Amendment to the Statistical Analysis Plan

The Journey of the MAGNUM PA Trial

This Health Canada regulated trial started as a two-center randomized clinical trial at the Hospital for Sick Children (Toronto) and the Alberta Children's Hospital (Calgary) in 2011, funded by the Thrasher Research Fund.

In 2013, we received further funding from the Canadian Institutes of Health Research and the Physicians Services Incorporated Foundation to continue this trial at seven sites in Canada.

Because the design of the trial before and after 2013 was identical, we have kept the treatment allocation of the participants enrolled in the initial phase concealed and continued enrollment using the same procedures between 2013 and 2019. The final product therefore includes the participants from both phases.

There have been the following changes in the final analyses of this trial:

1- Secondary/other outcomes:

a) All-cause hospitalizations within 24 hours: no patient in the study has been hospitalized for any cause other than persistent respiratory distress. Therefore, the analysis of this outcome could not be done.

b) IV Mg administration represents an important outcome reflecting the need for further therapy due to persistent respiratory distress. Because this outcome has been integral part of the case report form throughout the study, we have included IV Mg therapy as "other outcome" and analyzed it appropriately.

2- Sample size:

The sample size calculation is based on the assessment of the between-group difference in proportions of hospitalizations. The sample size for the initial phase (280) was based on 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 (Appendix G). For the initial phase, we were targeting a minimally significant difference in hospitalizations of 15 percentage points (see protocol 2011).

However, we found that the overall hospitalization rate in the initial phase was much higher, over 40%, and the initially estimated sample size was therefore inadequate to reliably detect a minimum clinically significant difference in hospitalizations. For this reason, we have conservatively estimated the hospitalization rate in the control group to be as high as 50% and we proposed a substantially larger sample size (816) to achieve definitive results. This new sample size also reflected a revised targeted minimally significant difference in hospitalization of 10 percentage points (see protocol 2014). This estimate was based on a clinically relevant difference agreed upon by all study authors, one which led to a change in national practice recommendations and was considered an important difference in our North America-wide survey that would prompt adoption of Mg.

For these reasons, the sample size calculation was revised to 816 as part of the CIHR grant submission in 2013, the protocol was revised accordingly and received REB approval at all study sites.

3- Additional Analyses of the Primary Outcome:

a) We shall use logistic regression analysis to adjust the primary treatment effect for site.

b) We shall use logistic regression analysis to adjust the primary treatment effect for *a priori* defined covariates which predict hospitalization, namely age ≤ 5 years, male sex, baseline PRAM ≥8, personal history of atopy, as well as for site.

c) Per-protocol analysis of the primary association will be done to ensure that the results of the primary analysis are comparable to those using patients fully adhering to the study treatment.

4- Analyses of the Secondary Outcomes

d) To account for the multiple comparisons required to assess secondary outcomes, we shall use the Holm method, resulting in a significance level of 0.008 for each individual secondary outcome.

e) A two-tailed Fisher's Exact Test will be used to compare the proportions of asthma-related 1) hospitalizations and 2) re-visits to any medical facility within 72 hours and 3) IV Mg treatments after experimental therapy in the ED in the study groups and logistic regression analysis will be employed to adjust these associations for site.

5- Results not included in the manuscript due to space limitation (see SAP 2020):

f) Blood pressure changes within 240 minutes*

g) Respiratory rate changes within 240 minutes

h) Oxygen saturation changes within 240 minutes

i) Details of the logistic regression analysis adjusting the primary association for site and covariates