Protocol Title: Ideal **ST**eroids for **A**sthma **T**reatment in the PICU (**iSTAT PICU**): A prospective, comparative, single-arm study assessing dexamethasone versus methylprednisolone in severe status asthmaticus admitted to the pediatric intensive care unit.

Short Title: Ideal **ST**eroids for **A**sthma **T**reatment in the PICU [Acronym: **iSTAT PICU**]

Protocol / Johns Hopkins All Children's Hospital (JHACH) IRB Number: IRB00187813

National Clinical Trial (NCT) Identified Number: NCT03900624

Amendment Number: n/a

Date of Protocol Approval: 3/28/2019

Study Summary:

Title	Ideal STeroids for Asthma Treatment in the PICU (iSTAT PICU): a prospective, single center, open-label, parallel-group, nonrandomized clinical trial.
Short Title	Ideal STeroids for Asthma Treatment in the PICU [Acronym: iSTAT PICU]
IND	N/A
Phase	4
Design	Prospective, open-label, parallel-group, nonrandomized clinical trial
Study Duration	24 months
Study Center(s)	Single-center
Objectives	Determine if differences in (1) length of stay, (2) continuous nebulized albuterol duration, (3) a composite outcome of rate of advanced asthma pharmacologic and respiratory adjunctive therapies, and (4) corticosteroid-related adverse event rate for children hospitalized with critical asthma enrolled to receive IV dexamethasone (Intervention Arm) or methylprednisolone (Standard Care Arm).
Number of Participants	Minimum of 90 subjects will be enrolled allocated 2:1 to standard care to interventional arms
Diagnosis and Main Eligibility Criteria	Critical Asthma Admission (Status Asthmaticus / Acute Asthma Exacerbation) hospitalized in the pediatric intensive care unit (PICU).
Study Product, Dose, Route, Regimen	Dexamethasone, 0.25mg/kg/dose (Max 15 mg) every 6 hours, intravenous
Duration of Administration	Maximum of 48 hours
Statistical Methodology	Descriptive statistics, comparative statistics (Wilcoxon rank sum, Fisher's exact, and student's *t* tests). Type I error will be set at 0.05. All data will be analyzed using Stata v15.1 (Statacorp©, College station, TX).

STUDY PROTOCOL

1. Study Team Members:

a. *Senior Investigator*:
   i. Anthony A. Sochet, MD, MS (JHU, JH-ACH, Critical Care Medicine)

b. *Principal Investigator*:
   i. Meghan Roddy, PharmD (JH-ACH, Critical Care Medicine)

c. *Coinvestigators / Collaborators*:
   i. Kristina K. Darville, ARNP; (JH-ACH, Critical Care Medicine)
   ii. Neil Goldenberg, MD; (JHU, JH-ACH, Director of Research)
   iii. Meghan Martin, MD; (JH-ACH, Pediatric Emergency Medicine)
   iv. Scott McKinley, MD; (JH-ACH, Pulmonology and Sleep Medicine)
   v. Thomas A. Nakagawa, MD; (University of Florida, Critical Care Medicine)
   vi. Austin Sellers, MD; (JH-ACH, Institute for Clinical and Translational Research)
   vii. Beatriz Teppa, MD; (JH-ACH, Critical Care Medicine)

2. Abstract

Critical asthma is disease of immune dysregulation that is acutely treated with inhaled beta-agonists and systemic corticosteroids. Steroid agents are chosen at the discretion of clinical providers based upon a child's capacity to tolerate enteral medications and the specific clinical setting (outpatient vs. general inpatient vs. critical inpatient). Intravenous methylprednisolone (MP) is unanimously used in the critical care (PICU) literature and populations but little data exists comparing MP to other potent intravenous corticosteroids such as dexamethasone (DM). Both drugs have been FDA approved for the acute treatment of inflammatory disorders including asthma, but no superiority trials have been conducted in the inpatient setting for this specific population.

Our research group has conducted a retrospective study over a 2-year period to assess if differences in clinical outcomes or adverse events exist in cohorts defined by DM exposure in the ER. Our data revealed none, but most children were switched to MP during their PICU stay making data analyses severely confounded by exposure to the defining characteristics of the comparative cohort. As both agents are FDA approved and in an effort to appropriate power sample size calculations for a prospective non-blinded clinical trial of DM vs MP in status asthmaticus, we seek to first prospectively study individuals enrolled into an interventional arm (DM) during their PICU asthma treatment and compare outcomes to PICU asthmatics concurrently admitted to the PICU enrolled into a parallel group, standard care arm (MP). This research will provide much needed epidemiologic and basic comparative data required to power and conduct a definitive, trials of DM vs. MP assessing other clinical efficacy endpoints

3. Study Endpoints:

Primary endpoints include (1) length of stay, (2) continuous albuterol duration, (3) a composite outcome including frequency of critical asthma adjunctive pharmacologic and respiratory-based interventions, and (4) corticosteroid-related adverse events

4. Background

As the pathophysiology of an critical asthma is dysregulated inflammatory pathways, standard treatment includes the prompt initiation of intravenous systemic corticosteroids. Glucocorticoids are the mainstay of therapy for children treated for critical asthma (Taylor, 1993). Furthermore, corticosteroids

improve the efficacy of beta-2 agonists, such as albuterol (Svedmyr, 1990), a nebulized medication used for bronchodilation in acute asthma exacerbations. There remains an ongoing dialogue among the expert medical community regarding the superiority of specific IV corticosteroid, dosing, route and delivery. This debate continues secondary to a lack of definitive comparative data in the literature. While the benefits of receiving systemic corticosteroids has been demonstrated in multiple studies (Scarfone, 1993; Ho, 1994; Connett, 1994; Storr, 1987; Younger 1987; Gleeson, 1990; Kattan, 1980), to date, no superiority trials have been conducted comparing IV systemic corticosteroids in the PICU setting.

While many systemic corticosteroids are FDA approved for the treatment of asthma exacerbation including prednisone, prednisolone, MP and DM, standard care in management of critical asthma is IV MP 1mg/kg/dose (max 60mg) every 6 hours for a 5-day course. Recent data from emergency room literature would suggest there is equipoise in use of dexamethasone as an alternative for methylprednisolone due to its increased glucocorticoid (anti-inflammatory) potency and long elimination half-life (Keeney, 2014; Paniagua, 2017). Steroids are chosen at the discretion of clinical providers based upon a child's capacity to tolerate enteral medications and clinical setting (outpatient vs. general inpatient vs. critical inpatient).

Our research group has conducted a retrospective study over a 2-year period to assess if differences in clinical efficacy endpoints or safety endpoints exist in cohorts defined by DM exposure in the ER. Our data revealed no differences, but many children were switched to MP during their PICU stay making data analyses severely confounded by exposure to the defining characteristics of the comparative cohort. We seek to prospectively consent individuals to receive DM (intervention arm) during their PICU stay and compare outcomes to a standard care arm (MP). The JH-ACH admits approximately 150 asthmatics per year in the PICU and we aim to enroll 90 subjects (30 intervention and 60 standard care) to detect a 1-day change in length of stay with a power of 0.8 and alpha set at 0.05. Primary outcomes include (1) length of stay, (2) continuous nebulized albuterol duration, (3) a composite outcome including rate of critical asthma adjunctive pharmacologic and respiratory interventions, and (4) rates for corticosteroid-related adverse events. We plan to use the findings of our study to inform the methodology of upcoming superiority trials to better understand how choice of corticosteroid may impact clinical, molecular, physiology efficacy endpoints.

5. Study Procedures

a. *Study design*: After IRB approval, we will conduct a prospective, parallel-arm, non-randomized, open label, single-center, cohort study in children 5 to 17 years of age admitted to the JH-ACH PICU with critical asthma. Children consented to the interventional arm will receive intravenous (IV) DM 0.25 mg/kg/dose (max dose 15 mg per dose) every 6 hours for up to 2 days and those enrolled into standard care arm will receive IV MP 1 mg/kg/dose (max dose 60mg per dose) every 6 hours for up to 5 days.

b. *Study duration*: Up until 30-days after hospital discharge following study enrollment.

c. *Blinding*: None.

d. *Justification of why participants will not receive routine care or will have current therapy stopped*. DM has an FDA approved indication for asthma exacerbation management. The use of DM has been adopted in the emergency room and inpatient acute care setting as standard care.

e. *Definition of treatment failure or participant removal criteria*.: As the half-life for DM is such that 2 days of dosing is the equivalent of 5 days of steroid exposure, at the completion of day 4, if a child is still severely ill (at the discretion of the clinical provider in consultation with pediatric Pulmonlogy as part of standard care) was defined as treatment failure. Standard care would dictate further steroid administration at this time with either IV or PO corticosteroids beyond 5 days with planned taper in the inpatient/outpatient setting. If treatment failure occurs and IV steroids are elected to be continued beyond the prespecified duration, the clinicians could choose the corticosteroid type at their discretion.

f. *Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely*: After children receive up to 2 days of DM, no further corticosteroids are indicated as the elimination half-life is such that it is an equivalent of 5 days of treatment with MP. Standard care for children admitted to the PICU for critical asthma includes the route modification from IV to enteral largely dependent on respiratory and mental status improvements. At that time, a child may be transitioned to enteral prednisone or prednisolone during standard care management (MP). If a child enrolled into the intervention arm (DM) receives < 2 days of IV DM but are ready to initiate enteral medications, then they will be switch to enteral DM 0.5mg/kg/dose daily for a total duration of exposure not to exceed 2-days during protocolized treatment.

g. *Inclusion/Exclusion Criteria*: Inclusion criteria are children 5 to 17 years of age with primary admission diagnoses of critical asthma (including both acute asthma exacerbation or status asthmaticus in the PICU setting). Exclusion criteria are children with existing tracheostomy, cystic fibrosis, malignancy, transplantation status, and pulmonary hypertension.

6. Drugs/ Substances/ Devices

ARM Name	Intervention Arm
Intervention Type	Dexamethasone (Intervention)
Dose Route	Intravenous
Dose Units	mg/kg
Dose Strength	0.25/dose (Max 15mg)
Dose Frequency	Every 6 hours
Sourcing	Clinical pharmacy
Packaging/Labeling	Per clinical standard

ARM Name	Intervention Arm
Intervention Type	Dexamethasone (Intervention)
Dose Route	Enteral
Dose Units	mg/kg
Dose Strength	0.5/dose (Max 16mg)
Dose Frequency	Daily
Sourcing	Clinical pharmacy
Packaging/Labeling	Per clinical standard

ARM Name	Standard Care Arm
Intervention Type	Methylprednisolone
Dose Route	Intravenous
Dose Units	mg/kg
Dose Strength	1/dose (Max 60mg)
Dose Frequency	Every 6 hours
Sourcing	Clinical pharmacy
Packaging/Labeling	Per clinical standard

ARM Name	Standard Care Arm
Intervention Type	Prednisone / Prednisolone
Dose Route	Enteral
Dose Units	mg/kg
Dose Strength	1/dose
Dose Frequency	Every 12 hours
Sourcing	Clinical pharmacy
Packaging/Labeling	Per clinical standard

a. *Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed*: Not applicable.
b. *Justification and safety information if non-FDA approved drugs without an IND will be administered.*: Not applicable

7. Study Statistics

a. *Primary outcome variables*: Primary outcomes include (1) length of stay, (2) continuous nebulized albuterol duration, (3) a composite outcome including rate of critical asthma adjunctive pharmacologic and respiratory interventions (i.e., magnesium, methylxanthines, terbutaline, ketamine, inhaled anesthetics, invasive mechanical ventilation, non-invasive ventilation, extracorporeal life support, and heliox), and (4) rates for corticosteroid-related adverse events (corticosteroids (i.e., clinically relevant gastrointestinal bleeding, gastritis, necrotizing enterocolitis, hypertension, hyperglycemia, altered mentation [hallucinations and delirium], and adrenal suppression)
b. *Other study data to be collected*: anthropometrics, demographics, Pediatric Risk of Mortality-3 score Probability of Mortality, Pediatric Asthma Severity Score, National Heart Lung and Blood asthma classification, Pediatric Index of Mortality-3 score Risk of Mortality, comorbidities, and unplanned same-cause hospital readmission within 30 days
c. *Statistical plan*: Descriptive statistics such as proportions/frequencies, means ± standard deviation, and medians [interquartile range]. Comparative statistics will include Wilcoxon rank sum, Fisher's exact, and student's *t* tests where appropriate. Type I error will be set at 0.05. All data will be analyzed using Stata v15.1 (Statacorp©, College station, TX).

8. Risks

a. *Medical risks, listing all procedures, their major and minor risks and expected frequency*:
    i. There always exists a potential risk for data leak, loss of privacy and breach of confidentiality. All measures (described below) will be taken to minimize these risks.
b. *Steps taken to minimize the risks*:
    i. Patient data will be stored for research purposes as a HIPAA defined limited data set in a secure, password protected electronic database and analyzed with Stata v15.1. Each patient will be assigned a unique Participant ID number in the system. Access to the system will be restricted to research team members listed above. Data extractions as well as modifications or edits to data will be logged.

ii. Serious adverse events will be followed throughout study, officially reported within 24-hours, and adjudicated within the co-investigator and steering committee. In the event that > 5% of children have a serious adverse event during enrollment, trial enrollment will be halted to prevent potential harm.

c. *Plan for reporting unanticipated problems or study deviations*:
   i. The principal investigator will meet on a monthly basis with study members either face-to-face or via telecommunications to discuss study management, education / re-education of team members and mentorship. This will include any discussion related to unanticipated problems or study deviations. This will not exclude team members from meeting with the principal investigator on other occasions to discuss matters as it relates to this study protocol. These meetings will be confidential and take place in a secure meeting room in the Johns Hopkins All Children's Hospital Pediatric Critical Care Medicine office in the OCC Suite 702. Any deviations from the study protocol will be logged and immediately reported to the local JH-ACH IRB for review.

d. *Legal risks such as the risks that would be associated with breach of confidentiality:* see above.

e. *Financial risks to the participants*: none

9. Benefits

a. This research will provide the needed epidemiologic and basic comparative data required to power and conduct a definitive, head-to-head trial of DM vs. MP. As a result of these data, definitive study with a randomized, RCT could be conducted to confirm superiority or non-inferiority of DM vs MP as well as assessment of other relevant endpoints.

b. We expect that given the shorter treatment duration and potent glucocorticoid activity, DM will offer potential advantages related to patient compliance.

10. Payment and Remuneration: None

11. Costs: None

12. Discontinuation of Study Intervention and Participant Withdrawal:

a. If a patient has a serious or non-serious adverse event thought to be associated with DM, then the IRB, subject, and family will be notified of any adverse events immediately.

b. A participant may voluntarily withdraw from the study at any time at his/her own request (or consenting family member's request).

13. Regulatory and Ethical Considerations:

a. The investigator will be responsible for the following:
   i. Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
   ii. Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
   iii. Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

14. Informed Consent Process:

a. The investigator or his/her authorized designee will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
b. Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
c. The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form (ICF).
d. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
e. A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

15. Protocol Deviations

a. A protocol deviation is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research.
b. The JHM IRB requires the prompt reporting of protocol deviations which are:
    i. Emergency deviations (when immediate deviations are required to protect the life or physical well-being of a participant)
    ii. Major (representing a major change in the approved protocol), non-emergent deviation occurring without prior IRB approval
c. Minor or administration deviations, which do not affect the scientific soundness of the research plan or the rights, safety, or welfare of human participants, are reported to the JHM IRB at the time of continuing review.