Intravenous Magnesium: Prompt use for Asthma in Children Treated in the Emergency Department (IMPACT-ED)
PECARN Protocol Number 054

Pediatric Emergency Care Applied Research Network
National Heart, Lung, and Blood Institute (NHLBI)

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PROTOCOL TITLE:

Intravenous Magnesium: Prompt use for Asthma in Children Treated in the Emergency Department

Short Title: IMPACT-ED
PECARN Protocol Number: 054

Lead Investigator and Author:
Michael D. Johnson, M.D.
University of Utah

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I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: Michael D. Johnson MD

Principal Investigator Signature: 

Date: 16 March 2023

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Abstract

Asthma is the most common chronic illness of childhood and a leading cause of hospitalization and healthcare costs for children. Most children hospitalized for asthma first receive breathing treatments and steroid medicines in an emergency department (ED) according to national guidelines. An additional medicine, intravenous magnesium sulfate (IVMg), may help severely sick children avoid hospitalization. National asthma guidelines recommend IVMg for severely sick children, but note a lack of consistent evidence to support this recommendation. Only about one in four children hospitalized for asthma received IVMg in the ED. Estimates of the potential effects of broader use of IVMg on hospitalization are limited by the small size of prior trials, but increased use could potentially avoid 16,500 hospitalizations each year, producing direct cost savings of $65 million yearly in addition to saving significant indirect costs of missed school and parental work.

A few major questions remain about IVMg. First, it has not been tested early in ED treatment, when the impact on hospitalization would be greatest. Second, the clinical impact of hypotension, a driver of low utilization, is not characterized in prior trials or clinical databases. Third, no trials have compared different IVMg doses or measured serum magnesium levels to optimize dosing, so the most effective dose is unknown.

All prior trials of IVMg in children with asthma have been small. A large randomized, placebo-controlled clinical trial of IVMg that could answer whether IVMg can reduce hospitalization might be challenging for a few reasons. First, enrolling patients fast enough to give IVMg early in ED treatment is challenging. Second, understanding blood pressure changes after IVMg is essential to plan safety monitoring for a larger trial. Third, little pharmacologic information has been gathered to guide the doses of IVMg to be tested. We must conduct a small pilot clinical trial to test our procedures and gather necessary information to plan the large trial.

The Pediatric Emergency Care Applied Research Network (PECARN) is a network of children's EDs that has conducted similar research involving acutely ill children. Our goals in this project are to:

1. *Demonstrate the feasibility of enrolling children in the ED with severe acute asthma in a multicenter, randomized, controlled trial of placebo, low-dose IVMg, or high-dose IVMg.*
2. *Demonstrate the feasibility of timely delivery of study medication to enrolled patients and assessment of blood pressure and associated adverse events in a standardized protocol.*
3. *Externally validate a previously constructed PK model and develop a combined PK/PD model for IVMg using magnesium (total and ionized) serum concentrations and their correlation with measures of safety and respiratory distress in children with asthma.*

After completing this pilot trial in three sites, we will plan a multi-center randomized trial of IVMg in children with severe acute asthma at more sites to enroll enough children to know if IVMg can reduce hospitalization.

1 Study Summary

Many children currently being hospitalized with severe asthma could potentially avoid hospitalization and be sent home if their treatment in the emergency department was more effective. We will

conduct a pilot trial that will lead to a larger study to conclusively answer whether a simple and inexpensive medicine, intravenous magnesium sulfate, can be used in the emergency department to prevent hospitalization for these children.

1.1 Hypotheses

Hypothesis: we can identify, consent, and enroll an average of 1 subject per site per week, resulting in total enrollment of 90 patients in 7 months or less.

1.2 Specific Aims

This project has the following Specific Aims:

Specific Aim 1. Demonstrate the feasibility of enrolling children in the ED with severe acute asthma in a multicenter, randomized, controlled trial of placebo, low-dose IVMg, or high-dose IVMg.

Specific Aim 2. Demonstrate the feasibility of timely delivery of study medication to enrolled patients and assessment of blood pressure and associated adverse events in a standardized protocol.

Specific Aim 3. Externally validate a previously constructed PK model and develop a combined PK/PD model for IVMg using magnesium (total and ionized) serum concentrations and their correlation with measures of safety and respiratory distress in children with asthma.

2 Rationale and Background

2.1 Hospitalization for Children With Asthma is Common Despite Current Standard Treatment

Asthma is the most common chronic illness of childhood and a leading cause of pediatric hospitalization, disability, and healthcare-related costs.[1] Acute asthma resulted in 626,923 Emergency Department (ED) visits[2] and 75,905 hospitalizations[3] in 2017 for children 0–17 years old in the United States. Hospitalization is a primary driver of direct costs for asthma in children,[4] contributing $3.9 billion of the $5.9 billion in total pediatric asthma costs estimated in 2017,[5] in addition to indirect costs from school absenteeism and lost parental work.[6]

Current standard management of acute asthma in children is defined in guidelines published in 2007 by the National Heart, Lung, and Blood Institute (NHLBI) and includes inhaled bronchodilators (albuterol and ipratropium), systemic corticosteroids, oxygen, and further treatment depending on

response.[7] Although these guidelines have been broadly implemented, hospitalization remains a common outcome for children with asthma after ED treatment, ranging from 13% to 50% of all asthma visits among pediatric EDs nationally.[8]

2.2 Intravenous Magnesium Sulfate (IVMg) May Reduce Hospitalization for Children, But Is Used Variably

IVMg may reduce hospitalization in children with asthma. Eight prior clinical trials reported results of IVMg in children with acute asthma, though only five compared to placebo, and only three evaluated hospitalization, all as a secondary outcome (bold, Table 1). These three trials included 31,[9] 30,[10] and 54[11] patients each, and reported absolute hospitalization reductions of 27%, 50%, and 8% respectively. Meta-analysis of these three trials estimated the true reduction in odds of hospitalization to be between 26% and 86%, an estimate that was less precise and not significant after sensitivity analysis (OR 0.18, 95% CI 0.02 to 1.59).[12]

Table 1: Randomized Controlled Trials of IVMg in Children with Acute Asthma

lead author	year	n	age	treatment	control	outcomes
Irazuzta	2015	38	6–18	50 mg/kg/hr for 4 hours (max 8 gm in 4 hr)	IVMg 50 mg/kg (no max) over one hour	Discharge home within 24 hours
Singhi	2014	100	1–12	50 mg/kg over 20 min (no max)	IV terbutaline, IV aminophylline	Score reduction
Torres	*2012*	*143*	*2–15*	*25 mg/kg over 20 min (max 2 g)*	*None*	*Mechanical ventilation*
Scarfone	***2000***	***54***	***1–18***	***75 mg/kg over 20 min (max 2.5 g)***	***Saline placebo***	***Score reduction, hospitalization***
Ciarallo	**2000**	**30**	**6–18**	**40 mg/kg over 20 min (max 2g)**	**Saline placebo**	**PEFR, FEV_1, FVC, hospitalization**
Gurkan	1999	20	6–16	40 mg/kg over 20 min (max 2 g)	Saline placebo	PEFR and score reduction
Devi	1997	47	1–12	100 mg/kg over 35 min (no max)	Saline placebo	PEFR and SaO_2
Ciarallo	**1996**	**31**	**6–18**	**25 mg/kg over 20 min (max 2 g)**	**Saline placebo**	**PEFR, hospitalization**

PEFR: peak expiratory flow rate; SaO_2: oxygen saturation; FEV_1: forced expiratory volume in 1 second; FVC, forced vital capacity.

bold: hospitalization as secondary outcome; *italic*: enrolled on arrival to ED.

IVMg has been used to treat asthma for more than 70 years[13, 14] but its specific role in pediatric asthma is still unclear.[12] NHLBI asthma guidelines suggest that clinicians consider a 20-minute infusion of IVMg in children or adults as an adjunct for life-threatening exacerbations, or for severe distress after an hour of initial therapy, and do not suggest a specific dose, but rather provide a broad three-fold dose range of 25–75 mg/kg. Conflicting evidence prevents a definitive recommendation

or direction for clinical implementation.[7]

The clinical effect of IVMg in asthma may involve multiple components of pulmonary and immune physiology relevant in acute asthma. These mechanisms include directly relaxing smooth muscle,[15] blocking calcium uptake in smooth muscle membranes through N-methyl-D-aspartate receptor-gated channels,[16, 17] inhibiting histamine and acetylcholine release at neuromuscular junctions,[18, 19] and direct anti-inflammatory effects.[20] Compared to adjunctive bronchodilators in severe acute asthma such as IV aminophylline, IV terbutaline, and subcutaneous epinephrine, IVMg is better tolerated, more widely available, and less expensive.[21]

IVMg is widely used in EDs to treat children with asthma, but use is variable. The Pediatric Emergency Care Applied Research Network (PECARN), the first and only federally-funded pediatric emergency medicine research network, maintains a Registry that collects complete medical record data from the EDs of children's hospitals and affiliated community hospitals. In a review of 7 sites in the PECARN Registry conducted by Drs. Johnson (PI), Zorc (PI), Finkelstein (Co-I), Casper (OSC), and colleagues, IVMg was administered in 6,497 of 61,854 ED visits (10.5%) for children with asthma from 2011–2017.[22] Of 22,499 children hospitalized for asthma in the PECARN Registry, 5,774 (25.7%) received IVMg in the ED, varying by site from 15.9% to 50.6% (see Figure 1 in A5. Preliminary Work). In a comparable review of asthma care delivery in six pediatric EDs in Canada, ED clinicians administered IVMg to 12% of children hospitalized with asthma, and to only 0.2% of children discharged home.[23] When surveyed, US and Canadian physicians generally reserve IVMg to prevent admission to the intensive care unit (ICU), and only 7% of respondents use it to prevent hospitalization.[24]

More broad and standardized use of IVMg, if effective, may reduce hospitalizations and related healthcare costs for children, and would be cost-effective. An economic analysis of children with asthma at two hospitals concluded that IVMg reduced costs by 28% and increased Quality-Adjusted Life Years.[25] Though estimates are limited by the size and number of prior trials, if IVMg produces a 30% relative reduction in hospitalization, administering IVMg in the ED to children who do not receive it in the US could avoid 16,500 hospitalizations each year at an average cost of $3,600 each,[26] which would save $60 million yearly in direct costs in addition to indirect costs of missed school and parental work. If IVMg is found to not be effective in a well-powered clinical trial, its use could be appropriately guided and restricted by the trials results, future investigation can focus on other therapies, and these findings should be included in institutional and national asthma guidelines.

2.3 IVMg Has Not Been Adequately Studied in Children With Asthma

Sustained uncertainty persists about the role of IVMg for children with asthma. Each of the six meta-analyses published in the past two decades analyzed the same three small trials and concluded similarly that evidence to guide the use of IVMg is "extremely limited by the number and size of studies",[12] that IVMg "has not been widely tested against what is considered guideline based therapy",[27] that "further randomized controlled trials with large sample sizes are also required to establish the optimal dosage",[28] that estimates of the effect of IVMg on hospitalization are

imprecise[29] because "most of the included studies were small and not powered to detect potentially important differences in hospital admission rates",[30] and that "additional research is required to determine the optimal dose".[31]

Previous trials of IVMg are insufficient to guide the clinical use of IVMg. Dosage protocols in pediatric clinical trials ranged widely from a low of 25 mg/kg (maximum 2 grams)[9] to a high of 100 mg/kg (no maximum),[32] and *no trial directly compared differing doses*. No trial of IVMg has evaluated hospitalization as a primary outcome. The largest dose in a trial that evaluated effect on hospitalization as a secondary outcome was 75 mg/kg (maximum 2.5 grams).[11] Dosage in clinical practice is variable. Dosage in clinical practice ranged from 25–50 mg/kg in a review of IVMg use in Canada.[23] The majority (72.5%) of the 6,497 doses of IVMg recorded in the PECARN Registry were 50 mg/kg, though 63 doses in the PECARN Registry were 75 mg/kg.[22]

Because prior trials of IVMg in children were small and have not compared different doses of IVMg, the dose-response of IVMg with efficacy or safety is unknown.[29] The safety of IVMg in children with asthma in the ED has been systematically assessed in only 89 children who received it in five separate placebo-controlled clinical trials;[9–11, 32, 33] Fifteen children received 25 mg/kg in one trial,[9] 26 received 40 mg/kg across two separate trials,[10, 33] 24 received 75 mg/kg in one trial,[11] and 24 received 100 mg/kg in one trial.[32] *No hypotension or other clinically significant side effects were reported in these small trials*. No clinically significant side effects were reported in 35 children in a prospective observational study conducted by Drs. Johnson (PI) and Rower (Co-I)[34] and in 53 children who received IVMg in a review of clinical use,[35] *though in another larger review of clinical use by Dr. Zorc of 100 children who received IVMg 50 mg/kg in an ED, 11 (11%) had hypotension recorded* approximately 30 minutes after the start of infusion, 7 of whom received intervention after IVMg, limited to an intravenous saline bolus.[36] In an even larger cohort of 6,497 children who received IVMg in the PECARN Registry, 439 (6.8%) had hypotension recorded in the ED after IVMg. These larger retrospective studies found hypotension after IVMg that was not detected in small prospective trials, but lack detail necessary to understand the significance of blood pressure changes after IVMg, whether it was associated with poor perfusion, or whether it led to clinical interventions directed at hypotension.

The equipoise needed to study the effect of IVMg versus placebo on hospitalization in a large clinical trial is illustrated by a combination of possible but uncertain clinical benefit for ill children, variation in clinical use, lack of consensus regarding clinical benefit, and evidence gaps from prior trials repeatedly outlined in meta-analysis. IVMg is inexpensive and readily available in current clinical settings. IVMg has potential to improve the outcomes of ED treatment for children with asthma, but requires further evaluation of its efficacy, safety, and optimal dosage in a robust trial setting. PECARN has completed a prior NHLBI-funded randomized trial of IVMg in children with sickle cell disease, an indication with much less supporting data for efficacy.[37]

This study focuses on IVMg, though other administration methods for magnesium have been explored and deserve brief mention. Inhaled nebulized magnesium was suggested to have possible benefit in children with asthma in a systematic review.[27] However, a recent large multicenter randomized trial of nebulized magnesium in children with asthma in 7 EDs in Canada found no effect,[38] similar to the findings of a randomized trial conducted at 30 hospitals in the United Kingdom,[39] similar to results in adults.[40] Oral magnesium has no role in the treatment of acute

asthma in the ED due to limited oral absorption[41] and delayed onset of effect.[42]

2.4 Rationale

Before a definitive randomized, double-blind, placebo-controlled trial can be planned and completed to determine the efficacy of IVMg on preventing hospitalization in pediatric asthma, several specific knowledge gaps remain. ***We propose closing these knowledge gaps through a pilot trial that will mirror the large conclusive trial as closely as possible, including study design, intervention arms, procedures, study population, and outcome measures***. Real-world implementation of the study protocol in the pilot trial will allow us to test and refine trial procedures and simultaneously gather data necessary and sufficient to plan the large trial.[43] Specifically, the pilot trial will address the following knowledge gaps:

First, ***prior trials evaluated IVMg for acute asthma only in children refractory to initial treatment.*** This gave very little time during ED treatment to recognize improvement related to IVMg administration prior to hospitalization. Timing of medication delivery in pediatric acute asthma greatly affects a child's probability of hospitalization. For example, in 406 children with moderate or severe asthma in an ED, each 30 minute delay in administration of systemic corticosteroid after triage increased the odds of hospitalization by 23%.[44]

Though IVMg is currently infrequently used in clinical practice in the ED to prevent hospitalization,[24] earlier administration could have a greater effect on this important outcome. In a placebo-controlled trial in 30 children with suboptimal response to albuterol, those given IVMg versus placebo had significant improvement in spirometry 20 minutes after the completion of IVMg infusion.[10] For children with acute asthma, the decision to hospitalize is often made within the first 130 minutes of treatment.[45] For the effect of IVMg on hospitalization to be detectable within the first 130 minutes of a normal ED visit, it must be given within 90 minutes of arrival in the ED, providing 20 minutes for infusion of IVMg and 20 minutes after the end of infusion for a detectable physiologic effect before the clinicians disposition decision is made. One fourth of children who received IVMg in PECARN Registry EDs received it within 84 minutes after arrival, demonstrating that early administration is not common, but possible.[22] Administration early in the treatment course would better align with the NHLBI recommendation that IVMg be considered after the first hour of treatment.[7] Only one prior trial of IVMg with hospitalization as an outcome attempted to enroll children on arrival to the ED (bold and italicized, Table 1).[11] Before a large trial can determine the effect of early administration of IVMg on hospitalization, protocols to support administration in the first 90 minutes of treatment should be tested and refined in a pilot trial setting.

Second, ***the safety of IVMg is not well characterized in prior trials.*** Earlier small trials reported no significant adverse events after IVMg but included too few children to conclude adverse effects were rare. Retrospective reviews of clinical practice suggest adverse effects associated with IVMg are present, but lack sufficient detail to conclude if they have clinical impact. In a study by Dr. Zorc (co-PI) of 100 children who received a single dose of 50 mg/kg in an ED, 7 of the 11 who had hypotension after IVMg received an intravenous fluid bolus with normalization of blood pressure.[36] Of the 4,392 children in the PECARN Registry who had blood pressure recorded within two hours

both before and after IVMg, 294 (6.7%) had hypotension recorded after IVMg with an average reduction of 14 mmHg (SD 14) from baseline and an average reduction of 6 mmHg (SD 5) below normal age-adjusted values.[22] However, the retrospective nature of the study database and the lack of standardized monitoring prevents conclusions regarding the clinical impact of IVMg on blood pressure. Data that is more detailed than current clinical data is needed to inform safety.

Safety data plays a critical role in informing large randomized controlled trials. A large trial could attempt prolonged intensive blood pressure monitoring, but this places a major burden on clinical and study staff, decreasing the likelihood of successful study enrollment. In addition, there is no data to inform whether higher doses of IVMg have a dose-dependent effect on blood pressure, information necessary to define a threshold of safety for dosage. Before a large trial of IVMg is performed in an ED setting, intensive monitoring of blood pressure in patients receiving different doses of IVMg in a limited study setting is necessary to understand the timing of blood pressure changes, and whether hypotension after IVMg is transient without clinical impact, associated with other systemic signs, prolonged, or more common in children given higher doses of IVMg. This will inform planning for monitoring in the future trial that is focused, effective, and clinically feasible. In a multinational survey of ED physicians, 24% reported hesitancy using IVMg in children because of the risk of hypotension.[24] *Even if hypotension is transient, it is a major concern for physicians, making it essential that our trial clarify concerns conclusively for clinicians.*

The short half-life of IVMg may raise concern that by administering IVMg to a patient and then discharging that patient home, a clinician has merely masked asthma symptoms temporarily, placing the patient at risk for decompensation once the effect of IVMg resolves outside a healthcare setting. Of 723 children discharged from PECARN EDs after receiving IVMg for asthma, only 13 (1.8%) returned to the ED within 72 hours, which is less but not statistically different than the return rate in patients discharged without receiving IVMg (3.5%).[22] The size of a pilot trial does not allow sufficient power to make definite conclusions regarding safety. However, collection of safety outcomes in a trial environment, including data collected after discharge from the ED, will allow enhancement and refinement of safety monitoring procedures for the future trial.

An additional component of safety is the risk of adverse effects due to serum concentrations of magnesium above recommended thresholds. As an example from obstetric literature, therapeutic effect in eclampsia occurs with serum magnesium (srMg) concentration between 2 and 4 mmol/L, but srMg above 5 mmol/L can lead to loss of deep tendon reflexes and above 7.5 mmol/L to respiratory depression.[46] In the only published prospective examination of IVMg pharmacology in children treated for asthma in the ED, Drs. Rower, Johnson, and colleagues observed that of 32 children given an IVMg dose of 50 mg/kg (2 gm maximum), the highest srMg was 1.4 mmol/L and none experienced adverse effects.[34] There is no published data from the ED describing serum concentrations after children receive doses of IVMg larger than 50 mg/kg, though 24 children with asthma received 75 mg/kg in a prior trial with no adverse effects.[11] In eight children who received 75 mg/kg over 30–45 minutes followed by 40 mg/kg/hr for four hours in an ICU, the highest srMg measured was 3 mmol/L, below toxic thresholds established in obstetrics, with an average (SD) srMg at the end of infusion of 1.8 (0.4) mmol/L.[47] A pilot trial would provide valuable data in children with asthma to correlate dosing with both blood pressure and serum concentrations so that doses used in a future trial are safe.

Third, ***the optimal dosage of IVMg in pediatric acute asthma is unknown.***[28] Our current pharmacologic understanding of IVMg is insufficient to define which doses should be tested in clinical trials to carefully strike a balance between avoiding potential adverse effects and exploring maximal clinical effect. To safely explore thresholds of efficacy and safety in a large trial, we must fill gaps in the pharmacologic understanding of IVMg.

A serum biomarker for therapeutic effect would be valuable to allow rational dose selection for IVMg in future trials. Mechanistically, bolus IVMg affects target tissue through a cascade of increased ionized magnesium (ioMg) concentrations, first in the serum (extracellular) following infusion, then in the extracellular space of the target tissue, followed by diffusion to the intracellular space producing clinical effect. In this schema, the measurement of ioMg in the serum could be directly related to the potential effect in the target tissue. The concentration of magnesium inside blood cells, or intracellular magnesium (icMg), could be a closer surrogate for the concentration within the target lung tissues, but is uncommonly tested even in research laboratories. A measurement of all magnesium in the serum including ioMg and magnesium bound to serum proteins, srMg, is the most common clinical measurement of magnesium. In obstetrics, a srMg value between 2 and 4 mmol/L appears to correlate to the desired clinical effect.[48] In meta-analysis of obstetrical trials of IVMg, dosage protocols that produce these serum concentrations are associated with no significant toxicity.[46]

Unfortunately, directly applying the results of studies in pregnant adults to children with asthma is inappropriate due to difference in anatomy, physiology, health status, and site of action of IVMg. Pharmacologic data in children with asthma is limited to a very small case series,[49] severely ill patients in ICU settings[47] including one conducted by Drs. Johnson and Rower,[50] and one prospective pharmacokinetic (PK) study conducted at a single ED by Drs. Rower, Johnson and others.[34] We found that bolus doses of 50 mg/kg produce srMg concentrations of 1–1.6 mmol/L, below the low end of the range of therapeutic concentrations in pregnant adults. No study has clarified the pharmacodynamic (PD) association of serum concentrations in asthma with clinical effects such as change in respiratory distress or blood pressure. However, Drs. Johnson, Zorc, Rower, and Finkelstein presented preliminary results in 28 children showing possible correlation of increase in ioMg with decrease in clinical asthma severity score after IVMg, though the number of patients was too small to confidently quantify correlation.[51] All prior trials of IVMg in children with asthma relied on likely therapeutic serum ranges and thresholds of toxicity developed from pregnant adults. Therapeutic serum ranges for children have not been developed, and thresholds of toxicity are guided by the small handful of studies just described. Despite being the most common clinical measurement, srMg values are rarely obtained clinically in children with asthma; only four of the 6,497 administrations of IVMg across four sites in PECARN had srMg obtained before and after infusion and no patients had icMg or ioMg measured.[22] To define the optimal dose of IVMg, safety and efficacy outcomes (PD) must be correlated with srMg (PK) obtained from a range of doses.

Informative PD analysis requires a marker of respiratory status that can be measured reliably and repeatedly in all patients. Children in severe respiratory distress and young children are typically unable to complete objective measures of lung function such as spirometry or peak flow. In 456 children 6–18 years old in an ED with acute asthma, only 54% could perform spirometry at presentation.[52] In 101 children 6–17 years old at a different ED only 35% could successfully

perform spirometry at any point in the ED stay, however, clinical asthma scores were obtained in all eligible children.[53] The use of spirometry as inclusion criteria in most prior trials[9, 10] excludes most older patients in severe respiratory distress, and also excludes children four years and younger by design, as they can rarely cooperate sufficiently to perform adequate spirometry.

To circumvent the aforementioned limitations of spirometry, clinical asthma scores have been used as measures of respiratory status in prior trials, though rarely as inclusion criteria. The Pediatric Respiratory Assessment Measure (PRAM) is a clinical respiratory score that presents the clinician with a set of descriptors for 5 elements describing clinical findings, with each descriptor assigned a numerical value. The clinician selects descriptors, and numerical values are summed to give the overall score, with a scale 0–12. It is widely used to measure response in the ED as well as in prior trials that showed clinical effect of IVMg on hospitalization (Table 2).[9, 10] It has been validated in children to be predictive of hospitalization[54, 55] and to show change in respiratory status after a bronchodilator.[55] In a study performed by Dr. Johnson in 48 children 2–16 years old, 75% of children with a PRAM score in the severe range (8 or greater) at presentation to the ED were hospitalized after ED treatment,[56] demonstrating ability of the PRAM to identify children at high risk of hospitalization early in the ED course. For a future trial to be relevant to both prior trial results and to current clinical practice, we must use a respiratory score such as PRAM as inclusion criteria and as a mark of respiratory status to allow repeated measurement in every patient, comparison of respiratory status between arms, and to facilitate clinical translation of results.

Though children four years old or younger are often excluded out of concern that their respiratory distress is of a different phenotype than asthma, this age group accounts for more than half of children treated and hospitalized with a primary diagnosis of asthma[57] and for more than 30% of children who currently receive IVMg in clinical use.[22] The high burden of hospitalization and widespread use of IVMg in young children gives weight to the importance of studying IVMg in this age group. We will separately examine the PD response of children 2–4 years old in exploratory subgroup analysis to guide planning for the larger trial.

Table 2: Pediatric Respiratory Assessment Measure (PRAM)

score	suprasternal retractions	scalene muscle contraction	air entry	wheezing	O_2 saturation
0	absent	absent	normal	absent	≥95%
1			decreased at bases	expiratory only	92–94%
2	present	present	widespread decrease	inspiratory and expiratory	<92%
3			absent/minimal	audible w/o stethoscope or silent chest w/minimal air entry	

3 Subject Eligibility, Accrual and Study Duration

3.1 Eligibility Criteria

Eligible participants will be identified by on-site study staff.

Inclusion criteria are:

1. 2–17 years old
2. Emergency Severity Index (ESI) Triage acuity of 1 or 2
3. Albuterol ordered to be administered in ED
4. A prior physician diagnosis of asthma confirmed by a licensed independent practitioner (ED attending, fellow physician, nurse practitioner or physician assistant) in the ED who has spoken with the patient and family and reviewed the medical record
5. Severe acute asthma, defined as a PRAM score of 7 or greater as assessed by a treating physician at the time of screening using the study scoring instrument

Exclusion criteria are:

1. Positive pregnancy test in females of child-bearing potential (performed in all potential participants 12 years and older) or known pregnancy (by patient or parent report)
2. Age-adjusted hypotension at presentation using age-based Pediatric Advanced Life Support parameters (children >1 year to 10 years, SBP<(70 + 2 × age in years); >10 years, SBP < 90 mmHg)[71]
3. Application of assisted ventilation before enrollment assessment (intubated, bi-level positive airway pressure, continuous positive airway pressure)
4. Received IVMg within 24 hours prior to screening (by parent or patient report or medical record review)
5. Enrollment assessment is ≥ 60 minutes after the start of ED treatment (start of first albuterol treatment)
6. Previous enrollment in the same trial (by research coordinator review of trial records)
7. Known severe renal impairment (by parent or patient report)

3.2 Subject Accrual and Study Duration

Patients will be identified and recruited in three PECARN sites, with a goal of one patient per site per week. We plan to enroll 90 patients total in the pilot trial over 7 months of enrollment.

Table 3: Study Timeline

Activity	Study Year 1												Study Year 2											
	Month												Month											
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Hire/train site clinical research coordinates	◆	◆	◆	◆																				
Finalize protocol and manual of operations	◆	◆	◆	◆	◆	◆																		
Completion of reliance agreements for central IRB					◆	◆	◆	◆																
Submission to IRBs at all sites					◆	◆	◆	◆																
Approval of IRBs at all sites								◆																
Training meeting – site PIs/coordinators							◆																	
Monthly conference calls with all sites	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Patient enrollment									◆	◆	◆	◆	◆	◆	◆									
Data analysis/manuscript preparation																◆	◆	◆	◆	◆	◆	◆	◆	◆
Planning for subsequent trial																					◆	◆	◆	◆

4 Overall Study Design

The study design for this pilot trial mirrors the design that we expect to use in the larger, conclusive trial. The future trial will be powered to evaluate the effect of bolus IVMg on hospitalization and will be conducted at more sites, while the pilot trial is designed to demonstrate feasibility and collect safety and pharmacologic data needed to optimize the design of the future trial. The pilot trial will be a prospective double-blind placebo-controlled trial of children 2–17 years of age with severe acute asthma at three PECARN sites: PCH, CHOP, and NCH. Children will be randomized to one of three arms. University of California Davis will function as the research laboratory for the duration of this study.

5 Study Procedures and Data Collection

5.1 Screening Schedule

Research staff will identify children who present to the emergency department with acute asthma during screening hours maintained by each study site.

5.2 Screening and Enrollment

Research staff will identify children within the study age range who are ordered to receive inhaled albuterol and are triaged at an Emergency Severity Index (ESI) acuity of 1 or 2. They will approach the treating physician to determine if the child is being treated for asthma, and if any exclusions apply (Figure 2). If no exclusions apply, the research coordinator will introduce the study to

the patient and family, and the physician will examine the child and complete an asthma scoring instrument that provides the PRAM score. If the PRAM score is 7 or greater, the coordinator will approach the family for consent (including child assent and parental permission) and enrollment. We will prepare consent documents in Spanish and English, but will include patients whose primary language (or the language of their guardian) is not English or Spanish if a professional interpreter can communicate the content of consent documents to the family and discuss study consent. During the consent process, the child will receive standard asthma treatment according to study protocol. Females 12 years and older will provide a blood or urine sample for qualitative pregnancy testing and will be excluded from receiving study drug if positive. Clinical staff will report pregnancy results to patients and family following institutional policies and state regulations.

5.3 Randomization

The investigational pharmacy at each institution will prepare doses in a manner to maintain allocation concealment for all ED staff (see 5.4.2). A sequential randomization scheme with random-sized blocks stratified by each site will be prepared in advance by a study statistician. After informed consent is completed, pharmacy staff will deliver the assigned dose for administration. We will consider a subject to be enrolled when the earlier of two possible events occurs: the REDCap randomization module is invoked to generate a randomization code for the patient, which code is to be relayed to the pharmacy, or the pharmacy dispenses a study drug dose based on the sequential randomization scheme. Nursing staff will administer the dose regardless of the time since initiation of treatment.

5.4 Study Drug Administration

5.4.1 Acquisition

The specific study agent to be used in this pilot trial is Magnesium Sulfate in Water for Injection, a sterile, nonpyrogenic solution of magnesium sulfate heptahydrate in water. Study agent will be acquired by each hospital's research pharmacy from a common manufacturer as a solution of magnesium sulfate in water at 80 mg/mL. This agent is the commercially available preparation of IVMg manufactured by a common manufacturer and will be shipped directly to each study hospital pharmacy.

5.4.2 Preparation, Storage & Labeling

Doses for each IVMg arm will be prepared in identical manner, by drawing a specified volume of IVMg from the commercial container using sterile technique and mixing in a syringe or a polyvinylchloride container with a specified volume of sterile water. For the 50 mg/kg arm, this will be accomplished by mixing 25 mL of IVMg (80 mg/mL) with 15 mL of sterile water for a final concentration of 50 mg/mL and volume of 40 mL. For the 75 mg/kg arm, this will be accomplished

by mixing 37.5 mL of IVMg (80 mg/mL) with 2.5 mL of sterile water for a final concentration of 75 mg/mL and volume of 40 mL. For the placebo arm, 40 mL of 0.9% sodium chloride solution will be drawn into a polyvinylchloride container identical in appearance to the containers used for the IVMg arms.

Each prepared dose will be labeled according to the sequential randomization scheme and stored according to local pharmacy procedure. Either the pharmacist will draw equivolumetric dosages (1 mL/kg, with max of 40 mL) from the prepared vials, or the pharmacist will deliver the full dose to bedside study team with instructions for the volume to be delivered.

5.4.3 Dosing Schedule

After randomization the institutional pharmacist will draw equivolumetric dosages (1 mL/kg, with max of 40 mL) from prepared vials. Enrolled subjects will be randomized to one of three arms:

- IVMg 75 mg/kg arm: 75 mg/kg (max 3 gm) infused over 20 minutes through a peripheral IV catheter
- IVMg 50 mg/kg arm: 50 mg/kg (max 2 gm) infused over 20 minutes through a peripheral IV catheter
- Placebo arm: 1 mL/kg (max 40 ml) of normal saline over 20 minutes through a peripheral IV catheter

5.4.4 Dose Modification for Potential Toxicity

Clinicians will not administer IVMg to enrolled subjects outside of the study protocol until study outcomes have been determined 2 hours after the start of the infusion. The half-life of IVMg is approximately 2 hours.[49] Repeated-dose protocols in an ICU setting that gave as much as 125 mg/kg IVMg to children with asthma over two hours produced no hypotension or other serious adverse effects.[47] Because of this margin of safety, open-label IVMg 50 mg/kg can be administered safely 2 hours after the study infusion under strict study monitoring protocols without need for unblinding.

5.4.5 Accountability

The pharmacy will be responsible for recording the arm to which the child was randomized. Per local procedure, the pharmacist, clinician or other study staff member will be responsible to verify a weight for the patient and negative pregnancy test, if applicable. The patients clinical nurse will be responsible to record the time that the study infusion started and ended.

5.4.6 Unblinding Procedures

If a patient's asthma deteriorates before 2 hours, clinicians should assume that the subject received the highest dose of active study drug and can give IVMg at a dose as high as 50 mg/kg open label as soon as 120 minutes after the start of initial study infusion without unblinding, which would result in a maximum of 125 mg/kg over two hours if the patient was in the 75 mg/kg arm. Other interventions can be given as needed in response to patient condition. If unblinding is considered necessary, allocation information can be obtained from the site pharmacist and unblinding will be considered a study protocol violation.

5.4.7 Discontinuation of Study Drug

If hypotension is measured and perfusion is impaired (see C5. Data Collection), study infusion will be stopped, clinicians will give a 20 mL/kg bolus (max 1 L) of isotonic IV fluid, and may provide other interventions at the clinician's discretion. If perfusion is normal, study drug infusion will continue.

5.5 Withdrawal from Study

Subjects will be observed in the ED for a minimum of 2 hours after the start of study infusion unless they require transfer to the ICU due to escalation of therapy. Parents will be able to withdraw permission for their children to continue in the study at any time. If a parent or child chooses to not continue in the study, infusion of study drug will be stopped. The patient will be followed for adverse events and other symptoms as described in Section 10.3.

6 Data Collection

6.1 Baseline Data

The research coordinator who approaches the patient for enrollment will gather baseline information from the caregiver including age, sex, race and ethnicity, chronic asthma control status and medications, treatments received for the current illness prior to ED presentation, and chronic medical conditions (Table 3). The coordinator will collect data from the treating ED team including the following items. **Scoring:** The treating physician will complete a clinical asthma scoring instrument immediately before, 20–40 minutes after, and 2 hours after the start of study infusion, each taking approximately 60 seconds to complete. **Blood samples** will be drawn by clinical staff through the IV before, then using PIVO 20–40 minutes and using PIVO 90–150 minutes after start of study infusion, or if the blood draw is not possible using PIVO, through the existing peripheral IV. The samples will be processed locally and then shipped to the research lab. University of California

Davis will function as the research lab for this project. **Blood pressure** will be measured by the study staff using an automated device just before the start of study infusion (within 10 minutes prior to start of infusion), every 10 minutes (± 4 minutes) for 90 minutes following the start of infusion, and once more 2 hours (± 10 minutes) after the start of study infusion. **Perfusion:** If age-adjusted hypotension is detected, a treating clinician, which could be the treating nurse, will complete a standardized assessment of perfusion that is then reviewed with the coordinator. If perfusion is impaired during study drug infusion, study drug infusion will be stopped. **Timing:** The coordinator will record timepoints of screening, identification, consent, and randomization, as well as times of infusion and blood draws using the nurse's documentation. **Disposition:** The coordinator will approach the treating physician 2 hours after the start of study infusion and collect the stated disposition for the patient (hospitalization, discharge home, or uncertain), at which point study procedures will be finished for the ED visit.

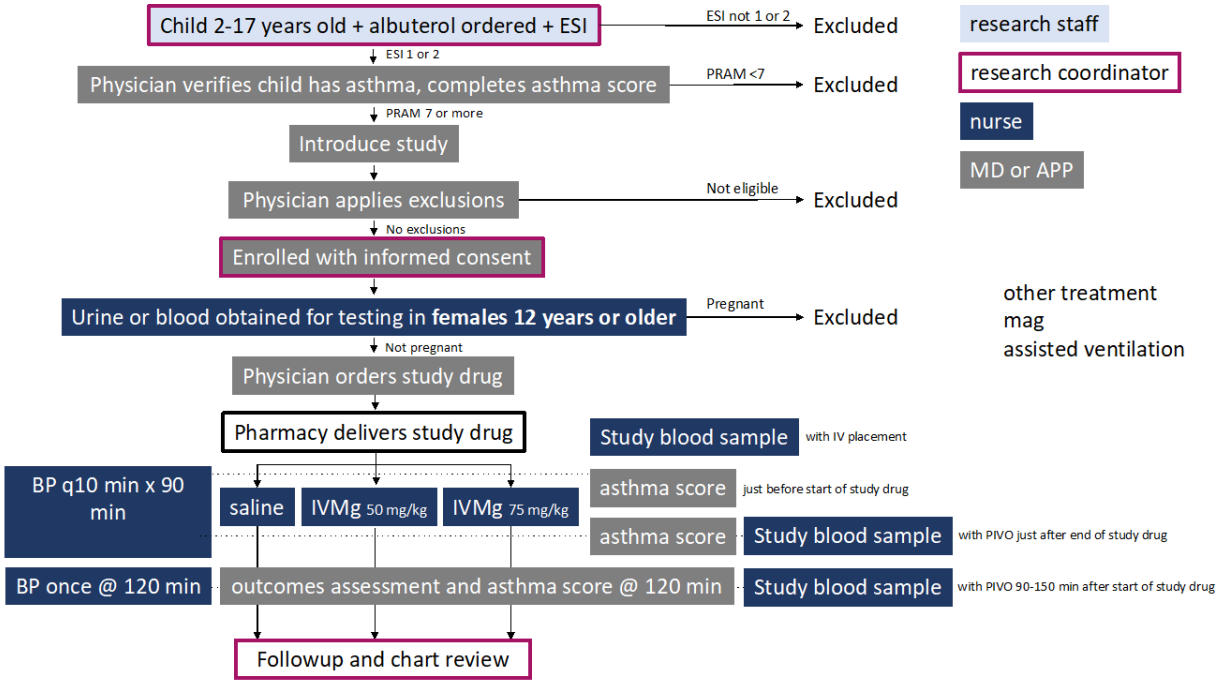

Figure 1: Schedule of Activities

6.2 Follow-up Assessment(s)

For patients discharged home study staff will call or text the family in 12–48 hours and in one week (5–10 days) to determine if they returned to any ED and the outcomes of the return visit, and to assess for AEs (see Table 3). All data points will be initially recorded on paper forms, securely stored, then entered into an electronic study database created by the Data Coordinating Center.

6.3 Medical Record Review

Study staff will review electronic medical records of all subjects one week after enrollment to determine the actual patient disposition and hospital course (see C6. Outcomes).

6.4 Instruments

The PRAM is outlined in Table 2 in Section 2.4.

7 Data Analysis

7.1 Specific Aim Analyses

Specific Aim 1. Demonstrate the feasibility of enrolling children in the ED with severe acute asthma in a multicenter, randomized, controlled trial of placebo, low-dose IVMg, or high-dose IVMg.

Conducting a pilot trial will help standardize and streamline enrollment across sites, minimize the number of patient enrollments needed for our aims, and inform the planning of the future trial. Primary study hypothesis: We will identify, consent, and enroll 90 patients in 7 months or less.

Our experience with prior trials within PECARN suggests a 7-month enrollment period is adequate to reach a stable rate of enrollment and demonstrate trial procedures. Because the future large RCT will need multiple sites for adequate enrollment, the pilot trial will test trial procedures at three sites with various patient volumes, research infrastructures, and patient populations. Based on applying the projected 8% of asthma visits in the PECARN Registry that would qualify based on prior volumes at study sites, we anticipate that approximately 360 patients will qualify for the study during the 7-month study period, allowing for study completion even if only 25% of qualifying patients are enrolled. The study will end once 90 patients are enrolled, even if this occurs in less than 7 months, but enrollment will not extend beyond 9 months even if fewer than 90 patients are enrolled. This enrollment rate would be sufficient to conduct a trial powered to detect a difference in hospitalization in 23 months. A slower rate would prompt adjustment of future trial length.

Specific Aim 2. Demonstrate the feasibility of timely delivery of study medication to enrolled patients and assessment of blood pressure and associated adverse events in a standardized protocol.

Our first objective in this aim is to assess our ability to administer study drug within 90 minutes after the start of asthma treatment. Timely delivery of study drug will be considered feasible with current

study procedures if 90% of study subjects receive study medication within this timeframe, giving time for study intervention to affect hospitalization, making hospitalization an outcome appropriate for the future trial. Delivery of study drug to less than 90% of study subjects will indicate a need to further refine study procedures prior to the larger trial. We will optimize delivery of study drug in the future trial by analyzing the impact of factors in the pilot trial that may influence study drug delivery including protocol adherence, variability in clinical care, time of day, ED volumes, research coordinator availability, pharmacy processes, consent processes, and parental availability. Factors associated with time to first study drug administration, administratively censored at 180 minutes, will be explored using Cox proportional hazards modeling. The Cox models are intended to identify features requiring additional planning to promote timely delivery rather than to find statistical significance.

Our second objective in this aim is to inform a monitoring plan for the future trial that is focused, clinically feasible, and effectively protects patient safety. We will intensively monitor blood pressure during the pilot trial for 90 minutes after the start of study drug infusion (see Data Collection) and will record all adverse events throughout the study period. We will consider the procedures of the pilot trial feasible for the larger trial if we can collect ≥90% of planned data points related to blood pressure. This will indicate that this data gathering does not pose an undue burden on the teams providing clinical care to study patients. We will use the degree to which data points are collected in coordination with the frequency and timing of blood pressure changes, the frequency and degree of age-adjusted hypotension and poor perfusion, interventions delivered to patients with measured hypotension, and other recorded adverse effects to devise a monitoring plan that would capture all adverse events and is maximally feasible.

Specific Aim 3. Externally validate a previously constructed PK model and develop a combined PK/PD model for IVMg using magnesium (total and ionized) serum concentrations and their correlation with measures of safety and respiratory distress in children with asthma.

We will use these data to validate a PK/PD model that will guide initial dosing for the large trial.

External validation of our prior PK model requires blood samples from a minimum of 30 patients who receive IVMg at sites outside of PCH for optimal model validation. We anticipated 40 subjects to meet this criteria. Data from the samples collected in this study will be used to externally validate our previously developed population PK model,[34] and if needed (i.e. MPE>15% or < −15%, MAPE>30%), update the model with this larger sample size. Concentration analysis, PK model validation, and updating our prior PK model (if needed) will use similar approaches as we have previously described.[34] Notably, this includes accounting for endogenous magnesium concentrations (Equation (1)) assumed to be at steady-state prior to IVMg administration.

$$\begin{aligned} C_{\text{endogenous,ind}} &= C_{\text{endogenous,pop}} \times \text{EXP}(\text{ETA(j)}) \\ C_{\text{total}} &= C_{\text{exogneous}} + C_{\text{endogenous,ind}} \\ C_{\text{observed}} &= C_{\text{total}} + \text{ERR(i)} \end{aligned} \tag{1}$$

$$\text{PE} = \frac{C_{\text{pred}} - C_{\text{obs}}}{C_{\text{obs}}} \tag{2}$$

$$\text{APE} = \frac{|C_{\text{pred}} - C_{\text{obs}}|}{C_{\text{obs}}} \tag{3}$$

Once the PK model has been confirmed, we will incorporate PRAM scores and other measures of respiratory distress to develop a population PK/PD model. PK/PD modeling will utilize NONMEM® software (v7.3, ICON Development Software, Ellicott City, MD, USA). The first-order conditional estimation with interaction (FOCE-I) method will be used throughout model building and evaluation. Model selection will be based on parsimony, objective function value (OFV), and visual diagnostic plots. Direct and indirect approaches for incorporating PD will be tested. After determining the base model, covariates will be tested for impact on PD using a forward inclusion ($p < 0.05$) backwards exclusion ($p < 0.01$) method. Covariates will be added to the model in a stepwise fashion, and allowed to remain in the model if covariate inclusion decreased the OFV by at least 3.84 and its exclusion increased the OFV by at least 6.63. Once the final PK/PD model is determined, we will evaluate model accuracy and robustness through bootstrapping methods and visual predictive checks.

The PK/PD model will be used to define Mg concentrations associated with adverse effects including hypotension, and patient outcomes including reduction in PRAM during treatment and hospitalization. Dose-exposure-response data simulated ($n = 1000$ datasets) from the PK/PD model will be used to select doses used in the future large trial. Specifically, we will use the simulated datasets to determine the dose at which 10% of participants are expected to have adverse effects (i.e. hypotension), to establish an upper limit of dosing for the future trial. Importantly, this analysis will allow us to evaluate the role of an upper dose limit (i.e. the 2 or 3 gm maximum dose, regardless of patient weight) on preventing hypotension. Similarly, we will use the simulated PK/PD data to define doses expected to yield 20, 40, and 60% reductions in PRAM/hospitalization. We will target the use of these doses in the future study as doses expected to maximally reduce hospitalization in the future trial.

If we are unable to build a robust population PK/PD model using NONMEM®, we will evaluate correlations between PK and PD using Pearson Rho correlation analyses in GraphPad Prism v6.05 software. In this scenario, the population PK model will be utilized to identify doses that generate simulated concentration data within the target therapeutic range established by the correlation analyses.

Approximately one fourth of children receiving IVMg for asthma weigh more than 40 kg, the weight at which a 2 gm or 3 gm dose is reached (Registry). As a result of this maximum, approximately one half of children weighing more than 40 kg receive less than 30 mg/kg IVMg. As a drug that exhibits first-order kinetics, delivering IVMg with an arbitrary maximum may reduce the benefit of the drug in a substantial portion of children. We will use the newly developed PD model and validated PK model to determine if patients above 40 kg have less improvement in clinical score, and if any associations found are related to changes in serum values.

7.2 Sample Size Calculations and Statistical Power

Sample size for this pilot trial is driven by the first aim, which is to demonstrate ability to enroll children severely ill with asthma in a randomized controlled trial. The second aim is focused on the feasibility of study drug delivery and the collection of safety data, and the third aim is focused on pharmacologic modeling for dose estimation to be used in the large trial to follow this pilot trial. All three aims of the pilot trial are focused on generating data to inform the structure of the larger trial to follow, and accordingly they do not have sample size calculations or have associated calculations of statistical power.

7.3 Other relevant statistical topics...

Sample size estimations of the Future Trial The future trial is designed to have up to two chances to find a significant reduction in hospitalization: the test of lower dose vs. placebo may be significant, and if this first test is not significant then higher dose vs. placebo will be tested and may be significant. The overall one-sided type I error rate is controlled at 0.025 by conducting each test at a one-sided alpha of 0.0125. The following table shows approximate sample sizes with observed outcomes needed to achieve 80% power. The sample sizes are such that the higher dose of IVMg has 3/8 of the overall sample, and the lower dose of IVMg will have 3/8 or 2/8 of the sample (3/8 if superiority to placebo is demonstrated, 2/8 otherwise) with the balance in the placebo arm (2/8 or 3/8 of the sample). To account for missingness in the hospitalization outcome, a reasonably accurate approximation is to divide the sample size by the expected proportion of nonmissing outcomes (e.g., with 7% missingness, the 0.5 IVMg, 0.6 Placebo cell suggests enrolling 1032/.93 ≈1110 participants).

Approximate observed sample size to have 80% power that at least one IVMg arm lowers the probability of hospitalization. To adjust for missingness, divide by (1−[expected proportion of missing values]).

Approximate # with nonmissing outcome to yield 80% power		Probability of Hospitalization for Placebo arm		
		0.6	0.7	0.8
Probability of hospitalization for each IVMg arm	0.4	256	120	64
	0.5	1032	248	104
	0.6	–	944	216
	0.7	–	–	776

The following table has the same framework but was created to yield 90% power:

Approximate # with nonmissing outcome to yield 90% power		Probability of Hospitalization for Placebo arm		
		0.6	0.7	0.8
Probability of hospitalization for each IVMg arm	0.4	336	152	80
	0.5	1360	336	136
	0.6	–	1240	288
	0.7	–	–	1024

8 Data Management

8.1 Clinical Site Data Management

Each clinical site will maintain study records in secure locations that may include password protected electronic files or locked filing cabinets. The site will maintain an Essential Documents Binder, which may be in paper or electronic form. Copies of all informed consent documents will be kept on file and be available for site monitoring inspection (on site or remote).

8.2 Data Coordinating Center

8.2.1 Data Center Description

Overview The Data Coordinating Center (DCC) in the Department of Pediatrics at the University of Utah School of Medicine provides data coordination and management services for a variety of national research networks. Anchoring these services is a state-of-the-art, energy efficient data center. The data center facility supports more than 3500 users around the country and provides a secure, reliable, enterprise-wide infrastructure for delivering mission critical DCC systems and services.

Facility, Hardware, Storage, Data Backup and System Availability The data center was built using industry standards and energy efficient cooling solutions. The data center is cooled by Liquid Cooling Package (LCP) inline cooling technology, providing the desired efficiency, redundancy and the modularity. The LCP utilizes a hot/cold aisle design that allows for even air distribution to minimize hot spots. The data centers electrical power system contains an uninterruptible power supply (UPS) with a diesel backup generator. The data center is protected with an FM-200 backed fire suppression system, which provides waterless fire suppression without leaving behind residue or particulate. Enhanced security measures are implemented to safeguard the equipment and the data within in it. Security measures are enforced 24 hours a day, 7 days a week, 365 days a year by a combination of on-premise security guards, University police officers and video surveillance.

The data center has a virtualized environment. This environment consists of more than 415 virtual servers across 25 host servers. Virtualization provides key advantages: High availability (HA) – in the event of hardware failure, virtual machines (VM) automatically restart on healthy resources, minimizing impact to end-users; Flexible infrastructure - compute and storage is seamlessly scaled as current needs change; Rapid deployment - new resources are provisioned on-demand.

Production servers running mission critical applications are clustered and configured for failover events across multiple clusters. Entire servers are backed-up to a dedicated infrastructure. The backup repositories are encrypted-at-rest using AES-256. The storage area networking (SAN) applications, clusters, and switch-to-switch links are highly redundant. Incremental backups of data

occur Monday through Friday. A full data backup occurs weekly. Full backups are sent off-site on a weekly basis to a secure secondary location. The data center currently manages over 125 terabytes (TB) of data.

Information systems are available 24/7/365 unless a scheduled maintenance period or mitigation of an unexpected event is required.

8.2.2 Security, Support, Encryption, and Confidentiality

The data center coordinates the network infrastructure and security with University Information Technology (UIT) at the University of Utah. This provides us with robust firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Centralized authentication and communication over public networks are encrypted using transport layer security (TLS) and/or virtual private network (VPN) technologies. Direct access to data center machines is only available while physically on premise or via a VPN client.

All network traffic is monitored for intrusion attempts. Security scans are regularly run against data center servers and IT staff are notified of intrusion alerts. Security is maintained with Windows user/group domain-level security. Users are required to change their passwords every 90 days. All files are protected at user/group levels and database security is handled in a similar manner with group-level access to databases, tables, and views. Finally, all laptops used by faculty and staff in the DCC are whole-disk encrypted.

The data center uses monitoring tools to continuously monitor applications and servers. Environmental and network systems are also monitored to ensure up-time. System Administrators are on-call 24/7/365 to respond to urgent events.

All personnel involved with the DCC have signed confidentiality agreements concerning data encountered in the course of their daily work. All personnel (including administrative staff) have received Human Subjects Protection and Health Information Portability and Accountability Act (HIPAA) education. We require all users to sign specific agreements concerning security, confidentiality, and use of our information systems before access is provided.

8.3 Electronic Data Capture System

The Data Coordinating Center (DCC) will develop an electronic data capture system for this trial. Currently the DCC uses multiple applications, such as OpenClinica or REDCap, and will elect to use the most appropriate application at the time of implementation of the study. Data will be entered by each clinical site.

The DCC will use an electronic discrepancy management system to notify sites of inconsistent or erroneous data entry, which will be corrected by the clinical site. The discrepancy management system maintains an audit trail of all discrepancy resolution.

8.4 Study Monitoring

The investigators recognize the importance of ensuring data of excellent quality. Study monitoring is critical to this process. Monitoring has been a very effective tool for maintaining data quality in previous Pediatric Emergency Care Applied Research Network studies, and we will utilize this process to ensure excellent quality data in the proposed study. The DCC utilizes risk-based methodology to identify and correct problems that may arise at sites. The risk-based approach to monitoring focuses on oversight activities and preventing or mitigating key risks to data quality, as well as to processes critical to human subject protection and integrity of the trial or study.

Study monitors must be provided with appropriate access to study materials and the medical records for study subjects. If the medical records are in electronic form, the clinical investigator or an authorized individual must provide any assistance necessary to facilitate the study monitor's review of data in the electronic medical record.

8.4.1 Site Monitoring Plan

A supplemental study-specific risk-based monitoring plan, separate from the protocol will be completed which outlines specific criteria for monitoring. This plan may include the number of planned site visits, criteria for focused visits, additional visits or remote monitoring, a plan for chart review and a follow up plan for non-compliant sites. The monitoring plan also describes the type of monitoring that will take place (e.g., sample of all subjects within a site; key data or all data), the schedule of visits, how they are reported and a time frame to resolve any issues found.

8.4.2 Clinical Site Monitoring

Site monitoring visits will be performed by a trained site monitor during the study period to ensure regulatory compliance, patient safety, and to monitor the quality of data collected. Essential document binders, regulatory documents and data collection forms may be reviewed. Interim visits will take place depending on grant budget, site enrollment, and compliance issues identified. The site monitor will provide each site with a written report, and sites will be required to follow up on any deficiencies. It is anticipated that the study monitoring visits for this protocol will consist of a site initiation visit (prior to patient enrollment), interim visits, and a close out visit. The site initiation may take place as group training made up of site investigators and research assistants.

8.4.3 Remote Monitoring

The Data Coordinating Center may supplement on-site monitoring with remote monitoring activities. Remote monitoring involves detailed review of the data entered by the Clinical Center and consultations with the Clinical Center investigator and/or research coordinator to review safety and data quality. This may require uploading copies of medical records, patient study files, regulatory

documentation, or other source documents for the monitor to review. Alternatively, other methods, such as remotely viewing source documentation, may be utilized. This helps assure protocol compliance and accurate data collection. The Data Coordinating Center may conduct more remote monitoring activities early in the trial to assure protocol compliance and identify any training issues that may exist. Remote monitoring documents will be retained in accordance with federal requirements. Safety of subjects will be monitored and ensured in accordance with the Data and Safety Monitoring Board (DSMB) plan.

8.4.4 Pharmacy Monitoring

The Clinical Center pharmacy must maintain adequate records of all dispensed study drug. Each pharmacy will be monitored and may be requested to send copies of these documents to the Data Coordinating Center. Since this study will use a central pharmacy, that pharmacy must also maintain adequate records and will also be monitored.

8.5 Record Access

The medical record and study files (including informed consent, permission, and assent documents) must be made available to authorized representatives of the Data Coordinating Center, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives (when applicable) of the Food and Drug Administration (FDA), NIH, other Federal funders or study sponsors, and the Institutional Review Board (IRB) for each study site.

9 Protection of Human Subjects

9.1 Institutional Review Board (IRB) Approval

A Single IRB (SIRB) will be used for this study. The University of Utah IRB will serve as the IRB of record. Study sites will rely on the University of Utah IRB to act as central IRB. The Data Coordinating Center and each clinical center must obtain IRB approval prior to participating in the study.

The Data Coordinating Center will track IRB approval status at all participating centers and will not permit participant enrollment without documentation of initial SIRB approval and local review sign-off. The Data Coordinating Center will also track the maintenance of that approval throughout subsequent years of the project.

The Data Coordinating Center and each clinical center must obtain IRB approval prior to participating in the study. A Central IRB (CIRB) will be used for this study. The University of Utah IRB will

serve as the IRB of record.

The Data Coordinating Center will track IRB approval status at all participating centers and will not permit subject enrollment without documentation of initial SIRB approval and local review sign-off. The Data Coordinating Center will also track the maintenance of that approval throughout subsequent years of the project.

9.2 Informed Consent

We will seek a waiver of authorization for screening and recruitment only to allow the review of patient's medical problems and treatments being provided prior to approaching patients for enrollment. All other research activities will be performed with parental authorization and patient assent (when applicable). Written documentation of informed consent from the patient's parent or guardian will be obtained as soon as possible in the Emergency Department at the bedside. For females 12 years and older being considered for enrollment, we will include consent for a screening pregnancy test as part of the consent process, and test blood or urine for pregnancy only once consent is complete. Under Food and Drug Administration (FDA) Regulation 21 CFR 50.55, where clinical investigations are more than minimal risk but presenting the prospect of direct benefit to individual subjects (50.52) and permission is to be obtained from guardians, permission of one guardian is sufficient. Under FDA Regulation 21 CFR 50.55 we will also solicit the assent of older children to participate in research as directed by the site IRB. The clinical research coordinator or study investigator will complete the capacity for assent assessment. If the child is determined to have capacity, assent for participation will be sought and documented appropriately. If at any time during the consent process a prospective subject who is determined to have capacity or their parent or guardian indicates that they do not want the child to be enrolled in the research study, the research team will cease proceeding with the protocol. If both parents or legal guardians arrive with the child and there is a disagreement between the parents about whether or not to enroll the child, the child will not be enrolled into the research study. For Spanish speaking patients or guardians, we will utilize hospital medical interpreting services in the consent process to address any questions or concerns that a Spanish-speaking guardian may have. A Spanish version of the consent document will be created and provided. For patients or accompanying guardians who do not speak English or Spanish, we will pursue consent if a professional interpreter is available by phone or videoconference service in the preferred language.

9.3 Potential Risks

Administration of IVMg requires placement of a peripheral intravenous (IV) line, which carries the risk of pain at the insertion site (common), infection, phlebitis, thrombophlebitis, emboli, hematoma, extravasation, and needlestick injuries (all less common). The short duration of the use of the IV line used for IVMg (2 hours for study procedures, median 2 days in usual clinical care) minimizes the risk of complications. Blood samples will be drawn directly through the IV at IV placement and through the peripheral IV using a PIVO catheter (manufactured by BD Medical) both 20–40

minutes after the start of study infusion and 90–150 minutes after study infusion. Total blood drawn will not exceed 5 mL, a volume of blood loss that presents no foreseeable risk to participants.

Though IVMg is approved for use in late pregnancy to prevent and treat seizures in the setting of preeclampsia and eclampsia, it is unknown how it affects pregnancy when given for asthma, especially at other points in the pregnancy. For this reason, we will not include any patients who are pregnant. A pregnancy test will be done in all females 12 years and older who are not already known to be ineligible and who consent to this study procedure. The pregnancy test must be negative to participate in this study.

The administration of IVMg includes the risk of physical effects from IVMg which range from mild (diarrhea, nausea, stomach cramping, facial flushing, change in blood pressure) to more severe (hypotension with poor perfusion, urinary retention, lethargy, apnea, or irregular heartbeat). The incidence of hypotension in children after IVMg in the ED for asthma ranges from 6.8% in a retrospective review of 6,497 children across 7 sites[22] to 11% in an abstract of clinical care delivered to 100 children at a single site.[36] Interventions for hypotension were limited to a fluid bolus and no subjects had persistent hypotension requiring intervention after ED treatment.

The incidence of poor perfusion in children who experience hypotension after IVMg is unknown. Other effects of IVMg infusion have been described in other medical conditions including diarrhea, nausea, stomach cramping, facial flushing, change in blood pressure, urinary retention, lethargy, apnea, or irregular heartbeat, but their incidence has not been described in children given IVMg for asthma.

Subjects will be observed in the ED for a minimum of 2 hours after study infusion unless they require transfer to the ICU due to escalation of therapy. We will record the physicians stated disposition for the patient (hospitalization or discharge home) 2 hours after receiving study infusion. For all patients we will review electronic medical records one week later to determine the actual patient disposition, length of ED and hospital stay, ICU admission and length of stay, intubation, and any assisted ventilation. For patients discharged home we will call the family 12–48 hours after discharge from the ED and in 5–10 days to determine if they returned to any ED and the outcomes of the return visit, and to assess for AEs. All other risks in the study are related to the privacy of protected clinical information gathered during ED treatment, in chart review, and in followup contact with the family.

9.4 Protections Against Potential Risks

All children enrolled in this study are being cared for in the emergency departments of tertiary pediatric hospitals by physicians with subspecialty training in pediatric critical care using evidence-based protocols in coordination with nurses with pediatric training and experience. All children enrolled will receive standard-of-care asthma treatment throughout the study. The study intervention is in addition to current standard-of-care. Monitoring planned for the study mirrors routine clinical monitoring guidelines and standards for critically ill patients.

Adverse events will be monitored closely during the ED visit through standard clinical monitoring

for critically ill children as well as blood pressure measurement every 10 minutes (± 4 minutes) for 90 minutes after the start of IVMg infusion. If age-adjusted hypotension is detected, a treating clinician, which could be a nurse, will complete a standardized assessment of perfusion that is then reviewed with the coordinator. If perfusion is impaired during study drug infusion, study drug infusion will be stopped. Clinicians will give a 20 mL/kg bolus (max 1 L) of isotonic IV fluid, and may provide other interventions at the clinicians discretion.

If patients experience hypotension and poor perfusion, all study sites have experience and current capability to administer IV fluid boluses and other interventions as clinically indicated. All facilities have Pediatric Intensive Care Units should enrolled child require further critical care, including supported ventilation or other interventions as clinically indicated. All patients not eligible for the study or who withdraw from the study will continue to receive standard-of-care treatment at the discretion of the attending clinical team. Blood or urine pregnancy test results will be reported to the subject and the parent or legally authorized representative signing the consent for screening according to institutional policies and state regulations. The study participants contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the PECARN Data Coordinating Center (DCC). This will not include the participants name. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by PECARN DCC research staff will be secured and password protected. At the end of the study, a de-identified database will be prepared and archived at the PECARN DCC and provided for public use as specified in the PECARN standard operating procedures and, if applicable, NIH requirements.

9.5 Potential Benefits

Enrolled subjects may benefit directly in this study by receiving IVMg, which may reduce their risk of hospitalization and improve asthma symptoms. These benefits may be possible even in patients who do not improve with treatment including standard asthma medications. Children who are randomized to receive placebo also receive current standard asthma therapy. Findings of the trial will be used to inform the treatment of children with asthma treated in Emergency Departments, which could help deliver better treatment that avoids hospitalization, or could help avoid unnecessary treatment or excessive monitoring.

9.6 Risk Benefit Assessment

Children are vulnerable subjects and are the primary focus of this study. Asthma is the most common chronic illness of childhood and a leading cause of pediatric hospitalization, disability, and healthcare-related cost.[1] In 2013, acute asthma resulted in 679,643 emergency department (ED) visits and 70,429 hospitalizations for children 2–17 years old in the United States.[3] Hospitalization

is a primary driver of direct costs in asthma in children,[4] contributing $3.4 billion of the $9.3 billion in total pediatric asthma costs estimated in 2008,[58] as well as indirect costs from school absenteeism and lost parental work.[6] Prior trials of IVMg in children with asthma were too small to conclude whether IVMg can reduce hospitalization in children with asthma. To date, these small trials of IVMg in acute asthma have not been followed by larger conclusive trials. Comparison to placebo in a large trial is needed to evaluate the effect of IVMg on hospitalization. Though any estimates of the potential effects of broader use of IVMg on hospitalization rates for acute asthma are limited by the size and number of prior trials, a recent meta-analysis of previous small trials suggests that IVMg given in the ED may reduce hospitalization in children by 30%. Applying a 30% reduction in hospitalization to the remaining hospitalized children who do not receive IVMg in the US could potentially avoid 16,500 hospitalizations each year, each at an average cost of $3,600, producing direct cost savings of $65 million yearly in addition to avoiding indirect costs of missed school and work.

As outlined in Section 9.3, risks of IVMg have been described in prior literature but not sufficiently to dismiss them as minor. This study will help ensure that monitoring for children enrolled in future trials is feasible and complete.

Considering the potential benefits and the anticipated risks, the research outlined in this proposal will provide important evidence to guide the care of children with asthma. By clarifying the efficacy, safety, and dose of IVMg for children with asthma, these results will influence the care provided to severely ill children with asthma nationally and globally through inclusion in NHLBI guidelines and other guidelines such as those developed by the Global Initiative for Asthma.

10 Data and Safety Monitoring Plan

10.1 Data Safety Monitoring Board (DSMB)

Assuring patient safety is a central and an essential component of this protocol. Each clinician caring for a study patient has primary responsibility for the safety of individual subjects under his/her care. A DSMB will be established prior to the initiation of enrollment. The DSMB will consist of at least three members. At least one of these individuals will have statistical expertise and at least one of these individuals will have experience in emergency medicine. All individuals will have experience in the conduct of randomized clinical trials and will not have direct association with the sites to be included in the trial nor have other conflicts of interest that would interfere with their objectivity. Because this pilot trial is structured to evaluate the adequacy of trial procedures and will not be powered to fully evaluate efficacy or safety, we do not anticipate having sufficient interim data during the trial for the DSMB to reach conclusions regarding efficacy or safety, though safety data will be considered in interim analysis.

The DSMB will be responsible for:

1. Approval of the final study design;

2. Reviewing and analyzing the progress of the study;
3. Monitoring the safety of the study treatments (as outlined below);
4. Reviewing reports of data quality.

The unblinded DCC statistical team will provide information to this committee as requested. In the pilot trial, the DSMB will meet before the first site is activated for enrollment and again after approximately 30 subjects have been enrolled. The DSMB or study PI have the power to request additional meetings. The DSMB will have the power to halt the study should safety reasons exist.

10.2 Safety Monitoring

Data that will be considered in the DSMBs evaluation of safety will include the following categories:

Appropriate enrollment: Patients enrolled and later found to be ineligible.

Intervention safety: Dose of study drug prepared by pharmacy, dose and volume of study drug delivered to patient, blood pressure measurement after study drug, perfusion assessments and interventions in those with measured hypotension, application of assisted ventilation after study drug, ICU admission, serum magnesium measurements after study drug, and other medication delivered to participants for the treatment of asthma.

10.3 Adverse Event Reporting

10.3.1 Definition of Adverse Event and Serious Adverse Event

Adverse Event (AE) is any untoward medical occurrence in a subject that occurs during the conduct of a clinical study of a pharmaceutical product that does not necessarily have a causal relationship to the study drug. This can, therefore, be any unfavorable and unintended physical sign, symptom, laboratory parameter, or disease entity that develops or worsens in severity during the course of the study, whether or not considered related to the study drug. Hypotension will be defined as any systolic blood pressure meeting the following age-specific norms:

- Children 1–10 years: $< 70 + (\text{age in years} \times 2)$
- Children >10 years : < 90

Measured hypotension without associated symptoms would be categorized as a mild AE; the presence of symptoms would be categorized appropriately based on the degree of impairment of activity.

Serious Adverse Event (SAE): A serious adverse event (SAE) for this population is an adverse event that:

- results in death; or
- is life-threatening (the patient was, in the view of the site investigator, in immediate danger of death from the event as it occurred); or
- requires inpatient hospitalization or prolongs an existing hospitalization; or
- results in persistent or significant disability or incapacity; or
- results in congenital anomaly/birth defect; or
- any other event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

As stated above, the presence of hypotension with impaired perfusion is categorized as an AE and is an indication to stop study infusion, though it may or may not be categorized as an SAE depending on the degree of impairment of activity. Hypotension with impaired perfusion is the only specified condition that should trigger study infusion to be stopped. Study infusion can be stopped in the setting of other AEs as deemed appropriate by the clinical team caring for the patient.

Unanticipated Problems(UP) We consider unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

10.3.2 Classification of an Adverse Event (Relatedness, Severity, and Expectedness

Relatedness: The suspected relationship between study interventions and any adverse event will be determined by the site investigator using the criteria below. *Relatedness must be assessed by an investigator and may **not** be assessed by a research coordinator.*

Not Related: The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Possibly Related: The event follows compatible temporal sequence from the time of beginning the assigned study intervention, but could have been produced by other factors such as the

subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Probably Related: The event follows a reasonable temporal sequence from the time of beginning the assigned study intervention, and *cannot be reasonably explained* by other factors such as the participants clinical state, therapeutic interventions, or concomitant drugs administered to the participant.

Severity: The severity, which is a measure of intensity, of clinical adverse events and laboratory abnormalities will be recorded by the site investigator and categorized. The following guidelines will be used to describe severity.

Mild: The event requires minimal or no treatment and does not interfere with the participant's daily activities.

Moderate: The event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe: The event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Expectedness of the Event: All adverse events, including serious adverse events, will be evaluated as to whether their occurrence was expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information described for the study intervention or underlying condition.

Expected: An event is considered expected if it is known to be associated with the underlying condition or is related to the study intervention and is mentioned in the protocol, informed consent, or other study documents. An event may be expected despite the study subjects clinical state immediately prior to the event.

Unexpected: An event is considered unexpected if there are no prior data linking this event with either the condition or intervention under study or an event that occurred unexpectedly in the course of treatment.

Treatment or Action Taken: For each adverse event, the site investigator will record whether an intervention was required:

- Medical or surgical procedure
- Concomitant medication: started, changed, or discontinued
- Other, specify
- No action taken

Outcome of Event: Finally, the site investigator will record the clinical outcome of each adverse event as follows:

- Death
- Recovered and the patient returned to baseline status
- Recovered with permanent sequelae
- Symptoms persist

10.3.3 Data Collection Procedures for Adverse Events

Adverse events must be recorded starting from the time of randomization until the follow-up call approximately one week after enrollment. All AEs whether or not they are considered related to the study, shall be recorded on a Case Report Form including information characterizing the timing, severity, relatedness, and outcome of each AE and actions taken in response to the AE. Any medical condition present at the time of randomization, recorded in the patient's baseline history at study entry, which remains unchanged or improves (unless the clinician feels it is clinically relevant), will not be recorded as an adverse event at subsequent evaluations. However, worsening of a medical condition that was present at the time of randomization will be considered a new adverse event.

Adverse events will be coded using the MedDRA coding vocabulary. Coding will be done centrally at the Data Coordinating Center as this requires specific training.

The Clinical Center investigator will report all *serious, unexpected, and study-related* adverse events to the DCC within 24 hours. A detailed completed report will be required to be sent to the DCC within 3 working days of the event. After receipt of the complete report, the DCC will report such serious, unexpected, and study-related adverse events to the NHLBI in an expedited manner according to NHLBI policy found at the following link:

https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/nhlbi-adverse-event-and-unanticipated-problem-reporting-policy

In accordance with local IRB requirements, the Clinical Center investigator may be required to report such events to the IRB in addition to notifying the DCC. In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, and NHLBI staff cannot be reached expeditiously, the DCC will notify the study investigator (Dr. Johnson) and all Clinical Center investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NHLBI after discussion with the DSMB.

10.3.4 Reporting Monitoring Serious Adverse Events

A qualified physician will be designated to fulfill the function of the medical monitor for this study. Site investigators and/or research coordinators will report serious adverse events to the DCC within 24 hours of becoming aware of the event. A detailed completed report will be required to be sent to the DCC within 3 working days of the event, and the medical monitor will assess all serious adverse

events reported from site investigators.

For each of these serious adverse events, the site investigator will provide sufficient medical history and clinical details for a safety assessment to be made with regard to continuation of the trial. The medical monitor will sign off on each SAE report after review. All SAE reports will be retained at the DCC, and all SAE reports will be available for review by DSMB members and NHLBI staff. The SAE reporting process may be incorporated into the Electronic Data Capture (EDC) System in use for the study.

In accordance with local IRB requirements, the site investigator may be required to report such events to the IRB in addition to notifying the Data Coordinating Center.

The DSMB will review all adverse events (not necessarily serious, unexpected, and study-related) during scheduled DSMB meetings. The Data Coordinating Center will prepare a Summary Report of Adverse Events for the DSMB meetings with the MedDRA coding system.

10.3.5 Reporting and Monitoring Unanticipated Problems (UP)

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigators responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PIs name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

The site investigator will report unanticipated problems to the DCC within 24 hours of becoming aware of the event. A detailed completed report will be required to be sent to the DCC within 3 working days of the event. After receipt of the complete report, the DCC will report these unanticipated problems to the NHLBI in an expedited manner (as close to 24 hours as possible). In accordance with local IRB requirements, the site investigator may be required to report such unanticipated problems to the IRB in addition to notifying the Data Coordinating Center.

10.3.6 Possible Emergent Enrollment Suspension

In the event that the medical monitor believes any UP or unexpected, study-related SAE warrants emergent suspension of enrollment in the trial, the medical monitor must immediately notify the DCC. Attempts will be immediately made to consult NHLBI staff and the DSMB chairperson. If they are consulted expeditiously, decisions will be made whether to continue the study without change, and whether to convene the entire DSMB for an emergent meeting. If a decision is made

to suspend enrollment in the trial, this will be reported to the study investigator (Dr. Johnson) and all clinical investigators, who will be instructed to report this to their local IRB. If NHLBI staff and the DSMB chairperson are not reached expeditiously, the DCC will notify the study principal investigator (Dr. Johnson) and all site investigators to suspend enrollment in the trial until the NHLBI staff and DSMB chairperson are consulted. Resumption of enrollment will not occur without consent of the NHLBI staff after discussion with the DSMB.

10.3.7 Early Study Termination

There are no prespecified thresholds for early termination of the pilot study. The guidelines in the previous section describe how the study could be emergently suspended for safety reasons, and if not satisfactorily resolvable then safety concerns could naturally lead to study termination. There are no formal interim efficacy analyses designed to terminate the study early, either for futility or for demonstrated efficacy. In this feasibility study, poor enrollment, substandard protocol adherence, or low rates of data collection could prompt changes to study conduct but would be anticipated to lead to corrective actions rather than early study termination.

Note that the DSMB has the ability to halt the trial at their discretion for any reason if they deem this appropriate.

10.3.8 Follow-up of Serious, Unexpected and Related Adverse Events

All serious, unexpected and related adverse events, that are unresolved at the time of the patient's termination from the study or discharge from the hospital, will be followed by the Clinical Center investigators until the events are resolved, subject is lost to follow-up, the adverse event is otherwise explained or has stabilized, or 12 months have passed from the time of last study dose.

10.3.9 Reporting Mechanisms for Changes or Amendments to Protocol or Consent Form

Any changes to the protocol or consent forms will be first submitted to the single IRB for approval. Once approved, documents are deposited by the sIRB in IREx. The project manager in the DCC will then upload them into the project-specific eRoom/eBinder maintained by the DCC for study documents, which will make the documents available to all study personnel. Any changes to protocol or consent documents, as well as any other changes to study procedure, will be communicated by the project manager by email to all relevant study personnel, with further communication within a clinical center to be performed by the site investigator and study personnel at the center, as applicable.

10.3.10 IND Information

Investigation of IVMg in this study is supported and supervised by the FDA through Investigational New Drug Application (IND) #133781.

11 Study Training

A formal training program for investigators and research staff will be held prior to the start of enrollment. The training will cover regulatory topics including applicable drug regulations and training in good clinical practice. The training will also provide in-depth explanations regarding study procedures, clinical care, adverse event reporting, data entry procedures, quality assurance, site monitoring and the informed consent process. A manual of study operations will be created and provided to each site investigator prior to the start of enrollment. The manual will detail specific information about the study procedures, regulatory information, safety reporting, and other necessary information. Updates and revisions to the manual will be made available electronically. The DCC, in collaboration with the study PIs and clinical Co-Investigator (Drs. Johnson, Zorc, and Stanley), will be the main contact for study-related questions.

Prior to the start of enrollment, lead investigators and each sites research coordinator, along with DCC staff will meet virtually or in person for a training session. Each site investigator will instruct the ED physician colleagues at their home institutions about the study, serve as a local advocate and champion for the study, and answer questions as they arise. Throughout the study, the study investigators and research coordinators will also have at least monthly scheduled telephone conference calls and/or webinars for all study personnel, or more frequent group communications as necessary. BD medical, which recently acquired Velano Vascular, the developer of the PIVO device, will conduct training on the use of PIVO with blood-collection staff prior to subject enrollment.

Monitoring of the research activities conducted during the pilot trial will be supported by quality assurance (QA) visits conducted regularly by the nodal administrators of the involved PECARN sites, including regular assessment of support and funding for study effort, and preparation for monitoring by the PECARN DCC and other data regulatory bodies including the FDA. Regular QA visits by the DCC at each site ensures a proactive rather than reactive approach to addressing study-related issues. Each QA visit is followed by joint discussion with the nodal administrator and study staff to define isolated, structural, or study-related barriers to study success. These ensure that oversight of PECARN sites is timely, comprehensive, and effective.

12 Regulatory Considerations

12.1 Food and Drug Administration

We have obtained IND #133781 from the FDA and anticipate close coordination with the FDA going forward as we prepare our study protocols, including our Investigators Brochure.

12.2 Health Insurance Portability and Accountability Act

Data elements collected include the date of birth and date of admission. Prior to statistical analyses, dates will be used to calculate patient age at the time of the study events. The final data sets (used for study analyses and archived at the end of the study) will be de-identified, and will exclude these specific dates.

Data elements for race, ethnicity, and gender are also being collected. These demographic data are required for Federal reporting purposes to delineate subject accrual by race, ethnicity, and gender.

For purposes of the DCC handling potential protected health information (PHI) and producing the research data sets that will be used for analyses and the de-identified public use data sets, all study sites have been offered a Business Associate Agreement with the University of Utah. Copies of executed Business Associate Agreements are maintained at the DCC.

12.3 Inclusion of Women and Minorities

There will be no exclusion of patients based on gender, race, or ethnicity.

12.4 ClinicalTrials.gov Requirements

This trial will be registered at ClinicalTrials.gov in accordance with Federal regulations.

12.5 Retention of Records

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR].

12.6 Public Use Data Set

After subject enrollment and follow up have been completed, the DCC will prepare a final study database for analysis. A releasable database will be produced and completely de-identified in accordance with the definitions provided in the Health insurance Portability and Accountability Act (HIPAA). Namely, all identifiers specified in HIPAA will be recoded in a manner that will make it impossible to deduce or impute the specific identity of any patient. The database will not contain any institutional identifiers.

The DCC will also prepare a data dictionary that provides a concise definition of every data element included in the database. If specific data elements have idiosyncrasies that might affect interpretation or analysis, this will be discussed in the dictionary document. In accordance with policies determined by the investigators and funding sponsors, the releasable database will be provided to users in electronic form.

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