Amendment to the Statistical Analysis Plan from April 12th 2019

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

September 16, 2020

Protocol Date: **February 1st, 2019**

Preface

1.1. Purpose of SAP

This amendment to the Statistical Analysis Plan (SAP) from April 12th 2019 describes the final analyses 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 Additional analyses and reporting performed in addition to those pre-specified in the April 12th SAP:

1.21 Sample size

As mentioned in the previous SAPs, this trial was initially launched as a two-center trial, with a targeted sample size of 284 patients, to detect a minimally significant difference of 15 percentage points to decrease the hospitalization rate from 30% to 15%, with a power of 80%. However, during this phase, the primary outcome rate had an overall event rate of 50% and thus we would be under-powered to evaluate our primary outcome. Therefore, this phase of the study was considered to be a pilot phase which informed the final protocol sample size calculations targeting a difference of 10 percentage points between groups in the primary outcome. Because the study remained blinded, and no analyses were performed, the final significance threshold remained unchanged.

The new targeted difference of 10 percentage points was based on a national survey of pediatric emergency medicine physicians (unpublished data), and on the evidence that this difference has

previously led to changes in national guidelines. Employing a type I, two-sided error of 0.05 and 80% power, our new targeted sample size was 816 participants.

1.3 Planned Analyses

1.31 Amendment to all analyses:

a) Because the randomization was stratified by age group (≤ 5 years versus ≥6 years) and by site, all previously planned analyses were also adjusted for these stratification factors using generalized linear mixed modeling for the primary and all other outcome analyses, where the site was treated as a random effect. This method was also used in the per-protocol analysis to estimate treatment effect of magnesium in children who received all experimental treatments.
b) Instead of the odds ratios, adjusted relative risk differences were used to quantify effect sizes.

Overall significance for primary and secondary outcomes was set at 0.05 (two-sided). Statistical analysis was performed using version 9.4 of the SAS system for Windows, 2002-2012 SAS Institute, Inc., Cary, NC. USA, and the open source statistical software R version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria, 2019).

1.32 Analysis of the Primary Outcome

The primary analysis consisted 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 was performed at a two-sided 0.05 level.

1.33 Additional analyses of the Primary Outcome

a) In addition, generalized linear mixed modeling was used to adjust for stratification at randomization for the age group (≤ 5 years versus ≥6 years) and site.
b) Instead of the odds ratios, adjusted relative risk differences were used to quantify effect sizes.
c) Instead of the logistic regression analysis, the subgroup analysis was performed using generalized linear mixed modeling with treatment group-subgroup interaction factor, controlling for the aforementioned stratification variables, and reported adjusted risk differences for each subgroup. We used the following *a priori* identified subgroups for subgroup analyses: post-

randomization baseline PRAM ≥ 8 (indicating severe asthma), age ≤ 5 years, male sex, personal history of atopy, and historical report of viral-induced preschool wheeze (age ≤ 5 years, no cough between colds, no atopy).

1.34 Sensitivity analysis of the Primary Outcome

We carried out a per-protocol analysis using the methods above, including only patients who received all three study treatments in order to find out if the results from the entire study population were maintained in the population adhering to the protocol.

1.35 Analyses of the Secondary Outcomes

a) To analyze our secondary outcomes, we used mixed model method to compare changes from baseline in PRAM score, respiratory rate and oxygen saturation between groups from baseline (measured post-randomization) to 60, 120, 180 and 240 minutes and to compare changes from in blood pressure from baseline to 20, 40, 60, 120, 180 and 240 minutes.

b) We used generalized linear mixed modeling with negative binomial distribution to compare the number of additional albuterol ED treatments administered within 240 minutes between groups.

1.36 Analyses of Other Outcomes

The aforementioned generalized linear mixed modeling was also used to examine magnesium treatment effect on hospitalizations within 72-hours, re-visits within 72 hours, and IV magnesium treatment after the experimental therapy.

1.4 Adverse Events

1.41 Expected Occurrences

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

1.42 Adverse Events

Basic summaries of these events (observed in the ED or reported by the caregiver) with their incidence rates, severity and relationship to the study intervention were prepared. Because these events were uncommon, they were not formally analyzed but were reported in a descriptive way.

1.43 Serious Adverse Events (SAEs)

The SAEs consisted 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, no formal analysis of this outcome was done.