Statistical Analysis Plan

Protocol Title: **Magnesium Nebulization Utilization in Management of Pediatric Asthma (MAGNUM PA) Trial**

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Abbreviations

Table 1. Abbreviations

Abbreviation	Definition
SAP	Statistical Analysis Plan
MAGNUM PA	Magnesium Nebulization Utilization Management in Pediatric Asthma
PERC	Pediatric Emergency Research Canada
PRAM	Pediatric Respiratory Assessment Measure
ED	Emergency Department
PI	Principal Investigator
REB	Research Ethics Board
DSMC	Data Safety Monitoring Committee
Mg	Magnesium
NNT	Number-Needed-to Treat
CONSORT	Consolidated Standards of Reporting Trials
ITT	Intention-To-Treat
URI	Upper Respiratory Infection
SAEs	Serious Adverse Events

Preface

1.1. Purpose of SAP

This Statistical Analysis Plan (SAP) describes the final planned analysis and reporting for the Magnesium Nebulization Utilization Management in Pediatric Asthma (MAGNUM PA) trial.

The structure and content of this SAP meets requirements and standards of the Pediatric Emergency Research Canada (PERC) Network.

1.2 Auxiliary/Other Documents

The reader of this SAP is encouraged to read the protocols for details on the conduct of this study, and the operational aspects of clinical assessments.
The purpose of this SAP is to outline the planned analyses to be completed for the MAGNUM PA trial. The planned analyses identified in this SAP will be included in future study abstracts and manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed. Any post hoc, or unplanned, analyses not explicitly identified in this SAP will be clearly identified as such in any published reports from this study.
It is possible that, due to updates or identification of errors in specific statistical software discussed in this SAP, the exact technical specifications for carrying out a given analysis may be

modified. This is considered acceptable as long as the original, pre-specified statistical analysis approach is completely followed in the revised technical specifications.

2 Study Objective and Outcomes

2.1 Study Objectives

2.1.1 Primary Objective

To determine if in children 2-17 years of age with acute asthma who have persistent moderate to severe airway obstruction [Pediatric Respiratory Assessment Measure (PRAM) ≥ 5 points] despite maximized initial bronchodilator and steroid therapy, there is a reduction in the hospitalization rate within 24 hours of randomization in those who receive three nebulized magnesium and albuterol treatments compared to those receiving three treatments with nebulized placebo and albuterol.

2.2 Study Outcomes

2.2.1 Primary Outcome

The primary study outcome is hospitalization to an inpatient unit within 24 hours of the start of the experimental therapy for persistent respiratory distress or for supplemental oxygen. The decision to admit is based on an unsatisfactory response to systemic corticosteroids and bronchodilators (usually with inability to tolerate bronchodilator therapy every 4 hours) in the ED. Incorporation of hospitalization within 24 hours into the primary outcome strengthens the definition by adding a measure of decision appropriateness. Hospitalization is a clinically powerful and policy-relevant marker of treatment failure, a finding which is likely to impact practice and influence decision makers since almost a half of pediatric acute asthma costs relate to hospitalizations[1,2].
As mentioned in the protocol, children remaining in the ED without a decision to admit will not be considered hospitalized.

2.2.2 Secondary Outcomes

a. PRAM score, respiratory rate and oxygen saturation at baseline (after randomization and before the start of the first experimental nebulization), 60, 120, 180 and 240 minutes and the systolic blood pressure at baseline, 20, 40, 60, 120, 180 and 240 minutes.
b. Number of additional albuterol treatments within 240 minutes of starting experimental therapy.
c. Association between hospitalization within 24 hours and age, gender[3], baseline PRAM score[4,5], personal history of atopy, and "acute viral induced wheeze" phenotype (defined as age ≤ 5 years, no atopy, and no cough/wheeze between colds).[6]

2.2.3 Other/exploratory outcomes

a. Unscheduled visits for asthma to any medical facility within 72 hours of the start of the study.
b. Hospitalization for asthma to any medical facility by 72 hours.
c. Administration of intravenous Mg in the ED following the experimental therapy.
d. Adverse effects: only unexpected and serious adverse effects will be reported. The expected adverse effects have been identified *a priori* in the protocol from February 2019 and these will not be analyzed.
Serious adverse events include hypotension (systolic blood pressure below 5th percentile for age) requiring medical intervention, apnea and admission to ICU.

2.2.4 Covariates

Although randomization should result in balance between treatment groups with respect to baseline variables affecting the outcomes, additional subgroup analyses will be conducted to assess the effects of treatment after adjusting for baseline covariates which may influence the primary outcome. The covariates considered are:[3-5,7]

Age ≤ 5 years versus ≥ 6 years[8]
Male sex[3]
Baseline PRAM ≥8 points[4] (severe asthma after optimized initial therapy)
Personal history of atopy (history of eczema, allergic rhinitis)
Acute viral induced wheeze ((defined as age ≤ 5 years, no atopy, and no cough/wheeze between colds).[9]

2.2.5 Adverse Effects

Adverse Events

All **unexpected adverse eve**nts will be reported to the Hospital for Sick Children Research Ethics Board and classified as <u>mild, moderate or severe.</u>

Expected adverse events will include cough, respiratory distress (disease-related), asthma-related hospitalization, IV insertion, sinus tachycardia, nausea and bitter/salty taste of the experimental solution.

The serious adverse events will consist of hypotension below the 5th percentile for age requiring intervention, apnea and admission to intensive care unit. These will be reported to the PI, SickKids REB, local REB and the DSMC.

3. Study Design and Methods

3.1 Overall Study Design

The MAGNUM PA trial is a 7 centre randomized clinical trial consists of a parallel group design with a placebo control. The specifics about the active agent and placebo are described in the protocol. We shall refer to the study groups as Magnesium and Placebo. Study participants will be randomized to the two groups, with equal allocation. Treatment with the assigned therapy will commence immediately following randomization. The primary analysis will be performed on an intention-to-treat basis.

3.2 Randomization and Blinding

3.2.1 Method and Delivery of Treatment Assignment

The Research Coordinating Pharmacist at the coordinating center will produce master randomization tables, stratified by site and age (≥ 6 years vs less), using a permuted block randomization of 6 and 8 in a 1:1 ratio of active Mg sulfate to placebo, using random number generating software at https://www.randomizer.org/. The master randomization tables will be held at the Research Pharmacy at the coordinating center. Consecutively numbered kits will be prepared by each pharmacy according to the step-by-step procedure manual provided by Research Coordinating Pharmacist at the coordinating center.

3.2.2 Blinding

The MAGNUM PA trial will be performed in a double-blind fashion. The patients, all study personnel and ED physicians/staff will be blinded to the treatment assignment. Only the research pharmacy at the coordinating center will retain the overall randomization code. The biostatistician involved in the interim analysis will know which patient has received treatment A versus B but will not be aware of the identity of the study groups.

The Research Pharmacist at the coordinating center will provide a manual with instructions as to how each site pharmacy will prepare blinded numbered kits containing Mg sulfate or hypertonic 5.5% saline placebo (to match tonicity of Mg Sulfate). Sterile water will be added as a diluent to both the experimental and control solutions (containing Mg plus albuterol and 5.5% saline and albuterol, respectively), to achieve identical tonicity of both interventional solutions, in order to prevent differential tonicity-related side-effects. The study solutions containing active Mg with albuterol and sterile water and placebo hypertonic saline with albuterol and sterile water are very similar in volume, color, taste and smell when nebulized (tested in the research pharmacy at the coordinating center).

3.3 Sample Size and Power Determination

Clinical Outcome: The sample size calculation is based on the assessment of the between-group difference in proportions of hospitalizations. This is a superiority study in which the adoption of the Mg therapy can only be recommended for future practice if the rate of the primary outcome in this group is significantly lower than in the controls. Calculations are based on a two-sided type I error of 0.05 and power of 80%.

Minimal Clinically Important Difference: The sample size is based on an absolute difference in hospitalizations between the study groups of 10 percentage points. This estimate is based on clinically relevant differences agreed upon by all study authors and it also represents NNT of 10. In the Cochrane reviews of anticholinergics and early corticosteroids by Plotnick and Rowe, respective NNTs of 12 and 8 led to a change in national practice recommendations[10,11]. In our North America-wide survey the majority of respondents considered a 10% reduced risk as a minimally clinically important difference that would prompt adoption of Mg.[12] Since almost a half of pediatric asthma costs relates to hospitalizations, this target difference would also have significant economic impact.

Outcome in the Control Group: The estimated hospitalization rate is based on our pilot data (blinded to the group assignment) where the overall (control plus intervention) hospitalization rate was over 40%. This rate is greater than that conducted by Dr Ducharme in a 2006 prospective audit of 1000 children presenting with acute asthma at Canadian EDs which showed that approximately 30% of patients with a PRAM score of ≥ 5 after bronchodilator therapy were hospitalized (personal communication, 2012). The one study in adults that focused on non-respondents to optimized initial Rx had an even higher admission rate of 71%[13]. To ensure adequate sample size, we have conservatively estimated that the control group hospitalization rate may be as high as 50%. With 408 patients per group (816 in total) a two-sided test with a type I error of 0.05 will have 80% power to achieve statistical significance if Mg therapy reduces the probability of hospitalization to 40% (i.e. absolute reduction of 10%). [14]

4 Study Subjects and Analysis Populations

4.1 Analysis Populations

4.1.1 Screened Population

The screened population includes all children screened for eligibility, regardless of randomization into the trial or treatment status. This population includes all children who meet inclusion criteria outlined in the protocol and who are screened in real time by study staff at the site. This population will be used for reporting of study flow as per CONSORT guidelines.

4.1.2 Intention-to-Treat Population

The ITT population includes all subjects who are randomized into the trial, regardless of adherence to the protocol or receipt of all experimental therapy. The ITT population will be used for the primary efficacy analysis, as well as for the efficacy analyses of the secondary outcomes. All analyses using the ITT population will be based on each patient's assigned treatment group, regardless of treatment actually received.

4.1.3 Per-Protocol Efficacy Population

This population includes all children in the ITT population who are verified to meet inclusion and exclusion criteria and who receive the study intervention according to their assigned study group (i.e. full three treatments of assigned Mg or placebo). This population will be used to

confirm if the results from the ITT population are maintained in the population adhering to the protocol.

4.1.4 Safety Population

This population will consist of all patients who received the study experimental intervention. The results will be summarized based on the treatment received. This population will be used for description of adverse events and (in addition to ITT) to examine safety outcomes.

4.2 Study Subjects

4.2.1 Inclusion and Exclusion Criteria

To be included, the patient must meet all of the following criteria:

Inclusion criteria:
(1) 2-17 years of age
(2) Diagnosis of asthma, defined as this diagnosis made by a physician or at least one prior acute episode of wheezing with cough and dyspnea treated with inhaled $ß_2$ agonists or oral corticosteroids. *Our study population will exclude bronchiolitis and first-time wheeze (potential alternate diagnoses).*
(3) *Persistent* moderate to severe airway obstruction after 3 doses of albuterol and ipratropium *(as per site specific standard of care guidelines),* defined as a PRAM 5 or higher. The PRAM score is a fully validated acute asthma score validated in the ED setting for children aged 12 months and older (see protocol Appendix F). *A PRAM score of 5 or more following initial therapy indicates the child has at least moderate disease severity[15] and has a high likelihood of being hospitalized[4,15-18]. This group of children includes 84% of all pediatric asthma hospitalizations; therefore, finding an effective therapy for this population has great potential to significantly reduce hospitalizations. (Protocol, Appendix B).* Although the admission rate for children with PRAM of 6 or more is high, randomizing only this population would miss 30% of asthma hospitalizations (Protocol, Appendix B).

Exclusion Criteria:
(1) No previous history of wheezing or bronchodilator therapy. *Some children who present with wheezing for the first time will have other diagnoses which would not be expected to respond to Mg.*
(2) Patients who have already received IV Mg therapy during the index visit.
(3) Critically ill children requiring immediate intubation. *These children need immediate ICU management and hospitalization.*
(4) Children who in the opinion of the treating physician require a chest radiograph due to atypical clinical presentation and are diagnosed to have lobar consolidation with pneumonia, felt to be the primary cause of respiratory distress. *These rare patients may have to be hospitalized primarily for treatment of the infection and may not respond to magnesium.*
(5) Known co-existent renal, chronic pulmonary, neurologic, cardiac or systemic disease. *These conditions may influence the response to Mg and hospitalization*.
(6) Known hypersensitivity to Mg sulfate.

(7) Patients previously enrolled in the study.
(8) Insufficient command of the English and or French language.
(9) Lack of a home or cellular telephone.
(10) Known allergy/sensitivity to latex.

5 General Analysis Issues

5.1 Analysis software
Analyses were performed with SAS, version 9.4

5.2 Withdrawals
As per the intention-to-treat principle, subjects who withdraw from the study will have all available data used in the analyses, unless the caretakers withdraw consent for the use of the data. In the event that a substantial number of patients are withdrawn or lost to follow up, baseline characteristics and hospital course will be reviewed and compared to patients not withdrawn, to assess if withdrawn subjects differ from those remaining in the trial.

5.3 Multicenter Studies
The randomization sequences will be stratified by site and age 2-5 years versus 6-17 years, to assure balance of sites and age distribution between the study groups at all times. The analyses will be stratified by site to account for baseline differences between sites.

5.4 Multiple Comparisons
The significance of the secondary outcomes will be adjusted for multiple comparisons. Specifically, the significance level for the secondary outcomes will be set at a two-sided level of 0.008 level to maintain the overall significance level at 0.05. The exploratory outcomes will not be adjusted, due to their exploratory nature.

5.5 Planned Subgroups and Covariates
The primary outcome will be analyzed by age ≤ 5 years, male gender, baseline PRAM score ≥ 8 points (severe asthma), atopy and viral-induced preschool wheeze (co-existent URI, no interval symptoms between colds, no atopy and age ≤ 5 years). In the event of significant co-linearity between variables (such as the age and pre-school wheeze), the clinically more important variable will be used in the regression analysis (in this case the age).

6 Overview of the Planned Analyses

6.1 Data Monitoring Committee

Data Monitoring Committee met after 200 patients randomized and yearly to review enrollment, study procedures, loss to follow up and serious adverse events.

This committee consisted of Dr Patricia Parkin (Division of Pediatric Medicine, the Hospital for Sick Children)-chair, Dr Neil Sweezey ((Division of Respiratory Medicine, the Hospital for Sick Children), Annie Dupuis (Statistician, Research Institute, the Hospital for Sick Children), and Judy Sweeney, the MAGNUM PA study manager.

To assure safety, there was one planned interim analysis on the first 200 patients randomized and evaluated by the independent data monitoring board. The interim analysis was based on a one-sided test of the null hypothesis of no difference versus the alternative hypothesis that the probability of hospitalization is higher on Mg therapy at the 0.01 level. That is, we were looking for evidence that Mg therapy is less effective, and the trial would have been stopped at an interim analysis only if the null hypothesis were rejected in favor of the control arm. Therefore, the interim analysis was only for safety and not for efficacy and it did not increase the probability of erroneously rejecting the null hypothesis in favor of Mg therapy at the final analysis. The reason we were doing one-sided (for harm) interim analysis is because if there was early strong evidence that Mg increases the probability of hospital admission, we wanted to stop the trial. On the other hand, we did not want to stop the trial early for benefit because a smaller sample size will not be convincing.

The committee was aware of the results of the interim analysis by treatment group, but not of the group identities. Study personnel and investigators were blinded to the interim analysis results until the time of the final analysis.

In addition, this committee met at least yearly to review enrollment progress and safety aspects- namely all serious adverse events and their management and reporting.

7 Planned Analyses

7.1 Analysis of the Primary Outcome

The primary analysis will consist of a two-sided Fisher's Exact test to determine the difference in the proportions of hospitalizations for asthma within 24 hours of randomization in the study groups. Significance for this analysis will be performed at a two-sided 0.05 level.

7.1.1 Additional analyses of the Primary Outcome

a) Logistic regression will be used to adjust for site.

b) In an exploratory analysis of the primary outcome, we plan to carry out a logistic regression analysis to examine for the treatment effect in the following *a priori* identified subgroups: baseline PRAM ≥ 8 points (i.e. severe asthma after initial therapy), age ≤ 5 years[19], male sex[3], personal history of atopy and viral-induced preschool wheeze (age ≤ 5 years, no cough between colds, no atopy).[20]

c) Logistic regression analysis to adjust the primary treatment effect for site and the aforementioned covariates prognostic of the outcome.

7.1.2 Sensitivity analysis of the Primary Outcome

We plan to carry out a per-protocol analysis including only patients who received all three study treatments. This will inform us if the results from the ITT population are maintained in the population adhering to the protocol.

7.2 Analyses of the Secondary Outcomes

The secondary outcomes will be analyzed for their association with the study group, using:

a) Analysis of covariance to compare the changes in the PRAM, respiratory rate, oxygen saturation from baseline (measured post-randomization) to 60, 120, 180 and 240 minutes between groups, adjusted for site.
b) Analysis of covariance to compare the changes in in blood pressure from baseline to 20, 40, 60, 120, 180 and 240 minutes, adjusted for site
c) A Poisson model to compare the number of additional salbutamol treatments (i.e. not including those given as part of the study treatments) within the 240 minute period in the ED.

7.3 Analyses of Other Outcomes

We shall use a two-sided Fisher's Exact test to examine the treatment effect on:

a) Hospitalizations for asthma within 72-hours,

b) Re-visits for asthma within 72 hours and

c) IV Mg therapy after experimental intervention in the ED.

Logistic regression will adjust these analyses for site.

7.4 Tables with Supplementary Results

Please see the next four pages.

Table 2. Primary Outcome – Hospitalization within 24 hrs

Logistic Regression Model, adjusted for site

PARAMETER	OR (95% CI)	p-value
Magnesium group	0.86 (0.64 – 1.15)	0.31
Placebo group	Reference	
Hospital for Sick Children (lead site)	Reference	
Alberta Children's Hospital	2.35 (1.56 – 3.58)	< 0.0001
Children's Hospital of Winnipeg	1.07 (0.35 – 3.30)	0.46
Stollery Hospital	2.31 (1.15 – 4.65)	0.03
St. Justine Hospital Montreal	1.08 (0.66 – 1.78)	0.60
Children's Hospital of Eastern Ontario	1.02 (0.61 – 1.72)	0.90
British Columbia Children's Hospital	0.62 (0.33 – 1.18)	0.17
Age ≤ 5 years	1.23 (0.91– 1.67)	0.19
Male sex	0.84 (0.62 – 1.14)	0.26
Atopy	0.95 (0.70 – 1.28)	0.72
Baseline PRAM ≥ 8	4.14 (2.69 – 6.36)	< 0.0001

OR: Odds Ratio
CI: Confidence Interval
PRAM: Pediatric Respiratory Assessment Measure

Interaction terms:

Site *Group *P=0.4056*

Group*Age ≤ 5 years *P=0.2987*

Group*PRAM ≥8 *P=0.6201*

Table 3. Respiratory rate changes within 240 minutes

Respiratory rate changes within 240 minutes*									
Time (min.)	**0**	**60**	**p-value**	**120**	**p-value**	**180**	**p-value**	**240**	**p-value**
Magnesium arm									
Mean RR (SEM)	38.25 (0.59)	35.27 (0.59)		34.73 (0.56)		33.54 (0.58)		33.46 (0.61)	
Change in RR from baseline Mg (SEM)		-2.93 (0.36)	<0.0001	-3.52 (0.39)	<0.0001	-4.71 (0.44)	<0.0001	-4.79 (0.50)	<0.0001
Placebo arm									
Mean RR (SEM)	38.40 (0.59)	37.32 (0.58)		35.92(0.56)		34.54(0.56)		34.14(0.59)	
Change in RR from baseline placebo (SEM)		-1.08 (0.36)	0.08	-2.47 (0.39)	<0.0001	-3.86 (0.44)	<0.0001	-4.15 (0.48)	<0.0001
Difference of changes Mg vs placebo		1.85 (0.55)	0.0002	1.05 (0.55)	0.06	0.85 (0.62)	0.17	0.54 (0.70)	0.44

RR – Respiratory rate
SEM = Standard error of the mean
Mg = Magnesium arm
*adjusted for study site

Table 4. Systolic blood pressure changes within 240 minutes

Systolic blood pressure changes within 240 minutes*									
Time (min.)	**0**	**60**	**p-value**	**120**	**p-value**	**180**	**p-value**	**240**	**p-value**
Magnesium arm									
Mean SBP (SEM)	109.28 (0.67)	111.07 (0.67)		109.15 (0.68)		108.88 (0.73)		109.06 (0.90)	
Change in SBP from baseline Mg (SEM)		-1.79 (0.55)	0.04	0.13 (0.58)	0.83	0.40 (0.62)	0.52	0.21 (0.83)	0.79
Placebo arm									
Mean SBP (SEM)	108.91 (0.67)	108.77 (0.66)		108.42 (0.67)		108.80 (0.71)		109.35 (0.85)	
Change in SBP from baseline placebo (SEM)		0.15 (0.54)	0.79	0.49 (0.5)	0.40	0.11 (0.60)	0.85	-0.43 (0.76)	0.57
Difference of changes Mg vs placebo (SEM)		-1.94 (0.78)	0.01	0.36 (0.82)	0.66	0.29 (0.86)	0.74	0.64 (1.10)	0.56

SBP – Systolic Blood Pressure
SEM = Standard error of the mean
Mg = Magnesium arm
*adjusted for study site

Table 5. Oxygen saturation changes within 240 minutes

Oxygen saturation changes within 240 minutes*									
Time (min.)	**0**	**60**	**p-value**	**120**	**p-value**	**180**	**p-value**	**240**	**p-value**
Magnesium arm									
Mean O_2 sat (SEM)	93.61 (0.17)	94.93 (0.17)		94.73 (0.17)		94.76 (0.18		94.80 (0.20)	
Change in O_2 sat from baseline Mg (SEM)		1.32 (0.13)	<0.0001	1.12 (0.13)	<0.0001	1.15 (0.15)	<0.0001	1.19(0.17)	<0.0001
Placebo arm									
Mean O_2 sat (SEM)	93.82 (0.17)	94.85 (0.17)		94.80 (0.17)		94.96 (0.18)		94.78 (0.19)	
Change in O_2 sat from baseline placebo (SEM)		1.03 (0.13)	<0.0001	0.98 (0.13)	<0.0001	1.14 (0.14**)**	<0.0001	0.96 (0.16)	<0.0001
Difference of changes Mg vs placebo		0.29 (0.18)	0.10	0.14 (0.18)	0.44	0.01 (0.21)	0.95	0.23 (0.24)	0.31

O_2 sat – Oxygen saturation
SEM = Standard error of the mean
Mg = Magnesium arm
*****adjusted for study site

8 Adverse Events

8.1 Expected Adverse Events

Expected adverse events will relate to expected components of asthma management and to the taste of the study solutions and will include cough, respiratory distress (disease-related), asthma-related hospitalization, IV insertion, sinus tachycardia, nausea and bitter/salty taste of the experimental solution. These events will be collected during the study data collecting process but will not be reported as adverse events.

8.2 Unexpected Adverse Events

Basic summaries of these events with their incidence rates, severity and relationship to the study intervention will be prepared. The analysis will include the aggregate outcome consisting of the presence of any of these events (observed in the ED or reported by the caregivers) in the two study groups, using logistic regression analysis, with adjustment for site.

8.3 Serious Adverse Events (SAEs)

The SAEs will consist of hypotension below the 5^{th} percentile for age requiring intervention, apnea and admission to intensive care unit. Because of the small number of anticipated SAEs, we do not plan to carry out a formal analysis of this outcome.

We shall report the SAEs in a descriptive way.

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