory support
3. Change in peak expiratory flow rate (PEFR) and physiological variables after initial treatment
4. Patient reported health utility
5. Patient satisfaction with care
6. Use of health and social services over the following month
7. Time taken by patients off work
8. Health and social care costs and productivity losses

Existing research
We have systematically reviewed the literature to identify meta-analyses or randomised trials comparing magnesium sulphate (IV or nebulised) to control treatment, or comparing between nebulised and IV magnesium sulphate.

IV magnesium sulphate compared to control
We identified four meta-analyses[1-4] (one in adults[1], one in children[2] and two mixed[3,4]) and 15 randomised trials[5-19] (nine in adults[5-13] and six in children[14-19]) comparing IV magnesium sulphate to placebo. The trials of adults used a bolus dose of either 1.2g or 2.0g of magnesium sulphate, given over 20 to 30 minutes. Only one trial followed the bolus dose with an infusion.

The three meta-analyses involving adults were all published in 2000. Each analysis identified a different number of trials and reached different conclusions. Rowe et al[3] identified five adult and two paediatric trials involving a total of 668 patients and concluded that over all trials magnesium sulphate therapy did not significantly improve peak expiratory flow rate (PEFR) or reduce admission to hospital. However, subgroup analysis suggested that in trials of severe asthma magnesium sulphate

therapy was associated with significant improvements in PEFR and reduced hospital admissions. Alter et al[4] identified seven adult and two paediatric trials involving a total of 859 patients and found that magnesium sulphate was associated with a significant improvement in spirometric airway function by 16% of a standard deviation. They concluded that the clinical significance of this effect was uncertain. Rodrigo et al[1] identified five adult trials involving a total of 374 patients and found no significant effect from magnesium sulphate upon pulmonary function or hospital admissions. Cheuk et al[2] undertook a meta-analysis of five trials[13-18] of IV magnesium sulphate in children with acute asthma. They did not include one trial that was published in Portuguese[19]. Magnesium sulphate was effective in reducing hospital admissions (OR 0.290; 95% CI 0.143 to 0.589) and improving pulmonary function tests and clinical symptoms.

We have updated the meta-analysis of IV magnesium sulphate in adults to include all nine adult trials[5-13]. The pooled relative risk for hospital admission after treatment with IV magnesium sulphate is 0.91 (95% CI 0.78 to 1.07; p=0.27) and the pooled standardised mean difference in pulmonary function is 0.15 (0.01 to 0.29; p=0.035). We conclude that treatment with IV magnesium sulphate is associated with a modest improvement in pulmonary function, but the clinical significance of this effect is uncertain. Although there is no significant effect upon hospital admission we cannot exclude a potentially important reduction in admissions of up to 22%. Current evidence is therefore insufficient to either recommend IV magnesium sulphate as standard treatment for acute severe asthma or rule out a potentially valuable role. This uncertainty is reflected in current guidelines from the British Thoracic Society (BTS) and Scottish Intercollegiate Guideline Network (SIGN)[20], which suggest that IV magnesium sulphate should be considered in patients with severe acute asthma that has not responded to initial treatment with salbutamol nebulisers and steroids.

Nebulised magnesium sulphate compared to control

We identified two meta-analyses[21,22] (both mixed adults and children) and eight randomised trials[23-30] (five in adults[23-27], two in children[28,29] and one mixed[30]) comparing nebulised magnesium sulphate to placebo. The meta-analyses both included the same six randomised trials[23-25,28-30] involving a total of 296 patients but did not include two recently published trials[26,27]. The dose of magnesium sulphate used ranged from 95mg to 500mg, given up to four times, with doses every 20 to 30 minutes. Both reviews concluded that current evidence could not conclusively determine the role of nebulised magnesium sulphate in acute asthma.

We have undertaken a meta-analysis of six trials of nebulised magnesium sulphate in adults[23-27] or a mixed population[30]. The pooled relative risk for hospital admission after treatment with IV magnesium sulphate was 0.66 (95% CI 0.44 to 1.00; p=0.048) and the pooled standardised mean difference in pulmonary function was 0.20 (-0.02 to 0.42; p=0.076). Although the effect of nebulised magnesium sulphate upon hospital admissions is just significant, most of the admissions in this analysis were in one trial[25] and the effect was not consistent across other trials. We conclude that there is currently inadequate evidence to either support nebulised magnesium sulphate as standard treatment for acute severe asthma or rule out a potentially valuable role.

Comparison between IV and nebulised magnesium sulphate

We identified no trials comparing intravenous to nebulised magnesium sulphate.

The need for a large randomised trial

A large randomised trial is needed to determine the role of intravenous or nebulised magnesium sulphate in acute severe asthma for the following reasons:

1. Studies included in both meta-analyses were relatively small and were powered to detect changes in pulmonary function. Even if meta-analysis shows a statistically significant difference in pulmonary function it is not clear whether such changes are important to patients or affect their clinical outcome.
2. Factors such as publication bias may influence selection of studies into meta-analysis, leading to over-estimates of effectiveness. It has been noted that 35% of subsequent large trials conflict with the results of previous meta-analysis[31].
3. The clinically important change in admission rate in patients with severe asthma identified in the meta-analysis by Rowe et al[3] was based upon post-hoc subgroup analysis. Such findings should be confirmed in a pre-planned analysis before they are accepted.
4. A large trial would allow head-to-head comparison of nebulised versus IV magnesium sulphate as well as comparing each treatment to standard therapy.

Trials in progress

A search of the National Research Register identified one trial of nebulised magnesium sulphate in children with acute asthma currently being undertaken in Wales[32], and a trial of nebulised magnesium sulphate in an unspecified population planned for 2002 that does not appear to have been undertaken[33]. A search of ClinicalTrials.gov identified no relevant studies in progress.

We conclude from the existing literature that there is some evidence that intravenous or nebulised magnesium sulphate can improve measures of pulmonary function, but there is no direct comparison between these two treatments and no reliable evidence that either treatment can improve measures that are important to the patient or effect their clinical outcome.

Research methods

We will undertake a multi-centre, double blind, placebo controlled, three-arm, randomised trial in up to 40 emergency departments in the United Kingdom. Eligible patients will be identified by medical staff and written or oral informed consent sought from the patient (as outlined in Medicine for Human Use (Clinical Trials) Regulations 2004).

Consented participants will be randomised either online via a secure browser or by telephone to the Sheffield Clinical Trials Research Unit (CTRU). A simple randomisation sequence[34] will be used to allocate participants to numbered treatment packs kept in the emergency department. The CTRU will only reveal the allocated pack number after patient details have been recorded and the patient irreversibly entered into the trial. Each treatment pack will contain an intravenous infusion and a nebuliser solution, either of which could be active treatment or placebo. Participants, hospital staff and research staff will all be blind to allocated treatment.

Clinical staff will record baseline data, details of co-interventions and outcome data up to two hours after presentation. Further data will be collected at one month after

recruitment by research nurses using routine data sources and by patient self-completion questionnaire.

Planned interventions
Patients will be randomised to one of three treatment arms. Each treatment arm will receive one intravenous and one nebulised treatment. The intravenous infusions and nebuliser vials will each be prepared as apparently identical solutions to ensure blinding. The treatment allocation method will be stratified randomisation, with stratification by Hospital.

The three treatment arms are as follows:

Treatment arm	Intravenous infusion	Nebulisers
1	Intravenous magnesium sulphate, 8 mmol (2g) in 100ml Water for Injections, adjusted to isotonicity with sodium chloride, given over 20 minutes	7.5ml vial of 0.9% saline, given 3 times 20 minutes apart
2	Intravenous 0.9% saline, 100ml given over 20 minutes	7.5ml vial of 2 mmol (500mg) magnesium sulphate, given 3 times 20 minutes apart
3	Intravenous 0.9% saline, 100ml given over 20 minutes	7.5ml vial of 0.9% saline, given 3 times 20 minutes apart

All three groups will receive standard therapy, according to BTS/SIGN guidelines. Recommended standard therapy will be high flow oxygen, nebulised salbutamol (5mg), nebulised ipratropium (500mcg) and oral prednisolone, administered during recruitment, followed by up to 5mg salbutamol added to each trial nebuliser. Other treatments will be given at the discretion of the attending clinician and recorded on the data collection form.

Patients will be managed in the emergency department and data collected until two hours after randomisation. At this point, if not already undertaken, a final disposition decision will be made (hospital admission or discharge) and initial data collection completed.

Planned inclusion/exclusion criteria
We will recruit adults (age>16) admitted to the emergency department with acute severe asthma as defined by the BTS/SIGN guidelines, i.e. acute asthma with either PEFR < 50% of best or predicted, respiratory rate > 25/min, heart rate > 110/min, or inability to complete sentences in one breath.

We will exclude:

1. Patients with life threatening features (oxygen saturation < 92%, silent chest, cyanosis, poor respiratory effort, bradycardia, arrhythmia, hypotension, exhaustion, coma or confusion).
2. Patients who are unable to provide written or oral informed consent
3. Patients with a contraindication to either nebulised or intravenous magnesium sulphate: pregnancy, hepatic or renal failure, heart block or known hypermagnesaemia.
4. Patients who have received IV or nebulised magnesium sulphate in the previous 24 hours prior to admission to the emergency department.
5. Known previous participants in the 3Mg Trial

We will collect basic details (age, sex and admission/discharge after emergency department management) on all eligible patients to allow completion of a CONSORT flow chart.

Proposed outcome measures

We will measure two primary outcomes:

1. The health service primary outcome will be the proportion of patients who are admitted to hospital, either after emergency department treatment or at any time over the subsequent week.
2. The patient-centred primary outcome will be the patient's visual analogue scale (VAS) (an existing validated measure) for breathlessness over two hours after initiation of treatment.

Secondary outcomes will include mortality, adverse events, use of ventilation or respiratory support, length of hospital stay, use of high dependency or intensive care, change in PEFR and physiological variables (oxygen saturation, heart rate, respiratory rate) over two hours, quality of life at baseline and one month (measured by EQ-5D- an existing validated measure of quality of life), number of unscheduled health care contacts (emergency department, walk-in centre or general practitioner attendances) over the subsequent month, and satisfaction with care (measured by a modified Group Health Association of America survey).

Choice of outcome measures

Previous studies (outlined in the meta-analysis) have used measures of respiratory function, such as PEFR, as their primary outcome. In some studies these have shown that treatment with IV or nebulised magnesium sulphate may be associated with significant changes in PEFR. However, it is not clear whether these changes lead to important changes in patient management or a clinically meaningful improvement in symptoms.

We have selected two primary outcomes to identify important changes in patient management and symptoms of asthma: admission to hospital and breathlessness measured on a VAS. These outcomes have been chosen after literature review and consultation with our consumer representatives, and reflect health service and patient perspectives respectively. Our consumer representatives have indicated that avoiding hospital admission is an important outcome for patients, as well as being an important health service outcome.

We have decided to include any admission over the following week in the primary outcome of hospital admission because this time period would encompass the expected duration of an asthma exacerbation and a typical course of associated treatment. Admission during this time would therefore represent an overall failure of treatment, whereas admission later than one week would more appropriately be considered as being a separate episode.

We considered two potential methods for measuring breathlessness: the VAS and the Borg Scale. Both have been used to measure breathlessness during exercise[35] but have only recently been tested in acute asthma. Kendrick et al[36] showed that the Borg Scale correlated with measures of respiratory function in a cohort of patients with asthma or chronic obstructive pulmonary disease, while Karras[37] and Gupta[38] showed correlation between the VAS and measures of respiratory function in cohorts with acute asthma. The study by Karras also showed that mean VAS change among patients who reported their asthma to be "a little better" after treatment was 2.2cm on a 10cm VAS, and concluded that this represented a minimum clinically significant change. On the basis of these studies we conclude that the VAS is the best-validated measure, it offers a simple and reliable means of measuring symptomatic breathlessness in people with acute asthma, and we have an estimate a minimum clinically significant change in VAS. Our consumer representatives have reviewed the VAS and found it acceptable.

We have abundant previous experience of measuring health utility, satisfaction with care and resource by postal questionnaire. The questionnaires we plan to use are based on validated instruments and have been used successfully by our group in clinical trials, typically achieving response rates of 70-80%. Our consumer representatives have reviewed the questionnaire and modifications have been made in accordance with their suggestions. The current draft of the questionnaire is attached as an appendix. Non-responders to the questionnaire will be sent one reminder after two weeks. Non-responders at four weeks after the original mailing will be contacted by telephone.

Outcomes will be measured in two phases: 1) Over two hours after randomisation, and 2) At one month after attendance. During the first phase we will measure variables, such as VAS, PEFR and physiological variables, which reflect patient response to emergency treatment. During the second phase we will measure variables, such as adverse events, use of health services, satisfaction with care and quality of life, that reflect the overall patient experience of an asthma attack and its subsequent treatment.

Proposed sample size

We plan to recruit 1200 participants divided equally between the three trial arms (400 per arm) over two years at up to 40 hospitals selected from those participating in the 3CPO, CRASH2 and ESCAPE trials. Hospitals have been selected on the basis of recruitment rates in previous trials. Audit data suggest that around ten patients per month will be eligible at each hospital. However, our experience (3CPO and CRASH2 trials) suggests that audit data substantially over-estimate the actual availability of eligible patients. Therefore, we assume that each hospital will recruit 50 patients per year, after exclusion of those recruited in error. We will carefully monitor recruitment at participating hospitals and will activate contingency plans,

including addition of new sites or replacement of under-performing sites, if recruitment is not close to target.

We anticipate that the health service primary outcome (see section 3.6) will be recorded for all participants, but it is possible that a small proportion of cases will not have their patient-centred primary outcome measured. The sample size will therefore provide the following statistical power:

1. Proportion of patients admitted: Audit data at participating hospitals suggest that 80% of patients with severe asthma are admitted after emergency department management. The study will thus have 90% power to detect a 10% absolute reduction in the proportion admitted (i.e. to 70%) for any pair of treatment groups compared (two-sided alpha=0.05).
2. Breathlessness measured on a visual analogue score (VAS): Previous data have established that the standard deviation of this measure on a 10cm VAS is 3cm, and that 2.2cm on a 10cm VAS represents a minimum clinically significant difference[37]. If we take a pessimistic assumption that 20% of participants will not have their VAS measured then the study will still have 90% power to detect a 0.8cm difference in a 10cm VAS at two hours after treatment initiation (two-sided alpha=0.05).

Statistical analysis

Analysis will be undertaken on an intention-to-treat basis with participants being analysed in the groups they were allocated to regardless of whether they actually received or completed the allocated treatment. Imputations will be made for missing data to check if results are affected by patterns of missing values. The analysis will use logistic regression for admissions and linear regression (with possible transformations) for breathlessness. The primary analysis will be adjusted for hospital. Further analyses will be performed to assess the robustness of the findings to potential differences in baseline characteristics, in particular initial breathlessness (VAS) and age. Although the primary analysis will be intention-to-treat, a secondary explanatory analysis will be undertaken limited to those who completed the treatment as per protocol.

We will use Simes's (1986) method, which is a modification of the Bonferroni method but has better power, to adjust for multiplicity arising from having two primary outcomes. We will obtain two P-values for the two outcomes. We will order them $P_1<P_2$. The null hypothesis (that the two treatments are equivalent in both dimensions) will be rejected at 5% if *either* $P_1<0.025$ *or* $P_2<0.05$[39]. Thus if $0.025<P_1<0.05$ and $P_2>0.05$ we would not reject the null hypothesis, but if both $0.025<P_1<0.05$ and $0.025<P_2<0.05$ we would reject the null hypothesis (unlike a strict Bonferroni interpretation). However, we would not adjust the confidence intervals associated with the estimate of the treatment effect with each outcome[40].

We will test the two hypotheses simultaneously through the analysis of variance. If we have three groups A=nebuliser, B=intravenous and C=control, we will have 2 degrees of freedom for analysis, which we will split into 2 orthogonal contrasts (-2, +1, +1) to contrast both active treatments versus control and (0, -1, +1) to contrast the active treatments.

We have planned three sub-group analyses in advance, within which patients will be stratified on the basis of:

1. Asthma severity, above or below median baseline PEFR (% predicted). A previous meta-analysis[3] has suggested that IV magnesium sulphate is more effective in patients with severe asthma.
2. Age, above or below 50 years. Older patients with a diagnosis of asthma are more likely to have chronic respiratory disease that may be less responsive to treatment with magnesium sulphate.
3. Treatment before arrival. We will be recruiting patients on arrival at hospital, thus testing magnesium sulphate as a first-line treatment. However, some patients may have received prehospital treatment with nebulisers, thus making magnesium sulphate in effect a second-line treatment. Patients with severe asthma after receiving prehospital treatment are likely to have more severe asthma than those presenting without prehospital treatment.

Economic evaluation

We will take a health care perspective to estimate the incremental cost per QALY and the incremental cost per change in breathlessness on the VAS for the two most effective treatments.

Measurement and valuation of costs

We will measure health care resource use (including emergency department visits, hospital admission, general practitioner and outpatient visits, tests and treatments), social care resource use and productivity losses over the subsequent month, using case record review and patient self-completion questionnaire. Resources will be valued using national units costs wherever possible including the Personal Social Services Research Unit Database[39] and NHS Reference Costs[40] to estimate health and social care costs. Where national costs are unavailable, local unit costs will be obtained from the health care centres in the trial locations. Average daily wage rates from the Office of National Statistics will be used to estimate the costs of lost productivity, up to one month after recruitment.[41]

Cost-effectiveness analysis

Cost analysis will compare bootstrap estimates of the mean cost per patient of the three groups, and will be presented alongside outcome data as a cost-consequences analysis. We will then estimate the incremental cost per QALY and the incremental cost per change in breathlessness VAS for the two most effective treatments. The primary analysis will take a health care perspective. Secondary analysis will explore the potential impact of including social care costs and costs due to productivity losses in the analysis. The validity of the base case results will be confirmed by a probabilistic sensitivity analysis using bootstrapping, where the original data is used to provide an empirical estimate of the sampling distribution through repeated re-sampling from the observed data.[42] Sensitivity analyses will explore the potential impact of changing key assumptions used in the main analysis and, in particular, the potential impact of rare but serious adverse outcomes upon the robustness of conclusions.

Additional analysis: Predictors of relapse after initial successful treatment

To maximise the value of this project, we plan to undertake an additional analysis of trial data to identify factors that predict relapse after initial successful treatment for

acute severe asthma. Predicting relapse after initial treatment would be helpful for deciding which patients need asthma nurse review after discharge[43], which need hospital admission, and which need high dependency or intensive care. Currently these decisions are made largely upon PEFR recordings, although it is not clear how useful these are as predictors of relapse.

Data collection for the trial will include variables that may be potentially useful predictors of subsequent relapse, such as baseline and post-treatment PEFR, physiological variables, age, sex, smoking status, and previous hospital, high dependency and intensive care admissions. We will examine the ability of these factors to predict asthma relapse, defined at two levels: 1) Relapse requiring high dependency or intensive care, i.e. any patient requiring airway management, respiratory support or cardiopulmonary resuscitation, or suffering respiratory arrest, cardiac arrhythmia or death within one week of initial attendance; 2) Relapse requiring hospital admission, i.e. any patient requiring emergency medical treatment within one week of presentation, either by attendance at the emergency department or unscheduled inpatient review. Univariate analysis will be undertaken using Chi-square test for categorical variables and t-test for continuous variables to identify factors that are associated with either outcome ($p<0.1$). These factors will then be entered into a multivariate model for each outcome to identify independent predictors of relapse ($P<0.05$).

Ethical arrangements

The Trial will be undertaken in accordance with the Medicine for Human Use (Clinical Trials) Regulations 2004. The main ethical challenge is that potential participants will be acutely ill and may initially lack capacity to provide informed consent, or the ability to complete a written consent form, yet the very nature of the trial requires that recruitment take place quickly in an emergency and includes acutely ill patients. We have extensive experience of seeking informed consent from acutely ill patients in the emergency setting and, through the CRASH2 Trial, have specific experience of developing consent procedures under the EU Clinical Trials Directive. Professor Tim Coats, as Principal Investigator of the CRASH2 Trial, has pioneered the development of Professional Legal Representatives in the emergency setting[44,45].

Participants will only be recruited into the trial if they can provide informed consent. We will use the following process for seeking consent, based upon Medicine for Human Use (Clinical Trials) Regulations 2004 and taking into account the opinions of ethics committee review (Scotland A Research Ethics Committee, 30 April 2007).

1. All patients will be given emergency treatment with high flow oxygen, salbutamol nebuliser (5mg) and ipratropium nebuliser (500mcg) while consent is being sought. Initial investigations, such as arterial blood gas sampling and chest radiography will continue simultaneously.
2. Potential participants will be given the initial information sheet and asked if they would wish to consider participation in the trial.
3. Those that would consider participation will be given further verbal information.
4. Potential participants who are able to express their consent and able to complete the consent form will be asked to provide written consent.

5. Potential participants who are able to express their consent, but unable to complete the consent form will be recorded on the consent form as having provided verbal consent.
6. If the potential participant is not competent to give written or verbal consent then they will not be recruited into the trial.
7. Every recruited participant will be reviewed at regular intervals during their treatment. As soon as their condition improves they will be provided with the full information sheet. Those who have completed a written consent form will be asked if they are happy to remain in the trial. Those who have not completed a written consent form will be asked to do so. We anticipate that most participants will be well enough to provide written consent by the end of their initial treatment in the emergency department. The few who are not will be identified and reviewed the following day by the Research Nurse. In the unlikely event that a patient leaves hospital without giving written consent the central trial team may write to the patient to ask them to confirm consent and complete the written consent form.

The risks to participants in this trial are low. Magnesium sulphate has been used by IV and nebulised routes in a number of trials and, although unlicensed, is frequently used in the treatment of acute severe asthma. It is also included as a possible treatment for acute asthma in current BTS/SIGN guidelines. Although minor side effects such as nausea or flushing are common, serious side effects (arrhythmias and coma) are uncommon. Potential participants will be advised of these risks when they are invited to participate.

We have consulted consumer representatives in developing patient information and consent procedures. Current drafts of the consent form and patient information sheet are included as appendices.

Research governance
The trial will be conducted in accordance with MRC Guidelines for Good Clinical Practice in Clinical Trials and Medicine for Human Use (Clinical Trials) Regulations 2004. Sheffield Teaching Hospitals NHS Foundation Trust will act as the Sponsor for the trial.

The trial will be covered by clinical trial regulations from the Medicines and Healthcare products Regulatory Agency (MHRA). We will apply for Clinical Trial Authorisation from the MHRA and have included an estimate of the costs of application, administration and audit in the budget for this project.

Blinded treatment packs will be manufactured in conjunction with the CTRU by Tayside Pharmaceuticals, who will maintain an Investigational Medical Products dossier and relevant documentation. The packs will be delivered to the Pharmacy Department at the Royal Hallamshire Hospital (RHH), Sheffield and labelled with a participant number in accordance with a randomisation schedule supplied by the CTRU. Blinded packs will be distributed to the study sites by RHH Pharmacy Department.

Three committees will be established to govern the conduct of this study:

1. Trial Steering Committee
2. Independent Data Monitoring and Ethics Committee
3. Trial Management Group

These committees will function in accordance with Sheffield CTRU standard operating procedures. The Trial Steering Committee will consist of the Principal Investigator, one of the co-applicants, an independent chair, two independent members and a consumer representative. We will also invite a representative of the HTA Board to join the committee. The Data Monitoring and Ethics Committee will consist of a minimum of an independent statistician, emergency physician and respiratory physician, who will be asked to review trial data at regular intervals and implement stopping rules in accordance with MRC guidance. The Trial Management Group will consist of the Principal Investigator, Co-applicants, Project Manager, Statistician and Research Nurses.

Reporting of serious adverse events

Serious adverse events (SAEs) will be reported in accordance with the 3Mg Trial SAE reporting protocol and the sponsor's (STH) Standard Operating Procedure for Recording, Managing and Recording Adverse Events for STH studies. All SAEs will be reported immediately to the sponsor on learning of their occurrence. Site trial staff and delegated ED staff are responsible for recording all adverse events that are reported by the participant and making them known to the PI. The sponsor's (STH) SAE reporting procedures require that all concomitant medications given during the trial duration (30 days post-trial drug administration) are listed on the SAE reporting form.

Magnesium sulphate is a naturally occurring compound that is a normal constituent of the human body, and since the trial involves administering magnesium sulphate over a single one-hour period, it can be expected that any effect upon other medications would be limited to the first few hours after administration. Thus, the SAE reporting procedure for the 3Mg trial will record only those concomitant medications given in the 48-hour period after the trial drug (IV or nebulised magnesium sulphate or sodium chloride) is administered.

Data management

Trial data will be entered into a validated database system built to a specification agreed between Sheffield CTRU and the Principal Investigator. The system will be accessible remotely via a web browser, with the data stored securely on a central server. Access will be controlled by the use of assigned logins and encrypted passwords. The system will have a full electronic audit trail and will be regularly backed up. Quality control procedures will be applied to validate the trial data. Error reports will be generated where data clarification is required. Output for analysis will be generated in a format and at intervals to be agreed between Sheffield CTRU and the Principal Investigator. All activities will be performed in accordance with Sheffield CTRU Standard Operating Procedures.

Project timetable and milestones

The project will commence on 1st June 2007 and be completed over three years. The first six months will involve staff recruitment, setting up data management processes, local ethics review and research governance. Patients will be recruited over a two-year period from month 7 to month 30. The final six months will involve completion of follow-up, data analysis, writing-up and dissemination. Project staff employment and key milestones are outlined on the GANTT below.

	Month of project											
	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36
Trial Manager	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Clerical Assistant	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Health Economist											XXX	XXX
Lead nurse	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Other nurses		XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	
Set-up, LREC, R&D	XXX	XXX										
Recruitment*			XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX		
Follow-up			XX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XX	
Analysis											XXX	
Writing-up												XXX
Dissemination												XXX

*Recruitment rate to the trial was less than originally predicted and so the recruitment period of the trial was extended until 31st March 2012; with follow-up, analysis and writing up to be completed by 30th September 2012.

We will submit 6-monthly progress reports to correspond with the following milestones:

- Completion of set-up, ethics and governance, and commencement of recruitment.
- All sites recruiting. Target of 200 participants recruited.
- Target of 500 participants recruited.
- Target of 850 participants recruited.
- Target of 1200 participants recruited.
- Completion of analysis and final report.

We will use these recruitment targets to set targets for each participating hospital. We have developed a system for monitoring recruitment rates for the 3CPO Trial and will augment this by using CTRU data management systems. The CTRU will monitor recruitment at each hospital and will provide monthly updates to the Project Management Group, Research Nurses, Local Lead Investigator and Lead Nurse, and on the trial website. Any site that is recruiting at less than 50% predicted for three consecutive months will be flagged at the Project Management Group meeting for identification of potential incentives and barriers to recruitment. Any site that continues to recruit at less than 50% of predicted for three months after intervention will be considered for replacement by another trial site.

Expertise

We have unparalleled experience and expertise in undertaking trials in emergency care. The trial will be undertaken by the Medical Care Research Unit (MCRU) in the University of Sheffield and will be supported by the Sheffield Clinical Trials Research Unit (CTRU). The MCRU has undertaken numerous trials in emergency care, including trials of prehospital intravenous fluid therapy, chest pain units, paramedic practitioners, nurse practitioners and helicopter emergency services. The CTRU will provide trial support, including an experienced trial manager, statistical expertise and health economic expertise.

The research team includes four emergency physicians with direct experience of recruiting patients in emergency care. Three of the applicants (AG, TC and SG) have led multi-centre trials in emergency care (the 3CPO, CRASH2 and ESCAPE trials respectively). We will base recruitment on the 3CPO trial network and have invited the best recruiting hospitals from our three existing trials to participate. Twelve hospitals have agreed to participate and will form the initial recruitment centres. Letters of agreement have been sent to the Principal Investigator and are available on request. We will carefully monitor recruitment and enrol additional hospitals from our networks if targets are not being met.

We have unique expertise in addressing the challenges of recruiting seriously ill patients in the emergency setting. Both the 3CPO and CRASH2 trials involve recruiting patients with life-threatening illness. The recruitment plans set out in this proposal are based upon our experience of recruitment in the 3CPO trial. During this trial we identified a number of barriers to recruitment and developed methods to overcome these barriers. The 3CPO Trial is now progressing towards successful recruitment of the target of 1200 participants.

Tim Coats is Chair of the Research Committee of the College of Emergency Medicine and Principal Investigator for the CRASH2 Trial. In the former role he has been central to efforts to apply the Medicine for Human Use (Clinical Trials) Regulations 2004 in the emergency setting, and in the latter role he has led the first trial to implement these regulations in practice. This has specifically involved the development of procedures for Personal and Professional Legal Representations. We therefore have unique expertise in addressing ethical and legal issues relating to trials in emergency care.

Consumers

We have consulted with Asthma UK during development of this proposal and have identified two people with asthma who have agreed to act as consumer representatives for the trial (Kirsten Flett and Jenny Negus). They have assisted with the development of the proposal, particularly with regard to choice of outcome measures and ethical issues, and will be invited to join the Trial Steering Committee. Draft copies of the one-month questionnaire, the Patient Consent Form and Patient Information Sheet are included as appendices. These have been developed in consultation with our consumer representatives.

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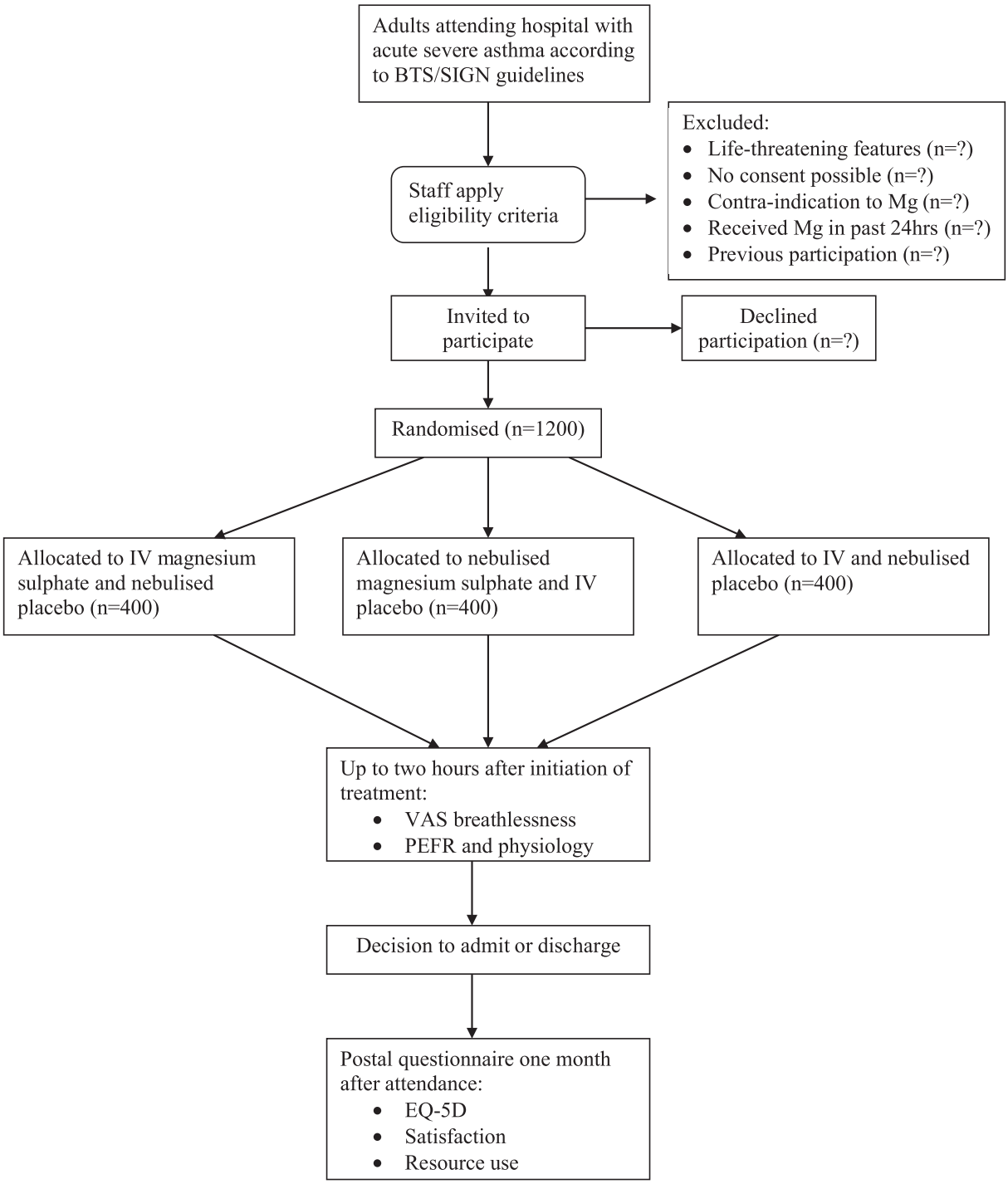
CONSORT Flow Chart: The 3Mg Trial



Appendix 12 Original project description

Project Title: The 3Mg Trial

How the project has changed since the outline proposal was submitted
There have been no substantive changes since the outline proposal was submitted.

Planned investigation

Research objectives
We aim to measure the effectiveness and cost-effectiveness of intravenous (IV) and nebulised magnesium sulphate in acute severe asthma and thus determine whether either should be standard first-line treatment for patients presenting to the emergency department with acute severe asthma.

We plan to test the following specific hypotheses:

1. IV or nebulised magnesium sulphate will reduce the proportion of patients who require admission at initial presentation or during the following week
2. IV or nebulised magnesium sulphate will improve patient's assessment of their breathlessness over two hours after initiation of treatment

We will also measure the effect of IV or nebulised magnesium sulphate upon:

1. Length of hospital stay and use of high-dependency or intensive care
2. Mortality, adverse events and use of respiratory support
3. Change in peak expiratory flow rate (PEFR) and physiological variables after initial treatment
4. Patient reported health utility
5. Patient satisfaction with care
6. Use of health and social services over the following month
7. Time taken by patients off work
8. Health and social care costs and productivity losses

Existing research
We have systematically reviewed the literature to identify meta-analyses or randomised trials comparing magnesium sulphate (IV or nebulised) to control treatment, or comparing between nebulised and IV magnesium sulphate.

IV magnesium sulphate compared to control
We identified four meta-analyses[1-4] (one in adults[1], one in children[2] and two mixed[3,4]) and 15 randomised trials[5-19] (nine in adults[5-13] and six in children[14-19]) comparing IV magnesium sulphate to placebo. The trials of adults used a bolus dose of either 1.2g or 2.0g of magnesium sulphate, given over 20 to 30 minutes. Only one trial followed the bolus dose with an infusion.

The three meta-analyses involving adults were all published in 2000. Each analysis identified a different number of trials and reached different conclusions. Rowe et al[3] identified five adult and two paediatric trials involving a total of 668 patients and concluded that over all trials magnesium sulphate therapy did not significantly improve peak expiratory flow rate (PEFR) or reduce admission to hospital. However, subgroup analysis suggested that in trials of severe asthma magnesium sulphate therapy was associated with significant improvements in PEFR and reduced hospital admissions. Alter et al[4] identified seven adult and two paediatric trials involving a

total of 859 patients and found that magnesium sulphate was associated with a significant improvement in spirometric airway function by 16% of a standard deviation. They concluded that the clinical significance of this effect was uncertain. Rodrigo et al[1] identified five adult trials involving a total of 374 patients and found no significant effect from magnesium sulphate upon pulmonary function or hospital admissions. Cheuk et al[2] undertook a meta-analysis of five trials[13-18] of IV magnesium sulphate in children with acute asthma. They did not include one trial that was published in Portuguese[19]. Magnesium sulphate was effective in reducing hospital admissions (OR 0.290; 95% CI 0.143 to 0.589) and improving pulmonary function tests and clinical symptoms.

We have updated the meta-analysis of IV magnesium sulphate in adults to include all nine adult trials[5-13]. The pooled relative risk for hospital admission after treatment with IV magnesium sulphate is 0.91 (95% CI 0.78 to 1.07; p=0.27) and the pooled standardised mean difference in pulmonary function is 0.15 (0.01 to 0.29; p=0.035). We conclude that treatment with IV magnesium sulphate is associated with a modest improvement in pulmonary function, but the clinical significance of this effect is uncertain. Although there is no significant effect upon hospital admission we cannot exclude a potentially important reduction in admissions of up to 22%. Current evidence is therefore insufficient to either recommend IV magnesium sulphate as standard treatment for acute severe asthma or rule out a potentially valuable role. This uncertainty is reflected in current guidelines from the British Thoracic Society (BTS) and Scottish Intercollegiate Guideline Network (SIGN)[20], which suggest that IV magnesium sulphate should be considered in patients with severe acute asthma that has not responded to initial treatment with salbutamol nebulisers and steroids.

Nebulised magnesium sulphate compared to control

We identified two meta-analyses[21,22] (both mixed adults and children) and eight randomised trials[23-30] (five in adults[23-27], two in children[28,29] and one mixed[30]) comparing nebulised magnesium sulphate to placebo. The meta-analyses both included the same six randomised trials[23-25,28-30] involving a total of 296 patients but did not include two recently published trials[26,27]. The dose of magnesium sulphate used ranged from 95mg to 500mg, given up to four times, with doses every 20 to 30 minutes. Both reviews concluded that current evidence could not conclusively determine the role of nebulised magnesium sulphate in acute asthma.

We have undertaken a meta-analysis of six trials of nebulised magnesium sulphate in adults[23-27] or a mixed population[30]. The pooled relative risk for hospital admission after treatment with IV magnesium sulphate was 0.66 (95% CI 0.44 to 1.00; p=0.048) and the pooled standardised mean difference in pulmonary function was 0.20 (-0.02 to 0.42; p=0.076). Although the effect of nebulised magnesium sulphate upon hospital admissions is just significant, most of the admissions in this analysis were in one trial[25] and the effect was not consistent across other trials. We conclude that there is currently inadequate evidence to either support nebulised magnesium sulphate as standard treatment for acute severe asthma or rule out a potentially valuable role.

Comparison between IV and nebulised magnesium sulphate

We identified no trials comparing intravenous to nebulised magnesium sulphate.

The need for a large randomised trial

A large randomised trial is needed to determine the role of intravenous or nebulised magnesium sulphate in acute severe asthma for the following reasons:

1. Studies included in both meta-analyses were relatively small and were powered to detect changes in pulmonary function. Even if meta-analysis shows a statistically significant difference in pulmonary function it is not clear whether such changes are important to patients or affect their clinical outcome.
2. Factors such as publication bias may influence selection of studies into meta-analysis, leading to over-estimates of effectiveness. It has been noted that 35% of subsequent large trials conflict with the results of previous meta-analysis[31].
3. The clinically important change in admission rate in patients with severe asthma identified in the meta-analysis by Rowe et al[3] was based upon post-hoc subgroup analysis. Such findings should be confirmed in a pre-planned analysis before they are accepted.
4. A large trial would allow head-to-head comparison of nebulised versus IV magnesium sulphate as well as comparing each treatment to standard therapy.

Trials in progress

A search of the National Research Register identified one trial of nebulised magnesium sulphate in children with acute asthma currently being undertaken in Wales[32], and a trial of nebulised magnesium sulphate in an unspecified population planned for 2002 that does not appear to have been undertaken[33]. A search of ClinicalTrials.gov identified no relevant studies in progress.

We conclude from the existing literature that there is some evidence that intravenous or nebulised magnesium sulphate can improve measures of pulmonary function, but there is no direct comparison between these two treatments and no reliable evidence that either treatment can improve measures that are important to the patient or effect their clinical outcome.

Research methods

We will undertake a multi-centre, double blind, placebo controlled, three-arm, randomised trial in twelve emergency departments in the United Kingdom. Eligible patients will be identified by medical staff and written, informed consent sought from either the patient, a personal legal representative or a professional legal representative (as outlined in Medicine for Human Use (Clinical Trials) Regulations 2004).

Consented participants will be randomised by telephone to the Sheffield Clinical Trials Support Unit (CTSU). A simple randomisation sequence[34] will be used to allocate participants to numbered treatment packs kept in the emergency department. The CTSU will only reveal the allocated pack number after patient details have been recorded and the patient irreversibly entered into the trial. Each treatment pack will contain an intravenous infusion and a nebuliser solution, either of which could be active treatment or placebo. Participants, hospital staff and research staff will all be blind to allocated treatment.

Clinical staff will record baseline data, details of co-interventions and outcome data up to two hours after presentation. Further data will be collected at one month after recruitment by research nurses using routine data sources and by patient self-completion questionnaire.

Planned interventions
Patients will be randomised to one of three treatment arms. Each treatment arm will receive one intravenous and one nebulised treatment. The intravenous infusions and nebuliser vials will each be prepared as apparently identical solutions to ensure blinding.

The three treatment arms are as follows:

Treatment arm	Intravenous infusion	Nebulisers
1	Intravenous magnesium sulphate, 2g in 100ml normal saline given over 20 minutes	5mg salbutamol nebulised in 5ml normal saline, given 3 times 20 minutes apart
2	Intravenous normal saline, 100ml given over 20 minutes	500mg magnesium sulphate and 5mg salbutamol nebulised in 5ml normal saline, given 3 times 20 minutes apart
3	Intravenous normal saline, 100ml given over 20 minutes	5mg salbutamol nebulised in 5ml normal saline, given 3 times 20 minutes apart.

All three groups will also receive standard therapy, according to BTS/SIGN guidelines, with high flow oxygen and oral prednisolone. Other treatments will be given at the discretion of the attending clinician and recorded on the data collection form, although adherence to BTS/SIGN guidelines will be promoted.

Patients will be managed in the emergency department and data collected until two hours after randomisation. At this point, if not already undertaken, a final disposition decision will be made (hospital admission or discharge) and initial data collection completed.

Planned inclusion/exclusion criteria
We will recruit adults (age>16) admitted to the emergency department with acute severe asthma as defined by the BTS/SIGN guidelines, i.e. acute asthma with either PEFR < 50% of best or predicted, respiratory rate > 25/min, heart rate > 110/min, or inability to complete sentences in one breath.

We will exclude:

1. Patients with life threatening features (oxygen saturation < 92%, silent chest, cyanosis, poor respiratory effort, bradycardia, arrhythmia, hypotension, exhaustion, coma or confusion).
2. Patients who are unable to provide written consent and for whom no personal or professional legal representative can be identified to act on their behalf.
3. Patients with a contraindication to either nebulised or intravenous magnesium sulphate: pregnancy, hepatic or renal failure, heart block or known hypermagnesaemia.
4. Previous participants in the 3Mg Trial

We will collect basic details (age, gender and admission/discharge after emergency department management) on all eligible patients to allow completion of a CONSORT flow chart.

4.1 Proposed outcome measures

We will measure two primary outcomes:

1. The health service primary outcome will be the proportion of patients who are admitted to hospital, either after emergency department treatment or at any time over the subsequent week.
2. The patient-centred primary outcome will be the patient's visual analogue scale (VAS) for breathlessness over two hours after initiation of treatment.

Secondary outcomes will include mortality, adverse events, use of ventilation or respiratory support, length of hospital stay, use of high dependency or intensive care, change in PEFR and physiological variables (oxygen saturation, heart rate, respiratory rate) over two hours, quality of life at baseline and one month (measured by EQ-5D), number of unscheduled health care contacts (emergency department, walk-in centre or general practitioner attendances) over the subsequent month, and satisfaction with care (measured by a modified Group Health Association of America survey).

Choice of outcome measures

Previous studies (outlined in the meta-analysis) have used measures of respiratory function, such as PEFR, as their primary outcome. In some studies these have shown that treatment with IV or nebulised magnesium sulphate may be associated with significant changes in PEFR. However, it is not clear whether these changes lead to important changes in patient management or a clinically meaningful improvement in symptoms.

We have selected two primary outcomes to identify important changes in patient management and symptoms of asthma: admission to hospital and breathlessness measured on a VAS. These outcomes have been chosen after literature review and consultation with our consumer representatives, and reflect health service and patient perspectives respectively. Our consumer representatives have indicated that avoiding hospital admission is an important outcome for patients, as well as being an important health service outcome.

We have decided to include any admission over the following week in the primary outcome of hospital admission because this time period would encompass the expected duration of an asthma exacerbation and a typical course of associated treatment. Admission during this time would therefore represent an overall failure of treatment, whereas admission later than one week would more appropriately be considered as being a separate episode.

We considered two potential methods for measuring breathlessness: the VAS and the Borg Scale. Both have been used to measure breathlessness during exercise[35] but have only recently been tested in acute asthma. Kendrick et al[36] showed that the Borg Scale correlated with measures of respiratory function in a cohort of patients with asthma or chronic obstructive pulmonary disease, while Karras[37] and Gupta[38] showed correlation between the VAS and measures of respiratory function in cohorts with acute asthma. The study by Karras also showed that mean VAS change among

patients who reported their asthma to be "a little better" after treatment was 2.2cm on a 10cm VAS, and concluded that this represented a minimum clinically significant change. On the basis of these studies we conclude that the VAS is the best-validated measure, it offers a simple and reliable means of measuring symptomatic breathlessness in people with acute asthma, and we have an estimate a minimum clinically significant change in VAS. Our consumer representatives have reviewed the VAS and found it acceptable.

We have abundant previous experience of measuring health utility, satisfaction with care and resource by postal questionnaire. The questionnaires we plan to use are based on validated instruments and have been used successfully by our group in clinical trials, typically achieving response rates of 70-80%. Our consumer representatives have reviewed the questionnaire and modifications have been made in accordance with their suggestions. The current draft of the questionnaire is attached as an appendix.

Outcomes will be measured in two phases: 1) Over two hours after randomisation, and 2) At one month after attendance. During the first phase we will measure variables, such as VAS, PEFR and physiological variables, which reflect patient response to emergency treatment. During the second phase we will measure variables, such as adverse events, use of health services, satisfaction with care and quality of life, that reflect the overall patient experience of an asthma attack and its subsequent treatment.

Proposed sample size

We plan to recruit 1200 participants divided equally between the three trial arms (400 per arm) over two years at twelve hospitals selected from those participating in the 3CPO, CRASH2 and ESCAPE trials. Hospitals have been selected on the basis of recruitment rates in previous trials. Audit data suggest that around ten patients per month will be eligible at each hospital. However, our experience (3CPO and CRASH2 trials) suggests that audit data substantially over-estimate the actual availability of eligible patients. Therefore, we assume that each hospital will recruit 50 patients per year. We will carefully monitor recruitment at participating hospitals and will activate contingency plans, including addition of new sites or replacement of under-performing sites, if recruitment is not close to target.

We anticipate that the health service primary outcome (see section 3.6) will be recorded for all participants, but it is possible that a small proportion of cases will not have their patient-centred primary outcome measured. The sample size will therefore provide the following statistical power:

1. Proportion of patients admitted: Audit data at participating hospitals suggest that 80% of patients with severe asthma are admitted after emergency department management. The study will thus have 90% power to detect a 10% absolute reduction in the proportion admitted (i.e. to 70%) for any pair of treatment groups compared (alpha=0.05).
2. Breathlessness measured on a visual analogue score (VAS): Previous data have established that the standard deviation of this measure on a 10cm VAS is 3cm, and that 2.2cm on a 10cm VAS represents a minimum clinically significant difference[37]. If we take a pessimistic assumption that 20% of participants will not have their VAS measured then the study will still have

90% power to detect a 0.8cm difference in a 10cm VAS at two hours after treatment initiation (alpha=0.05).

Statistical analysis

Analysis will be undertaken on an intention-to-treat basis with participants being analysed in the groups they were allocated to regardless of whether they actually received or completed the allocated treatment. Imputations will be made for missing data to check if results are affected by patterns of missing values. The analysis will use Cox regression for admissions and linear regression (with possible transformations) for breathlessness. Analysis will also be made using baseline covariates: initial breathlessness (VAS), age and hospital, and a comparison of the adjusted and unadjusted effects will be given. Although the primary analysis will be intention-to-treat, a secondary explanatory analysis will be undertaken limited to those who completed the treatment as per protocol.

We have planned three sub-group analyses in advance, within which patients will be stratified on the basis of:

1. Asthma severity, according to baseline breathlessness (VAS). A previous meta-analyis[3] has suggested that IV magnesium sulphate is more effective in patients with severe asthma.
2. Age, above or below 50 years. Older patients with a diagnosis of asthma are more likely to have chronic respiratory disease that may be less responsive to treatment with magnesium sulphate.
3. Treatment before arrival. We will be recruiting patients on arrival at hospital, thus testing magnesium sulphate as a first-line treatment. However, some patients may have received prehospital treatment with nebulisers, thus making magnesium sulphate in effect a second-line treatment. Patients with severe asthma after receiving prehospital treatment are likely to have more severe asthma than those presenting without prehospital treatment.

Economic evaluation

We will take a health care perspective to estimate the incremental cost per QALY and the incremental cost per change in breathlessness on the VAS for the two most effective treatments.

Measurement and valuation of costs

We will measure health care resource use (including emergency department visits, hospital admission, general practitioner and outpatient visits, tests and treatments), social care resource use and productivity losses over the subsequent month, using case record review and patient self-completion questionnaire. Resources will be valued using national units costs wherever possible including the Personal Social Services Research Unit Database[39] and NHS Reference Costs[40] to estimate health and social care costs. Where national costs are unavailable, local unit costs will be obtained from the health care centres in the trial locations. Average daily wage rates from the Office of National Statistics will be used to estimate the costs of lost productivity, up to one month after recruitment.[41]

Cost-effectiveness analysis

Cost analysis will compare bootstrap estimates of the mean cost per patient of the three groups, and will be presented alongside outcome data as a cost-consequences

analysis. We will then estimate the incremental cost per QALY and the incremental cost per change in breathlessness VAS for the two most effective treatments. The primary analysis will take a health care perspective. Secondary analysis will explore the potential impact of including social care costs and costs due to productivity losses in the analysis. The validity of the base case results will be confirmed by a probabilistic sensitivity analysis using bootstrapping, where the original data is used to provide an empirical estimate of the sampling distribution through repeated re-sampling from the observed data.[42] Sensitivity analyses will explore the potential impact of changing key assumptions used in the main analysis and, in particular, the potential impact of rare but serious adverse outcomes upon the robustness of conclusions.

Additional analysis: Predictors of relapse after initial successful treatment

To maximise the value of this project, we plan to undertake an additional analysis of trial data to identify factors that predict relapse after initial successful treatment for acute severe asthma. Predicting relapse after initial treatment would be helpful for deciding which patients need asthma nurse review after discharge[43], which need hospital admission, and which need high dependency or intensive care. Currently these decisions are made largely upon PEFR recordings, although it is not clear how useful these are as predictors of relapse.

Data collection for the trial will include variables that may be potentially useful predictors of subsequent relapse, such as baseline and post-treatment PEFR, physiological variables, age, gender, smoking status, and previous hospital, high dependency and intensive care admissions. We will examine the ability of these factors to predict asthma relapse, defined at two levels: 1) Relapse requiring high dependency or intensive care, i.e. any patient requiring airway management, respiratory support or cardiopulmonary resuscitation, or suffering respiratory arrest, cardiac arrhythmia or death within one week of initial attendance; 2) Relapse requiring hospital admission, i.e. any patient requiring emergency medical treatment within one week of presentation, either by attendance at the emergency department or unscheduled inpatient review. Univariate analysis will be undertaken using Chi-square test for categorical variables and t-test for continuous variables to identify factors that are associated with either outcome ($p<0.1$). These factors will then be entered into a multivariate model for each outcome to identify independent predictors of relapse ($P<0.05$).

Ethical arrangements

The Trial will be undertaken in accordance with the Medicine for Human Use (Clinical Trials) Regulations 2004. The main ethical challenge is that potential participants will be acutely ill and may lack capacity to provide informed consent, yet the very nature of the trial requires that recruitment take place quickly in an emergency and includes acutely ill patients. We have extensive experience of seeking informed consent from acutely ill patients in the emergency setting and, through the CRASH2 Trial, have specific experience of developing consent procedures under the EU Clinical Trials Directive. Professor Tim Coats, as Principal Investigator of the CRASH2 Trial, has pioneered the development of Professional Legal Representatives in the emergency setting[44,45]. We are currently training senior nursing staff to act as Professional Legal Representatives in a number of hospitals and anticipate that they will perform this role in the 3Mg trial.

Participants will only be recruited into the trial if they can provide written informed consent or if an appropriate legal representative is able to act on their behalf. Consent will be sought as follows:

1. Potential participants who are well enough to understand the trial information will be asked to provide written consent.
2. If they are too ill to understand the trial information then a relative or friend will be sought to act as a Personal Legal Representative and will be asked provide written consent on their behalf.
3. If the potential participant is too ill to understand the trial information and no suitable individual can be identified to act as a Personal Legal Representative then a trained member of the hospital staff will act as a Professional Legal Representative and be asked to provide written consent on their behalf.

The risks to participants in this trial are low. Magnesium sulphate has been used by IV and nebulised routes in a number of trials and, although unlicensed, is frequently used in the treatment of acute severe asthma. It is also included as a possible treatment for acute asthma in current BTS/SIGN guidelines. Although minor side effects such as nausea or flushing are common, serious side effects (arrhythmias and coma) are uncommon. Potential participants or their legal representative will be advised of these risks when they are invited to participate.

We have consulted consumer representatives in developing patient information and consent procedures. Current drafts of the consent form and patient information sheet are included as appendices.

We have completed submission forms to a Multicentre Research Ethics Committee, but are delaying ethics committee review until December so that our submission can address issues raised by HTA referees and the HTA Board. We will complete Local Research Ethics Committee reviews during the first six months of the timetable (see section 4). We will appoint a Data Monitoring and Ethics Committee as outlined in section 3.11.

Research governance

The trial will be conducted in accordance with MRC Guidelines for Good Clinical Practice in Clinical Trials and Medicine for Human Use (Clinical Trials) Regulations 2004. The University of Sheffield will act as the Sponsor for the trial.

The trial will be covered by clinical trial regulations from the Medicines and Healthcare products Regulatory Agency (MHRA). We will apply for Clinical Trial Authorisation from the MHRA and have included an estimate of the costs of application, administration and audit in the budget for this project.

Treatment packs will be prepared in conjunction with the CTSU by Sheffield Teaching Hospitals Pharmacy, who will maintain an Investigational Medical Products dossier and relevant documentation.

Three committees will be established to govern the conduct of this study:

1. Trial Steering Committee

2. Independent Data Monitoring and Ethics Committee
3. Trial Management Group

These committees will function in accordance with Sheffield CTRU standard operating procedures. The Trial Steering Committee will consist of the Principal Investigator, one of the co-applicants, an independent chair, two independent members and a consumer representative. We will also invite a representative of the HTA Board to join the committee. The Data Monitoring and Ethics Committee will consist of a minimum of an independent statistician, emergency physician and respiratory physician, who will be asked to review trial data at regular intervals and implement stopping rules in accordance with MRC guidance. The Trial Management Group will consist of the Principal Investigator, Co-applicants, Project Manager, Statistician and Research Nurses.

Data management

Trial data will be entered into a validated database system built to a specification agreed between Sheffield CTRU and the Principal Investigator. The system will be accessible remotely via a web browser, with the data stored securely on a central server. Access will be controlled by the use of assigned logins and encrypted passwords. The system will have a full electronic audit trail and will be regularly backed up. Quality control procedures will be applied to validate the trial data. Error reports will be generated where data clarification is required. Output for analysis will be generated in a format and at intervals to be agreed between Sheffield CTRU and the Principal Investigator. All activities will be performed in accordance with Sheffield CTRU Standard Operating Procedures.

Project timetable and milestones

The project will commence on 1st February 2007 and be completed over three years. The first six months will involve staff recruitment, setting up data management processes, local ethics review and research governance. Patients will be recruited over a two-year period from month 7 to month 30. The final six months will involve completion of follow-up, data analysis, writing-up and dissemination. Project staff employment and key milestones are outlined on the GANTT below.

	Month of project											
	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36
Trial Manager	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Clerical Assistant	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Health Economist											XXX	XXX
Lead nurse	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Other nurses		XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	
Set-up, LREC, R&D	XXX	XXX										
Recruitment			XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX		
Follow-up			XX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XX	
Analysis											XXX	
Writing-up												XXX
Dissemination												XXX

We will submit 6-monthly progress reports to correspond with the following milestones:

1. Completion of set-up, ethics and governance, and commencement of recruitment.
2. All sites recruiting. Target of 200 participants recruited.
3. Target of 500 participants recruited.
4. Target of 850 participants recruited.
5. Target of 1200 participants recruited.
6. Completion of analysis and final report.

Expertise

We have unparalleled experience and expertise in undertaking trials in emergency care. The trial will be undertaken by the Medical Care Research Unit (MCRU) in the University of Sheffield and will be supported by the Sheffield Clinical Trials Support Unit (CTSU). The MCRU has undertaken numerous trials in emergency care, including trials of prehospital intravenous fluid therapy, chest pain units, paramedic practitioners, nurse practitioners and helicopter emergency services. The CTSU will provide trial support, including an experienced trial manager, statistical expertise and health economic expertise.

The research team includes four emergency physicians with direct experience of recruiting patients in emergency care. Three of the applicants (AG, TC and SG) have led multi-centre trials in emergency care (the 3CPO, CRASH2 and ESCAPE trials respectively). We will base recruitment on the 3CPO trial network and have invited the best recruiting hospitals from our three existing trials to participate. Twelve hospitals have agreed to participate and will form the initial recruitment centres. Letters of agreement have been sent to the Principal Investigator and are available on request. We will carefully monitor recruitment and enrol additional hospitals from our networks if targets are not being met.

We have unique expertise in addressing the challenges of recruiting seriously ill patients in the emergency setting. Both the 3CPO and CRASH2 trials involve recruiting patients with life-threatening illness. The recruitment plans set out in this proposal are based upon our experience of recruitment in the 3CPO trial. During this trial we identified a number of barriers to recruitment and developed methods to overcome these barriers. The 3CPO Trial is now progressing towards successful recruitment of the target of 1200 participants.

Tim Coats is Chair of the Research Committee of the College of Emergency Medicine and Principal Investigator for the CRASH2 Trial. In the former role he has been central to efforts to apply the Medicine for Human Use (Clinical Trials) Regulations 2004 in the emergency setting, and in the latter role he has led the first trial to implement these regulations in practice. This has specifically involved the development of procedures for Personal and Professional Legal Representations. We therefore have unique expertise in addressing ethical and legal issues relating to trials in emergency care.

Consumers

We have consulted with Asthma UK during development of this proposal and have identified two people with asthma who have agreed to act as consumer representatives for the trial (Kirsten Flett and Jenny Negus). They have assisted with the development of the proposal, particularly with regard to choice of outcome measures and ethical

issues, and will be invited to join the Trial Steering Committee. Draft copies of the one-month questionnaire, the Patient Consent Form and Patient Information Sheet are included as appendices. These have been developed in consultation with our consumer representatives.

Justification of support required

The budget will be divided between research support at Sheffield University and recruitment support at Edinburgh, Sheffield, Leicester and Bristol. The research budget has been estimated using full economic costing and 80% of support will be requested. The respective Universities will manage the recruitment budget at Sheffield and Leicester, so 80% of full economic costs will be requested. The Royal Infirmary of Edinburgh and Bristol Royal Infirmary will manage the recruitment budget at Edinburgh and Bristol respectively, where full economic costing is not used and 100% of costs will be requested.

The research budget will support a full-time Trial Manager, full-time Clerical Assistant and 10% of the Principal Investigator's time (Steve Goodacre). Together they will oversee day-to-day trial management, governance, data analysis, writing reports and dissemination. The CTSU will provide trial support, including data management (£30,000 total), statistical support (RA2, 20% for 3 years), health economic support (Julie Ratcliffe, 50% for 6 months), and 2% of Jon Nicholl's and Mike Campbell's time. Other research costs include: £2,000 for computing equipment, £1,920 for postal questionnaires (1,200 x £1.60), £34,250 for travel costs (based on actual travel costs from the 3CPO Trial), £14,700 for office costs (1,500 per wte/year), and £12,000 for randomisation services (£10 per patient).

The recruitment budget will support salary and office costs for a full-time G grade Research Nurse Co-ordinator in Edinburgh for 3 years and F-grade Research Nurses in Sheffield, Leicester and Bristol for 2.5 years, and will support 5% of the time of the co-applicants in Edinburgh, Leicester and Bristol (AG, TC and JB) who will provide managerial support and supervision for the Research Nurses. The research nurses will promote recruitment at surrounding centres by maximising awareness of the trial and providing staff training and support, and will identify all recruited and non-recruited but eligible patients, collect data, ensure availability of drugs and equipment, and liase with the researchers in Sheffield. The co-applicants will support the research nurses in their role and assist with promotion of the trial in participating centres.

Sheffield Teaching Hospitals Pharmacy will prepare treatments at a total cost of £19,885 (not full economic costs, 100% requested). This will include a £2000 set up fee including Investigational Medicinal Products dossier and study documentation, 1200 IV doses @ £4.50, 1200 nebuliser vials @ £3.50, assembly and labelling of 1200 treatment packs including randomisation @1.50, a £2000 support fee per year for distribution of the materials, dealing with any queries and transportation, and a £2485 fee for MHRA submission.

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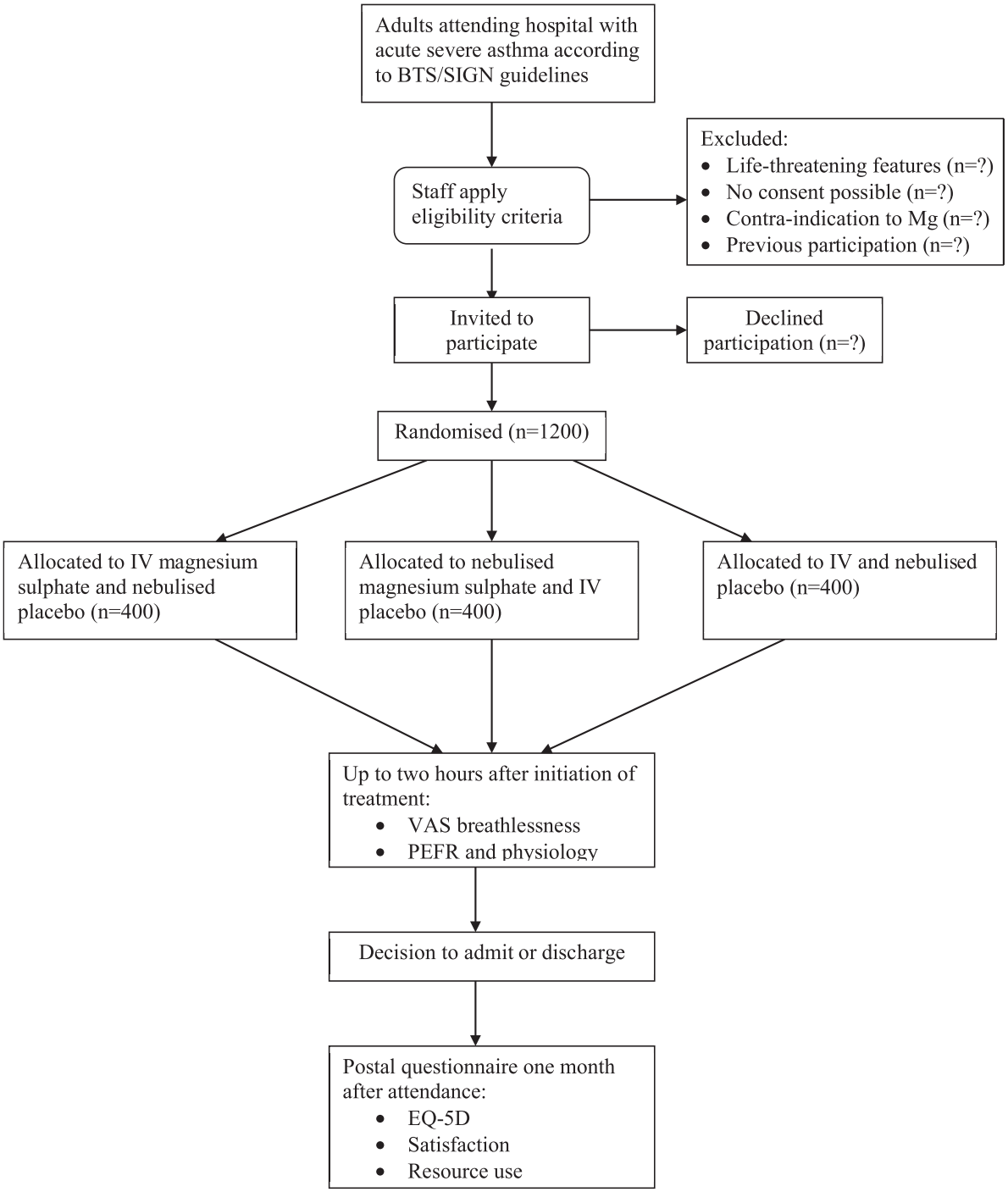
CONSORT Flow Chart: The 3Mg Trial



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