

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

### **1. Project Title: The 3Mg Trial**

### **2. Planned investigation**

#### **2.1 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

#### **2.2 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<sup>1-4</sup> (one in adults<sup>1</sup>, one in children<sup>2</sup> and two mixed<sup>3,4</sup>) and 15 randomised trials<sup>5-19</sup> (nine in adults<sup>5-13</sup> and six in children<sup>14-19</sup>) 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<sup>3</sup> 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<sup>4</sup> 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<sup>1</sup> 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<sup>2</sup> undertook a meta-analysis of five trials<sup>13-18</sup> of IV magnesium sulphate in children with acute asthma. They did not include one trial that was published in Portuguese<sup>19</sup>. 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<sup>5-13</sup>. 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)<sup>20</sup>, 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<sup>21,22</sup> (both mixed adults and children) and eight randomised trials<sup>23-30</sup> (five in adults<sup>23-27</sup>, two in children<sup>28,29</sup> and one mixed<sup>30</sup>) comparing nebulised magnesium sulphate to placebo. The meta-analyses both included the same six randomised trials<sup>23-25,28-30</sup> involving a total of 296 patients but did not include two recently published trials<sup>26,27</sup>. 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<sup>23-27</sup> or a mixed population<sup>30</sup>. 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<sup>25</sup> 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<sup>31</sup>.
3. The clinically important change in admission rate in patients with severe asthma identified in the meta-analysis by Rowe et al<sup>3</sup> 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<sup>32</sup>, and a trial of nebulised magnesium sulphate in an unspecified population planned for 2002 that does not appear to have been undertaken<sup>33</sup>. 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.

### **2.3 Research methods**

We will undertake a multi-centre, double blind, placebo controlled, three-arm, randomised trial in up to 30 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<sup>34</sup> 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.

## 2.4 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.

## 2.5 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, gender and admission/discharge after emergency department management) on all eligible patients to allow completion of a CONSORT flow chart.

### 2.6 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<sup>35</sup> but have only recently been tested in acute asthma. Kendrick et al<sup>36</sup> 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<sup>37</sup> and Gupta<sup>38</sup> 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.

## **2.7 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 30 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<sup>37</sup>. 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  $\alpha=0.05$ ).

## 2.8 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*  $P_2 < 0.05$ <sup>39</sup>. 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<sup>40</sup>.

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<sup>3</sup> 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.

### **3.9 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 unit costs wherever possible including the Personal Social Services Research Unit Database<sup>39</sup> and NHS Reference Costs<sup>40</sup> 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.<sup>41</sup>

#### **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.<sup>42</sup> 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.

### **3.10 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<sup>43</sup>, 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 ( $P < 0.05$ ).

### 3.11 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<sup>44,45</sup>.

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.

### **3.12 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:

- Trial Steering Committee
- Independent Data Monitoring and Ethics Committee
- 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.

#### 4. Project timetable and milestones

The project will commence on 1<sup>st</sup> 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 31<sup>st</sup> March 2012; with follow-up, analysis and writing up to be completed by 30<sup>th</sup> September 2012.

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.

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.

## **5. 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.

## **6. 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**